Republic of Malawi
Ministry of Health

NATIONAL TUBERCULOSIS AND LEPROSY GUIDELINES

Ninth Edition • 2024

National Tuberculosis and Leprosy Guidelines

NINTH EDITION • 2024

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Foreword

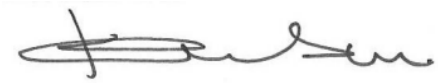
The Ministry of Health in Malawi through the National Tuberculosis and Leprosy Elimination Program (NTLEP) of the Community and Promotive Health Directorate is mandated to offer technical and policy guidance in the implementation of tuberculosis and leprosy preventive, diagnosis, care and treatment services in the country.

Its vision is to have a TB and leprosy free Malawi with a mission of ensuring effective, equitable and accessible TB and leprosy prevention, diagnosis, treatment and care services in Malawi. Its goals are to reduce the incidence of tuberculosis by 50 % and its mortality by 75% by the end of 2025 compared to the 2015 baseline and elimination of leprosy in all districts by 2025 (occurrence of less than 1 case per 10,000 population).

The program has over the years recorded tremendous improvements in some of the key indicators. TB incidence has declined by 31% in the last seven years. This has been complemented by a decline in the TB/HIV co-infection rate by 43% coupled with a decline in the overall mortality rate by also 43%. The treatment coverage has increased from 55% in 2021 to 75% in 2022. This entails that more work needs to be done to reduce the treatment coverage gap. The country has also over the years managed to sustain the treatment success rate for drug susceptible tuberculosis at 90% against the WHO target of 80%. In order to sustain the gains that have been made over the years and at the same time addressing the prevailing gaps in the fight against tuberculosis and leprosy, he Ministry has revised the guidelines in order to accommodate emerging evidence, normative guidance from the World Health Organization (WHO) and epidemiological trends from programmatic data updates. This treatment guideline responds to the 2021-2025 national tuberculosis strategic plan, the international end TB strategy, and the sustainable development goals which have set ambitious targets for drug susceptible and drug resistance TB treatment coverage and prevention.

This edition of the guideline has combined both Tuberculosis and Leprosy treatment manuals in one document. The addition of leprosy has been necessitated by the need to have an approved manual that will standardize leprosy preventive, care, treatment and rehabilitative services in the country. For so many years the country has been operating without a leprosy treatment manual.

It is envisioned that the manual will be used by all players both in public and private facilities who are engaged in the TB and leprosy control in Malawi. It is expected that this treatment guideline will override all other documents in this area in our country. The Ministry of Health will continue to offer technical assistance and supervision to all districts and peripheral health facilities. We strongly believe that with your cooperation at all levels in the adherence to the guidance that is expressed in this manual, we can strengthen our fight against TB and leprosy and achieve our national goals.



Honourable Khumbize Kandodo Chiponda MP
Minister of Health, Malawi
February 2024

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The development of this treatment guideline was made possible by the financing of the Ministry of Health, the World Bank through the Southern Africa Tuberculosis Health Systems Strengthening Project (SATBHSSP) and the Global Fund. The financial support of these institutions is accordingly appreciated.

The MoH is committed to effectively providing its stewardship role in the implementation of the Tuberculosis and Leprosy treatment manual, 9th edition to honour all the aspirations, efforts and contributions that all different stakeholders made in the development of this manual. We are highly indebted for your enormous contribution in making this document a reality.

Dr Samson Kwazizira Mndolo
Secretary for Health, Malawi
February 2024

TUBERCULOSIS

Guidelines

1. Introduction

1.1. Tuberculosis in Malawi

The National Tuberculosis Control Programme (NTP) was established in 1964 in the Ministry of Health (MoH) to coordinate the national response to the fight against tuberculosis (TB) in Malawi. Within MoH, NTP falls under the Directorate of Preventive Health Services. The day-to-day management of the programme is the responsibility of a Programme Manager who is supported by a Deputy Programme Manager and various programme officers at national, zonal, district and facility levels. TB control activities are fully integrated within Malawi's decentralized public health system, and private health facilities also provide TB control services under a central government-brokered Public Private Partnership (PPP) framework.

In general, TB services are provided free of direct cost to clients at points of care and TB is among the priority Essential Health Package (EHP) conditions since it is an epidemic of public health concern. Decentralization of TB diagnostic and treatment services to facilities lower than the district hospitals is an ongoing process.

Microscopy (both light and florescent) remains the mainstay for TB diagnosis in Malawi, with radiology as an adjunctive technology where available. As of December 2021, 445 public and CHAM health facilities across the country had capacity for both TB diagnosis and treatment initiation. Additionally, 418 peripheral laboratories had capacity for TB diagnosis through florescent or light microscopy. GeneXpert coverage has improved over the period from 51 in 2016 to 144 sites in 2022. The National TB Reference Laboratory (NTRL) provides high level diagnostic services, including solid and liquid culture as well as LPA to confirm TB and drug sensitivity testing on selected specimens from across the country. NTRL is also responsible for quality assurance services to peripheral laboratories for both microscopy, LF-LAM and GeneXpert. Furthermore, there have been introduction of Point of Care (PoC) diagnostic method i.e., LF-LAM to test for TB among HIV Positive eligible patients. As of December 2021, a total of 129 facilities across the country had capacity to provide LF-LAM services.

MoH is the only source of all anti-TB medications and commodities. This ensures quality assured treatment and rational drug use in all public and private health facilities in the country. The tight drug regulation and management has helped the country to register one of the lowest prevalence rates of drug resistant TB in the region at 2.3% among new and 6.1% among previously treated patient populations.

1.2. TB National Strategic Plan 2021-2025

Year 2021 marks the beginning of the new Strategic Plan (NSP) spanning from 2021 to 2025 with the aim to reduce the morbidity, mortality, and transmission of tuberculosis until the disease is no longer a public health problem in the country. The key strategic approaches are to pursue and improve coverage and quality of patient care; to address TB comorbidities and key populations and strengthen supporting policies and systems. The Plan emphasize on further decentralisation of quality assured TB diagnosis and treatment services to peripheral facilities and community levels in the public and private sectors; to consolidate programmatic management of drug resistant TB (PMDT); and roll out further implementation of TB/HIV collaborative activities and interventions as part of both TB and HIV Control strategies.

It is a framework that guide the actions of MoH and other decision-makers, implementers within the government and non-governmental sectors who support the TB and leprosy responses in the country. The strategic plan is aligned with the Malawi Growth and Development Strategy (MGDS), At a global level, it has been aligned with the End TB Strategy and the UN Sustainable Development Goals (SDGs) aspirations.

To achieve the country's health aspirations and people level results specified in this strategic plan, increased human and financial resources and close collaboration between government ministries, agencies, departments,

non-governmental organizations (NGOs), civil society, development partners and the communities themselves will be critical.

The interventions for TB and Leprosy response under this NSP are organised under the following four main pillars; Patient Centred Care and Treatment, TB Comorbidities and Key Populations, Bold Policies and Supportive Systems and Program Management M&E, Research, and Innovation

1.3. Scope of the Guidelines

The consolidated TB and leprosy guidelines will provide health care providers with comprehensive clinical guidance and programmatic management of both TB and leprosy. The guidelines aim to ensure that all health care providers have adequate knowledge and skills necessary to provide quality and universally acceptable Services in the diagnosis, treatment, prevention, and rehabilitation of patients with TB and leprosy. The Guideline offers recommendations for improving the overall quality of care, including laboratory diagnosis, drug-resistant TB, nutrition in TB, and management of non-tuberculous mycobacteria. The guidelines also emphasize the importance of infection prevention and control measures to reduce the transmission of TB and leprosy in healthcare facilities.

Moreover, the guidelines promote collaboration and coordination between healthcare providers, communities, public and private care providers in the fight against TB and Leprosy. Overall, the consolidated TB and leprosy guidelines aim to contribute to the reduction of the burden of TB and leprosy in Malawi by providing comprehensive guidance and building the capacity of healthcare workers. By promoting collaboration and partnership, these guidelines aim to increase the effectiveness of TB and leprosy elimination programs in Malawi, with the goal of providing universal coverage and comprehensive care in TB, leprosy, and lung health services.

1.4. Target audience

The primary target audience for the TB and leprosy guidelines includes healthcare professionals and practitioners involved in the prevention, diagnosis, and treatment of tuberculosis and leprosy in the country, such as doctors, nurses, clinical officers, laboratory technicians, and other healthcare workers working in both public and private healthcare facilities. Additionally, the guidelines are also useful for policymakers and public health officials involved in developing and implementing national strategies and policies for TB and the leprosy elimination programs in Malawi. The guidelines will serve as a reference for all partners and stakeholders involved in the management of TB and Leprosy patients.

2. Definitions

2.1. Case Definitions

Bacteriologically confirmed TB

Biological specimen is positive by smear microscopy, culture or WRD (e.g., Xpert MTB/RIF). All such cases should be notified, regardless of whether TB treatment has started.

A clinically diagnosed TB case

Does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. This definition includes diagnoses based on X-ray abnormalities or suggestive histology and extra pulmonary cases without laboratory confirmation. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

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

- Anatomical site of disease
- History of previous treatment
- Drug resistance
- HIV status.

Classifications based on anatomical site of disease

Pulmonary tuberculosis (PTB)
Any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Miliary TB is classified as PTB because there are lesions in the lungs.

Tuberculous intra-thoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extrapulmonary TB.

A patient with both pulmonary and extra pulmonary TB should be classified as a case of PTB.

Extrapulmonary tuberculosis (EPTB)
Any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g., pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges.

Classifications based on history of previous TB treatment

Classifications based on history of previous TB treatment are slightly different from those previously published. They focus only on history of previous treatment and are independent of bacteriological confirmation or site of disease.

- **New patients:** have never been treated for TB or have taken anti-TB drugs for less than 1 month.
- **Previously treated patients** have received 1 month or more of anti-TB drugs in the past. They are further classified by the outcome of their most recent course of treatment as follows:
    - **Relapse patients** are those who have previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).

- **Treatment after failure patients** are those who have previously been treated for TB and whose treatment failed at the end of their most recent course of treatment.
- **Treatment after loss to follow-up patients** are those who have previously been treated for TB and were declared lost to follow-up at the end of their most recent course of treatment. (These were previously known as treatment after default patients.)
- **Other previously treated patients** are those who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.
- **Patients with unknown previous TB treatment** history do not fit into any of the categories listed above.
- New and relapse cases of TB are **incident TB** cases.

Treatment outcomes-new definition (2021)

- **Cured:** A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy, with evidence of bacteriological response and no evidence of failure
- **Treatment completed:** A person who completed treatment as recommended by the national policy, whose outcome doesn't meet the definition of cure or treatment failure
- **Treatment failed:** A patient whose treatment regimen need to be terminated or permanently changed to a new treatment strategy
- **Died:** A patient who died before starting treatment or during the course of treatment
- **Lost to follow-up:** A patient who didn't start treatment or whose treatment was interrupted for 2 consecutive months or more
- **Not evaluated:** A patient for whom no treatment was assigned
- **Treatment success:** The sum of cured and treatment completed

3. TB Case Finding

3.1. Background

Detecting TB among people who present to health facilities is not adequate to find all people with TB disease as some are missed in the system. The remaining case-detection gap contributes to transmission in the community hence the need for a more active approach to early detection of TB. The TB and Leprosy Elimination Program (NTLEP) is mandated to ensure provision of high-quality care for TB patients. The key priority is to identify and diagnose people with active TB and promptly put them on treatment with the aim of minimizing the likelihood of continuous transmission in the community.

Individuals with high risk of TB should be Systematically screened for TB to ensure that TB disease is detected early, and treatment is initiated promptly, to reduce the risk of poor treatment outcomes, health sequelae and the adverse social and economic consequences associated with the course of TB disease. The following WHO recommendations [1] are the basis for the targeted systematic TB screening among sub population groups:

Strong recommendations

- Household contacts and other close contacts of individuals with TB disease including MDR-TB
- People living with HIV (PLHIV)
- Workers in silica exposed workplaces e.g., miners
- Prison staff, prison inmates, and people in penitentiary institutions

Conditional recommendations

- People with untreated fibrotic lesions on Chest X-ray
- People in high TB burden settings (estimated TB prevalence >100/100,000) who are seeking care or who are in care and belong to selected risk groups, and HCWs
- Subpopulations which have risk factors for TB including urban poor communities, the homeless, rural communities, migrants, refugees, internally displaced persons, and other vulnerable groups with limited access to health care services

3.1.1. Operational Definition of Terms for systematic TB screening

Presumptive TB case: This refers to a patient who presents with symptoms and /or signs suggestive of TB.

Systematic screening for active TB: This is the systematic identification of people at risk of TB disease in a predetermined target group, by assessing using tests, examinations, or other procedures that can be applied rapidly. Those screened to be presumptive TB cases should have their disease status established by one or several diagnostic tests and additional clinical assessments, which together have a high diagnostic accuracy.

Active TB case-finding (ACF): Is the systematic identification of presumptive TB cases from a predetermined target population/ community initiated by healthcare workers or volunteers through symptomatic screening, detailed history taking, physical examinations and further laboratory and/or radiological investigations to diagnose TB.

Passive Case Finding: Requires that affected individuals are aware of their symptoms, have access to health facilities where they present themselves spontaneously, and are evaluated by health workers or volunteers who recognize the symptoms of TB and who have access to a reliable laboratory.

Intensified case finding (ICF): This is a healthcare provider-initiated TB screening among high-risk population such as PLHIV.

Enhanced TB case finding (ECF): The creation of population awareness of TB symptoms through advocacy and community mobilization to encourage self-presentation for TB screening.

Initial screening: The first screening test, examination or other procedure applied in the population eligible for screening.

Computer-aided detection (CAD): The use of specialized software to interpret abnormalities on chest radiographs that are suggestive of TB. CAD may be used for screening or triage presumptive TB cases.

The number needed to screen (NNS): The number of persons that need to undergo TB screening to diagnose one person with TB disease.

Risk groups: Any group of people in which the prevalence or incidence of TB is presumed to be significantly higher than in the general population.

3.2. Overall organization of the Case finding strategy

Health facilities: The screening should be done in each service delivery point such as outpatient departments (OPD), under five clinics, inpatients department, HIV clinics, non-communicable disease clinic, and other service outlets.

At the community level as shown in Figure 3.2-1 TB screening will be done through house-to-house TB screening and mobile diagnostic units. Community-based Sputum collection and referral are considered to use an enhanced case-finding strategy (ECF).

In institutions and other overcrowded settings: The screening should be done in regular manner in areas such refugee settings, the workplace, Prison inmates, other correctional facilities, big factories, and other settings with overcrowding.

Sites for implementation of TB screening

- Health facilities including public, CHAM, and Private health facilities
- Community settings, including congregate settings such as prisons, schools, army barracks, places of worship, residential institutions, and marketplaces
- Immigration port of entry and refugee camps
- Workplaces with high occupational exposure

Key populations targetted for systematic TB screening

- Systematic TB screening should also be conducted among high-risk groups with prior exposure to TB infection or at high risk of progressing to TB disease
- Key population groups such as PLHIV, household and close contacts of people with TB, people exposed to silica (mainly miners and mining communities), prison inmates, and urban dwellers should be prioritized for active TB screening

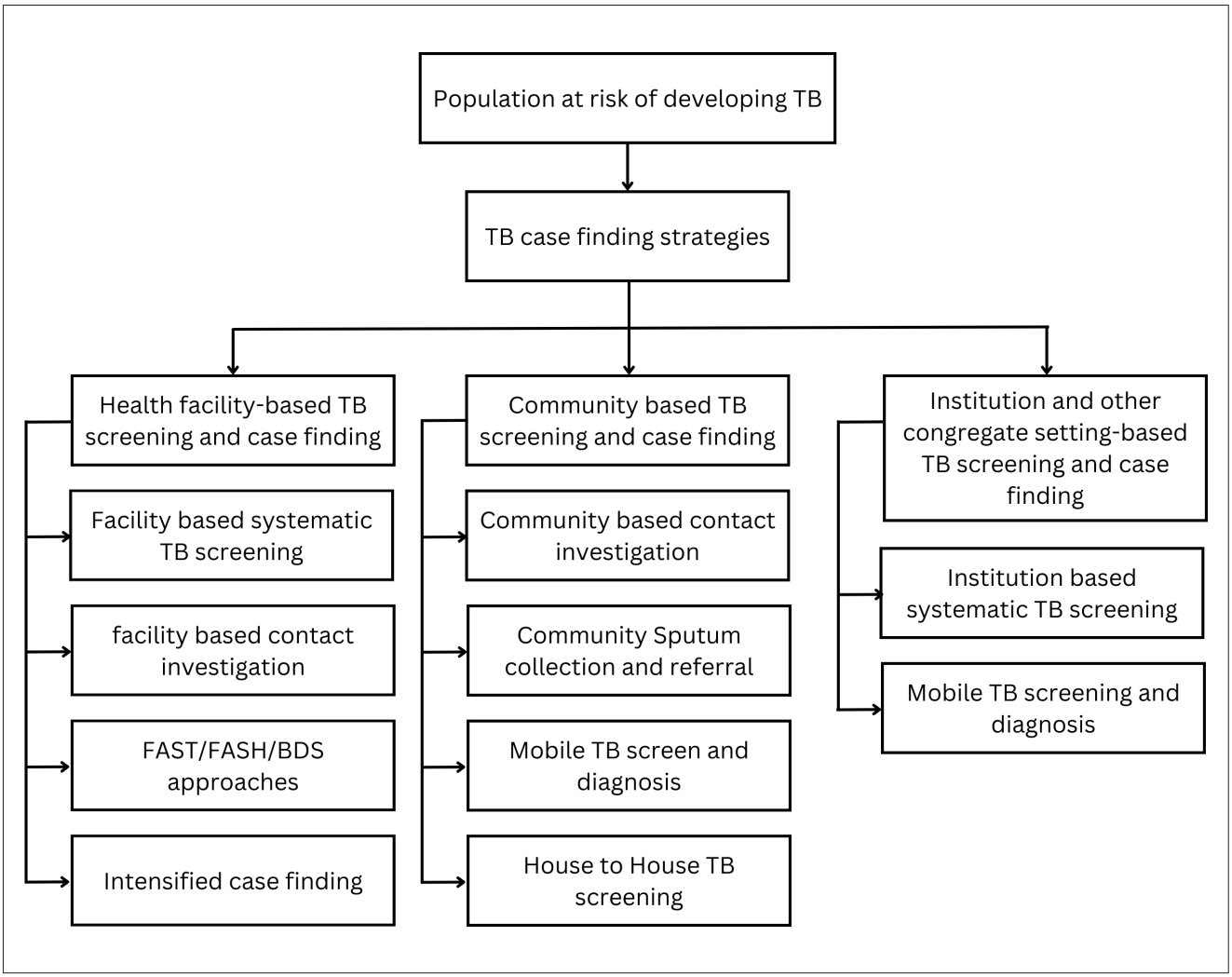


Figure 3.2-1 Strategic approaches for case finding in Malawi

3.2.1. Facility-based systematic TB Case Finding

This is a systematic TB screening approach that involves asking for the presence of TB symptoms among all persons visiting a health facility at all service delivery points regardless of the presenting signs and symptoms. The TB screening should be done at all outpatient departments (OPDs), under five clinics, inpatient departments, HIV clinics, non-communicable disease clinics, and other service outlets.

Priority target groups

While it is recommended to administer TB screening to all individuals presenting to the health facility at each service delivery point, priority should be given to individuals with a high risk for TB infection or risk of developing active TB disease.

The following groups of people presenting to health facilities should be given priority for Screening of TB at each service delivery point.	
• OPD attendees • Household contacts of index TB cases • People previously treated or exposed to TB • People with an untreated fibrotic lesion shown on CXR • People with chronic respiratory disease • People presenting with pneumonia • People with diabetes mellitus • People who smoke	• Prisoners and miners presenting to the health facilities • Undernourished people or people with a body mass index ≤ 18 • People in the in-patient department • People with chronic renal failure • People on treatments that compromise their immune system • Older people (60 years and older) • People in mental health clinics or institutions • Health care workers

Table 3.2-1 Priority groups for TB screening

Screening tool

Use the following WHO 4 symptom screen

High risk population groups: PLHIV/Prisoner/Miner/ mining community/HCWs	Other population Groups not included in High Risk for TB.
1. Cough (any duration) 2. Fever (any duration) 3. Night sweats (any duration) 4. Weight loss	1. Cough lasting >2 weeks 2. Fever lasting >2 weeks 3. Weight loss 4. Profuse night sweats lasting >2 weeks
Anyone fulfilling ANY of the above criteria will be labeled as a presumptive TB case	Anyone fulfilling ANY of the above criteria will be labeled as a presumptive TB case

Table 3.2-2 Symptomatic TB screening criteria

Chest X-ray together with computer-aided detection for TB can be used as a screening tool for the following high-risk group presenting to health facilities where applicable:

- PLHIV with advanced HIV disease and/or high viral load
- Prison Inmates
- Miners
- Household contact of index bacteriologically confirmed and PTB cases.
- Undernourished people or people with a body mass index ≤ 18,
- People with chronic renal failure
- Older people (60 years and older)

The TB screening can be done by health care workers **including nurses, clinicians, Disease Control and Surveillance Assistants (DCSAs), Patients/ward attendants and lab personnel**.

Screening can also be done using trained volunteers or non-clinical staff for example FAST promoters. Proper documentation of presumptive TB cases should be done in the presumptive TB register.

Where: Adult OPD, Under five OPDs, HIV clinic, Inpatient departments, Diabetes clinics clinic, TB clinic, and all other facility entry points.

Diagnostic tool

- GeneXpert and other WRD tests for all priority group
- Microscopy for non-priority group

3.2.2. FAST strategies (Finding TB patients, Actively Separate safely and Treat effectively)

It focuses health care workers on the most important administrative TB transmission control intervention and effective treatment.

FAST is one approach that is focused on stopping TB spread in healthcare facilities.

The strategy is built on a renewed appreciation of evidence showing that effective TB treatment reduces TB spread rapidly, even before sputum smear and culture turn negative.

Finding TB Patients: ask patients about the presence of WHO recommended 4 symptoms in waiting rooms, registration areas, and admission holding areas.

Actively: the health care provider-initiates screening and asks for TB symptoms (cough, fever, night sweat & weight loss)

Separating safely: While waiting for a laboratory diagnosis, patients identified through FAST strategies should be educated on respiratory hygiene (cough etiquette and separation) and moved to a designated, well-ventilated area away from other patients to prevent further spread of TB.

Treatment: Effective treatment is the most important step in preventing TB spread to others.

Target group

- All individuals presenting to a health facility for any reason should be asked for TB symptoms
- Individuals with a high risk for TB infection or developing active TB disease who present to health facilities with any form of respiratory symptoms

Screening & testing tools

- WHO recommended 4 symptom screens
- Xpert, Microscopy, and CXR for eligible groups– in selected sites (CXR)

By Whom: FAST can be done by nurses, clinical officers, health surveillance assistants, lab personnel, volunteers based in the facility.

Where: Health facilities designated to implement the FAST approach.

- Adult OPD, under five OPDs, HIV clinic, in-patient departments, Diabetic clinic, TB clinic, and all other facility entry points

Diagnostic tool

- Gene Xpert and other WRD test for priority groups
- Microscopy for non-GeneXpert site

3.2.3. Contact investigation

Definitions of terms in contact investigation

Contact investigation: Contact investigation is a systematic process intended to identify undiagnosed cases of TB among the contacts of an index case. In some settings, this includes testing for LTBI to identify possible candidates for preventive treatment.

Index Case/Index patients: the index case is the initially identified and diagnosed case of new or previously treated pulmonary TB **(bacteriologically confirmed TB, including MDR /XDR TB and new clinically diagnosed Pulmonary TB)** of any age in a specific household or other comparable settings in which others may have been exposed. TB contacts are categorized into household and close contacts.

Household Contact: A person who shared the same enclosed living space for one or more nights or frequent or extended periods during the day with the index case during the 3 months before the commencement of the current treatment episode.

Close TB Contact: A person who is not in the household but shares an enclosed space (such as a social gathering, workplace, or facility) for extended periods with the index case (definition above) during the 3 months before the commencement of the current treatment episode.

Identification of contacts of an index TB case

Contact investigation should be conducted for household or other close contacts of the index TB case. Priority should be given when the index TB patients have any of the following characteristics.

- Bacteriologically confirmed PTB
- Presumptive or confirmed or clinically diagnosed drug-resistant TB
- Children under 5 years of age with TB (to find the source of infection)

Contact investigation consists of two components, identification and prioritization and clinical evaluation.

Contact identification and prioritization

This is a systematic process that identifies contacts with or at increased risk for the development of TB. This includes:

- An interview with the index case to obtain the names, physical addresses, and ages of contacts
- Line listing of all contacts in the contact investigation register
- An assessment of contacts' risk for having or developing TB, based on the presence of symptoms, to determine those for whom clinical evaluation is indicated.

Clinical Evaluation

A systematic process for the diagnosis or exclusion of active TB among contacts who have symptoms or screen positive results on Xray screening.

Clinical evaluation should be done following the TB diagnostic algorithm.

Priority should be given to the following contacts;

- People of all ages with signs and symptoms suggestive of TB
- Children <5 years of age
- People with known or suspected immunocom promising conditions (especially PLHIV)
- Contacts of index cases with DRTB (proven or suspected)

Reverse Contact Investigation

- It is recommended to conduct a reverse contact investigation to identify the source case and investigate TB. (Also known as a 'reverse contact investigation'). It is a type of contact investigation conducted to identify the source case of someone recently diagnosed with active TB disease.
- It is recommended when children less than 5 years old are diagnosed with active TB disease, particularly pleural TB (primary TB), in a younger person.
- The source case investigations focus on identifying and screening those most likely to have TB disease among those who spent more time with the index case.
- Contact investigation should be initiated by the TB focal persons as soon as the index case/patient is registered to receive TB treatment.
- The TB focal person at the health facility must arrange the screening of the identified individuals upon a visit to the clinic. Contacts should be evaluated for the presence of active TB disease.

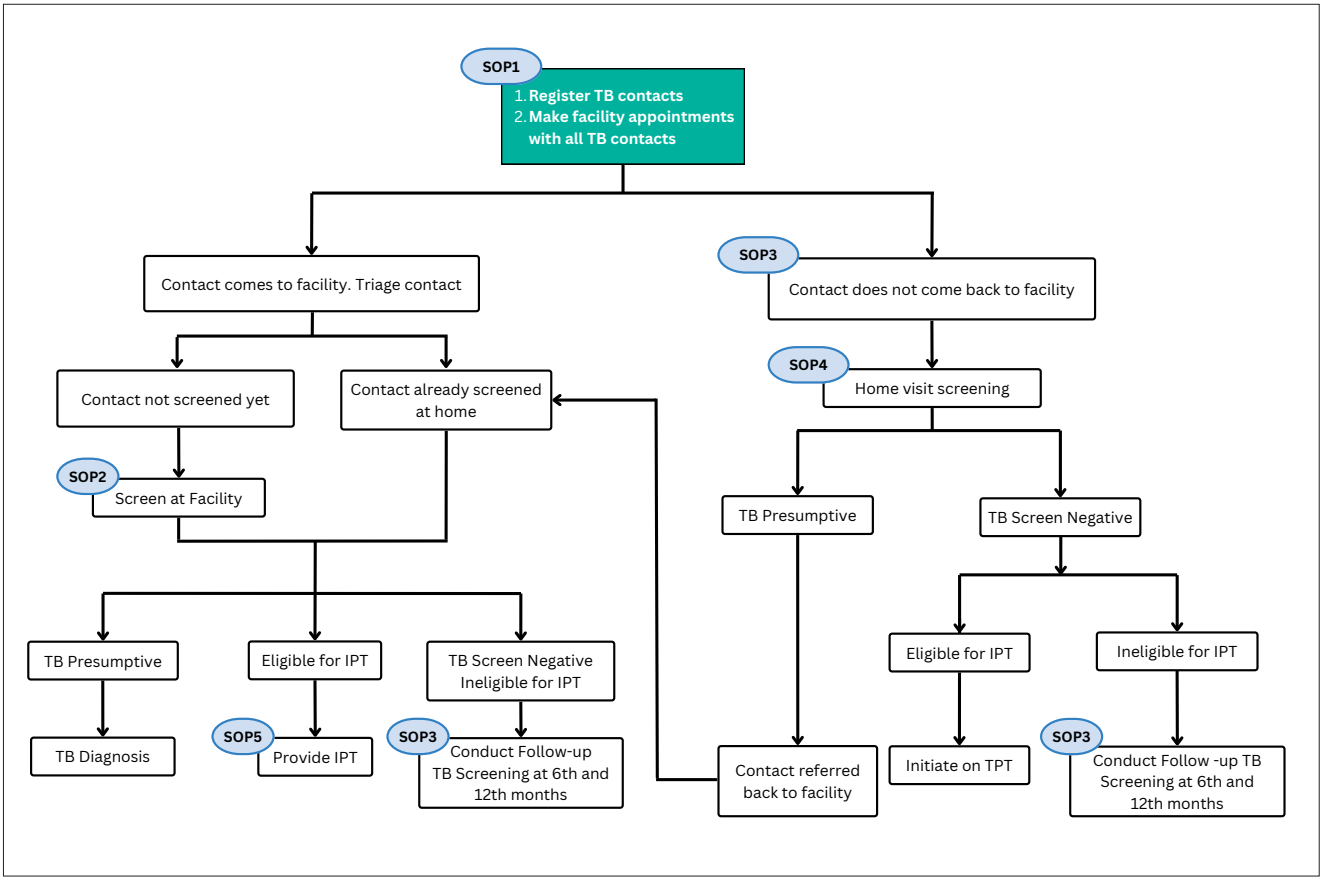


Figure 3.2-2 TB Contact identification flow chart

TB Screening and Care Cascade

Screening of contacts should be conducted using two approaches

- The contact is invited to a facility (contact invitation) or
- The contact is visited at home.

Contact Invitation: Contact invitation is when the index patient brings his/her contacts to the health facility for TB screening. All invited contacts should undergo the following:

- TB symptomatic screening for children should include a history of frequent respiratory tract infections, failure to thrive, reduced playfulness, lethargy, and irritability, and a history of contact with a known TB case should be considered.
- Presumptive TB cases should be sent to the laboratory/designated area for a sample in which the patient is advised on how to collect their results, then exited through normal facility procedures.
- Initiate all contacts who screen negative for all the symptoms and are eligible for preventive therapy on TPT (see LTBI section).

Contact investigation at home:

- A Home visit is initiated when an index TB patient fails to bring the contacts to the health facility for TB screening in 7 days.
- Community health care workers (CHCWs) or volunteers shall be given a list of all household contacts to trace from their respective communities.
- All contacts should undergo symptom screening using **WHO 4 symptom screens**.
- For children, evaluation for a history of frequent respiratory tract infections, failure to thrive, reduced playfulness and lethargy, and irritability.
- Sputum samples should be collected from all eligible presumptive TB cases and sent to the laboratory for bacteriological examination.

Diagnostic Tool

- Xpert MTB RIF (Ultra) is the preferred diagnostic tool
- Microscopy in the absence of Xpert

Note: All contacts who screen negative for TB and are eligible for preventive therapy.

Registration and reporting

All households and close contacts of the index TB cases/patients should be registered in the contact investigation register.

3.2.4. Intensified case finding (ICF among PLHIV)

Intensified TB case finding is one of the case finding strategies for PLHIV at HIV clinics.

The screening should be done at initiation and each follow-up visit.

Screening criteria/algorithm: 4-symptom screening criteria for PLHIV

- Cough of any duration
- Fever of any duration
- Night sweats of any duration
- Weight loss

Chest X-ray can be used as a TB screening tool for PLHIV with advanced disease, patients with CD4 < 200 cells/µl and Outpatients clients not on ART.

- Symptomatic screening and to be followed with X-ray screening if symptom screening is negative.
- Chest X-ray screening should not delay the initiation of the ART
- The screening done at baseline and after six months of ART initiation
- Computer Aided Diagnostic software (CAD) can be used to identify abnormal X-ray findings suggestive of TB
- The screening using CXR can be done in health facilities where X-ray is available on site.

Target population: People living with HIV

A multidisciplinary team in the health facility (TB, ART, laboratory, facility in charge, OPD clinicians) will take part in the implementation of this intervention.

Diagnostic Tool

- GeneXpert should be used as an initial diagnostic test for all PLHIV.
- LF-LAM for PLHIV with advanced HIV disease (AHD) with WHO stage 3 or 4 before ART initiation and ``Seriously ill" PLHIV.

Recording and reporting: ensure proper documentation of presumptive TB and cascade in the presumptive TB register.

3.2.5. Community-based TB

3.2.5.1. Interventions (case finding)

Community-based TB approach uses both Active Case Finding (ACF) and passive case finding (PCF) strategies. The screening is done by HCWs in the case of mobile diagnostic units which use symptom and CXR as screening tools or CHCWs and volunteers which are mostly based on symptomatic screening.

The community-based TB case-finding approaches comprise the following four interventions.

- House-to-house TB screening
- Community Sputum collection points
- Mobile TB Screening and diagnostic unit
- community-based contact investigation

3.2.5.1.1. House-to-House TB screening

House-to-house TB screening is one of the active TB case-finding strategies which aim to identify presumptive TB cases at the household level in communities expected to have a high prevalence of TB.

The strategy entails regular house-to-house visits by trained community volunteers to identify presumptive TB cases using symptom screening criteria.

For all presumptive TB clients, the sputum samples should be collected and transported as per guidelines to TB testing sites. Consequently, those with positive laboratory test results should be linked to TB registration sites for treatment initiation.

Target group: All household members in specific communities identified by the program as urban or rural hotspots through a prioritization matrix.

Who will conduct the house-to-house TB screening: Volunteers

Note: The urban and rural hotspot areas should be updated regularly based on the local epidemiological data, notification, and case-finding effort

The screening tool: Use the WHO four symptom screen criteria as per guidelines (Cough, fever, night sweats, and weight loss)

Diagnostic tool: GeneXpert will be a preferred diagnostic test where available. Microscopy can be used in the absence of GeneXpert

For all presumptive TB cases identified at community level, the necessary arrangement should be done to collect the sputum samples and transported to the nearby TB diagnostic site.

Registration and Reporting

The facility receiving the sample should record the information in the presumptive TB register

- The volunteers should record all screened presumptive TB and cases identified (in the house-to-house TB screening logbook) **active case finding registers** and referral forms to capture data on screening activities, (Chichewa translated-"Kalondolondo wa Chifukwa cha TB")
- Community TB active case finding monthly reporting forms (Chichewa translated- "Lipoti wakalondolondo")
- Community TB drug adherence register ("Kaundula wa kamwedwe ka makhwala a TB")

3.2.5.1.2. Community sputum collection points

As part of the decentralization of TB services, the NTLEP established community sputum collection points (CSCPs), managed by volunteer teams that passively identify people with symptoms or signs suggesting TB, collect sputum samples, transport them to testing facilities, and support TB treatment adherence.

Target groups

- All TB patients in the catchment area for TB treatment adherence.
- All community members
- Miners, ex-miners and their families and mining communities
- Refugee camps/displaced population
- All household and close contacts of pulmonary TB index cases.

Implementation arrangement

The CSCPs are established in hard-to-reach areas. Each CSCP is composed of volunteers who undergo basic TB training, The volunteers are chosen by community members. The criterion for choosing the volunteers includes those:

- Who know their community well
- Dedicated
- Trusted and respected by members of the community.
- Able to read and write

Key responsibility of the volunteers

- Identify presumptive TB cases who present themselves with TB symptoms suggestive of TB
- Collect sputum samples and transport to the nearest health facilities.
- Conduct health education/talk to improve community awareness on TB and Leprosy

- Follow up on the results by linking up with facility TB officers.
- Communicate results accordingly
- Provide support to all TB patients for treatment adherence.
- Provide psychosocial support to TB and Leprosy patients
- Attend the monthly meeting with other volunteers
- Prepare and submit monthly reports to the nearby health facilities using the report format designated for the purpose.

Screening tool to be used by CSCP volunteers

- TB symptomatic screening tool where the WHO 4 symptom screen are reviewed

Reporting and recording tools

- Community TB register (Chichewa translation- "Kaundula wa chifuwa cha TB")
- Community TB monthly reporting forms (Chichewa translated- "Lipotiwakaundula)"
- Community TB drug adherence register ("Kaundula wa kamwedwe ka mankhwala a TB")

3.2.6. Community-based TB Contact Investigation

This should be done by community volunteers or CHWs through home visits of contact or close contact when an index TB patient fails to bring the contacts to the health facility within 7 days. The lists of all household contacts and close contacts of an index TB case should be communicated to the community volunteers or CHWs in advance for home visit planning.

Priority target Group: Household contact or close contact of index cases with Bacteriologically confirmed Pulmonary TB cases

Screening tool: WHO 4 symptom screen criteria

Diagnostic tool: GeneXpert as initial test or Microscopy if Xpert is not available

Registration and reporting: Contact investigation register,

Who conducts contact investigation: Community Volunteer, HSA, or health care workers

Where: Home based/Home visit

3.2.6.1.1. Mobile TB screening and diagnosis

This is another approach for active case finding (ACF) that targets high-risk groups and populations in urban and rural areas. The mobile screening and diagnostic units are equipped with a digital X-ray machine that is configured with CAD AI (CAD4TB) and it has a laboratory section with the GeneXpert platform. TB Screening can be done by trained HCWs which include radiography technicians, clinicians, lab technicians, and community mobilizers. The presence of HIV Diagnostic Assistants is highly needed to offer HIV testing to clients with unknown HIV status undergoing mobile Van TB screening.

3.2.6.1.1.1. Identification of specific sites for screening

- The site for the screening program should be done based on the local epidemiological data, disease burden, and risk factors which involve analysis of the routine data on case notification, and presumptive TB identified.
- Facility and district-level analysis of TB disease burden specifically the bacteriologically confirmed TB cases should be considered in the selection of specific sites for mobile screening.
- A population group at high risk of developing TB such as a community living in overcrowded areas, workplace,

marketplace, school, or internally displaced people should be prioritized for Mobile TB screening approaches.

- **Target group:** The following key population high-risk groups for TB are found in urban and rural settings.
  - Urban dwellers
  - Internally displaced people
  - The general population in areas with a high prevalence of TB
  - Miners, ex-miners, and the mining community
  - Health care workers
  - Outpatients in facilities without X-ray machines
  - ART clients
  - Industrial workers
  - Refugees in camps
  - Prison inmates and staff

Screening tool: Use WHO recommended 4 symptom screens followed by chest X-ray if symptom screen is negative and interpretation of chest X-ray will be supported with CAD or any other artificial intelligence (AI) used by the program

3.2.6.1. Procedure for screening

- Enroll the client in the screening program using a bar-coded card which is a unique identifier
- Ask of TB symptom using symptom questionnaire
- Perform CXR if symptom screen is negative
- Register the client as presumptive TB if they fulfill one of WHO recommended 4 symptom screens or abnormal CXR findings.
- Chest X-ray screening entails interpreting chest radiographs using CAD4TB using a predetermined threshold.
- Those who test positive on either or both screening tests should be evaluated for TB using the GeneXpert test.
- Offer an HIV test unless they have a recent documented negative test result or are on antiretroviral treatment.
- refer the client whose CAD4TB score is above the cut-off point but not confirmed by GeneXpert testing to the next level of health care for further evaluation diagnosis.

3.2.6.2. Linkage to TB registration sites

- The mobile TB diagnostic team should ensure that all diagnosed TB cases are referred to the nearby TB registration site for TB treatment initiation
- The district TB officer/facility TB focal point, assistant TB officer, and disease control assistants should be informed of necessary follow-up patients at the nearest health facility where they are managed under routine program conditions.
- All other patients who need medical/clinical evaluation are referred to the nearest health facility using a specific referral form filled in by the MDU coordinator.

3.2.6.3. Recording and reporting of mobile TB screening intervention

- Individual-level information about people screened using mobile TB diagnostic units should be captured in the Master Register (key population register) and database designated for this intervention
- All TB patients diagnosed through this iMDUs should be reported through a routine reporting system from the respective TB registration sites where the patient is initiated on TB treatment

3.2.6.3.1. Institution based and other congregated settings

By Whom: The screening can be done by Community volunteers, Health surveillance assistants (HSAs), and Health care workers (HCWs) using a mobile screening van or other institutional approach

Where and target group: The screening will be done regularly (at least once per year) as per schedule of the MDU team.

- Refugee camps: refugees in camps
- Prisons and temporary detention centres: inmates and prison staff
- Military barracks
- Workplaces: miners and mining communities, health workers
- Immigration at the port of entry
- Schools

Who: Wherever a mobile TB screening van is available, the HCW can use symptom screening criteria followed by chest X-ray with CAD/AI software as a screening tool

Frequency of screening: TB screening should be done routinely for the above population groups.

- It is also recommended to conduct screening at least twice per year using CXR combined with symptom screening specifically for prisoner inmates, miners, health care workers, soldiers, police officers, and factory workers.
- Screening tool
  - Screening criteria/algorithms: every miner, ex-miner, or mining community member presenting to the health facility should be screened for TB.
  - Both symptomatic and X-ray screening methods will be used.
  - All prisoners should be screened at entry (symptomatic screening), then every six months, every time they feel sick, and during exit, whereas prison staff should be screened once a year
  - Prison clinicians, patient attendants, peer educators, lab personnel, and x-ray technicians should take part in implementing this intervention

Diagnostic Tool

- GeneXpert should be used as a first test for presumptive TB cases where the service is available.
- Microscopy can be used where GeneXpert is not available.
- Where necessary, lung function tests will be done at the district hospital and health center level for miners and ex-miners.

3.2.6.3.2. Systematic TB screening among healthcare workers

- Healthcare workers (HCWs) in general should be screened on an annual basis using a combination of symptom screening and radiography (where available).
- GeneXpert will be used as the first test for presumptive TB cases among HCWs.

Key quality assurance measures to be maintained for any TB screening and case-finding activities

- Provision of training to HCWs, volunteers, and HSAs, job aids, and SOPs to HCWs
- Ensure clinician reviews all patients screened by non-clinicians and labelled as presumptive
- Adherence to standard NTLEP tools for recording, reporting, and diagnostic algorithm
- Following up with patients along the entire cascade of care to minimize leakages
- Ensure patients with active TB receive prompt treatment
- Correct and complete documentation and timely reporting

- Regular data reviews
- Mentorship and supervision by the facility, district health office, zone quality management unit, and central unit.

SYMPTOMATIC TB SCREENING CRITERIA

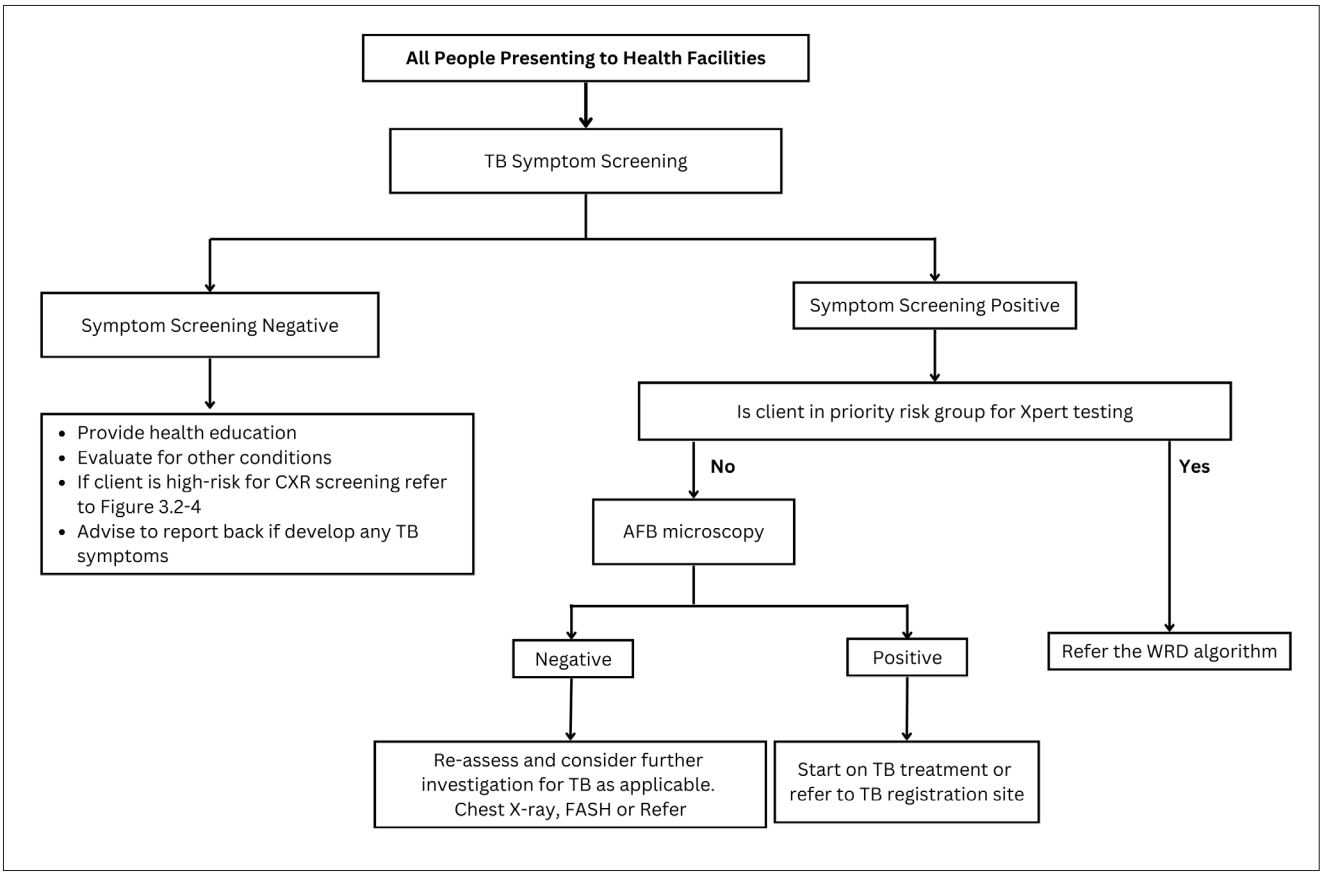


Figure 3.2-3 TB screening and diagnostic algorithms for all people presenting to Health facilities

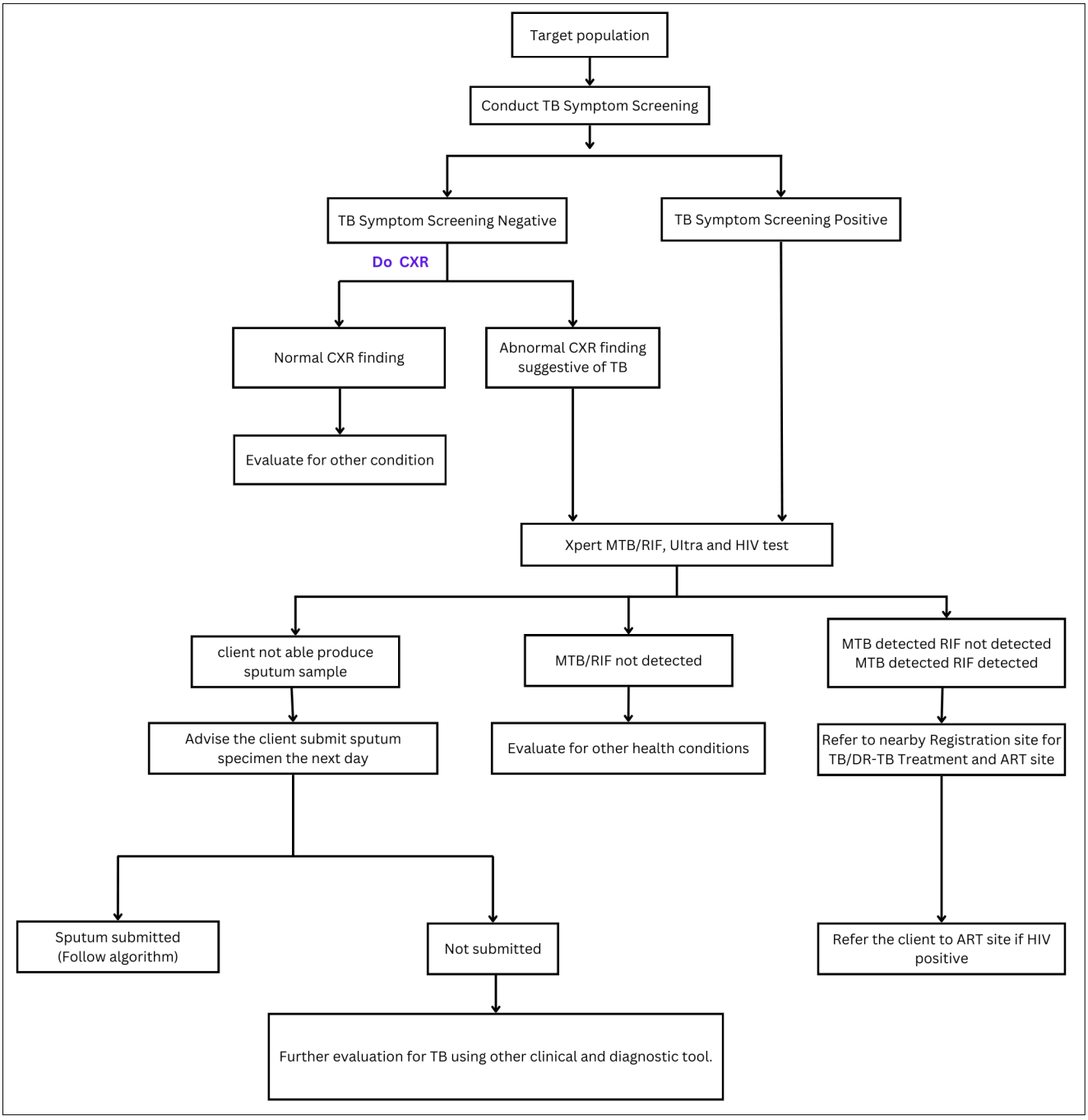


Figure 3.2-4 TB screening algorithm among High-risk group using symptom and CXR

4. Approach to TB diagnosis in Malawi

4.1. Introduction

Early identification and treatment of TB cases is important for TB elimination. The diagnosis of TB disease may be reached either by **bacteriological confirmation** using Identification of mycobacterium tuberculosis on ZN/LED-FM microscopic examination, culturing using liquid and or solid media to grow the mycobacterium tuberculosis from specimen and Identification of bacillary genetic material using mWRDs such as GeneXpert (MTB/RIF/Ultra assay, Xpert MTB/XDR), Truenat MTB plus Line Probe Assay (LPA) and whole genome sequencing. TB may also be diagnosed based on a **clinical decision** by TB experts by analysing the supportive evidence e.g., from radiography from the affected organs through CXR and computer-assisted diagnosis (CAD), histopathologic studies of a sample taken from body tissue and biochemical analysis of body fluids

4.2. Approach to clinical TB diagnosis

Early identification and treatment of TB cases is important for TB control. The diagnosis of TB disease may be reached either by:

- **Bacteriologic confirmation**
  - Identification of the bacillus on ZN/LED-FM microscopic examination
  - Culture media to grow the bacilli
- **Identification of tubercular genetic material using molecular techniques**
  - Xpert MTB/RIF assay and LPA
- **Identification of tubercular cell material**
  - LAM test
- **Clinical decision by TB experts**
  - Radiographic evidence from the affected organs through x-ray (XR), CT scan or ultrasound (possibly assisted by Computer Assisted Diagnosis (CAD))
  - Histopathologic and cytological studies of sample taken from body tissue or fluid
  - Biochemical analysis of body fluids (urine, effusions, CSF)

4.2.1. Clinical diagnosis

Active TB disease causes a variety of symptoms depending on the anatomical site(s) involved. In high HIV prevalence settings such as Malawi, patients may present with symptoms suggestive of extra-pulmonary disease or both pulmonary and extrapulmonary disease.

- Patients should be highly suspected of TB and undergo a thorough investigation for TB if:
  - They are children who have been in close contact with a known TB patient
  - They are HIV positive
  - They were previously treated for TB

4.2.1.1. Pulmonary TB (PTB)

In the early stages of the disease, symptoms are non-specific. Symptoms classically consist of cough, fever, night sweats, and weight loss, but also loss of appetite, general malaise, and weakness. The absence of fever or cough does not exclude a diagnosis of TB, particularly in patients with advanced HIV disease or malnutrition. Many patients may have no abnormalities detected on chest auscultation whereas others may have crackles overlying the involved areas.

4.2.1.2. Extra-pulmonary TB (EPTB)

EPTB may affect any organ outside of the lungs. Commonly involved sites include the lymph nodes, pleura, pericardium, peritoneum (and other abdominal organs), meninges, genitourinary tract as well as bones, joints, and spine.

TB Lymphadenitis	• Usually painless enlarged lymph nodes. • Commonly affects posterior cervical and supraclavicular lymph nodes but can involve any lymph node station.
Pleural TB	• Pleuritic chest pain and shortness of breath; • Effusion around the lungs.
Pericardial TB	• May present suddenly with shortness of breath, fever, oedema, and retrosternal chest pain. • Effusion around the heart
Gastrointestinal TB / Peritoneal TB	• Weight loss, fever, abdominal pain, swelling (exudative ascites), diarrhea, and bloody stools are common. • Abdominal lymphadenopathy and spleen abscesses may be visible. Thickening of the bowel wall is also a possible finding.
TB Meningitis	• Presents subtly with headache and mental status changes after 1-2 weeks of low-grade fever, loss of appetite, and irritability. • May progress acutely to severe headache, confusion/coma, and neck stiffness.
Osteoarticular including spinal TB	• Tender swelling of the back, sometimes with weakness of the legs due to compression of the spinal cord. • Most frequently affects the thoracic or lumbar portions of the spine. • Slow onset (> 4 weeks) osteomyelitis with little or no pain, usually affecting weight-bearing hip, knee, or ankle with signs of joint destruction (clinical or radiological).
Disseminated TB	• Weight loss, night sweats, and fever with increasing weakness and inability to walk. Focal symptoms (as mentioned above) are possible. • Anaemia of chronic disease

Table 4.2-1 Clinical features of the most common EPTB presentations

Type of TB	Investigation, finding suggestive of TB
Pleural TB	**Recommended investigation** • HIV test • Chest x-ray (CXR) and/or ultrasound • Sputum smear and/or Xpert MTB/RIF • Aspiration and inspection of pleural fluid with differential white blood cell count and protein determination (if possible) of aspirate, GeneXpert MTB/RIF **Finding suggestive of TB** • One-sided effusion • Aspirated fluid is clear and straw-coloured • Lymphocytes predominance in pleural fluid • Weight loss, night sweats, chest pain, fever • Evidence of TB in another part of the body **Non-suggestive of TB** • Bilateral pleural effusions • Clinical evidence of Kaposi sarcoma (KS) or other cancer • Aspirated fluid contains pus (empyema) or blood (usually cancer)
Lymph node TB	**Recommended Investigation** • Rapid HIV test • Sputum smear or Xpert MTB/RIF • Needle aspiration for AFB and GeneXpert MTB/RIF (flus material in 1cc normal saline) • Lymph node excisional biopsy **Finding suggestive of TB** • Lymph nodes (LN) > 2 cm • Painless swelling, asymmetrical/localized • Posterior cervical location • Firm/fluctuant/ presence of fistula **Non-suggestive of TB** • KS in skin or mouth • Symmetrical (concern for lymphoma or HIV) • Very large and very hard nodes • Tender or red/inflamed
TB Pericarditis	**Recommended investigation** • Rapid HIV test • Sputum smear or Xpert MTB/RIF • CXR and or ultrasound **Finding suggestive of TB** • Fever, chest pain, night sweats • Evidence of TB in another part of the body • Pericardial effusion or pericardial thickening on US, often with fibrin strands **Non-suggestive of TB** • Streaky shadowing of lung fields on CXR • Murmur • High blood pressure (BP)

Type of TB	Investigation, finding suggestive of TB
Peritoneal/ abdominal TB	**Recommended investigation** • Rapid HIV test, CXR • Sputum smear or Xpert MTB/RIF • Aspiration of ascetic fluid **Finding suggestive of TB** • Fever, cough, night sweats, weight loss • Large spleen and/or liver, enlarged abdominal lymph nodes, micro-abscesses in the spleen • Thickened bowel loops **Non-suggestive of TB** • Rigors • Massive watery diarrhoea
Osteoarticular, including TB of the spine	**Recommended investigation** • Rapid HIV test • Appropriate x-rays • Fine needle aspirate (FNA) or biopsy for AFB **Finding suggestive of TB** • Destruction of two or more adjacent vertebrae • Signs of spinal cord compression (paraplegia, urinary and bowel incontinence) • Fistula from bone to skin (material can be send for GeneXpert MTB/RIF) • Fever, night sweats, weight loss **Non-suggestive of TB** • Clinical evidence of cancer • Clinical evidence of rheumatologic disease (e.g., rheumatoid arthritis)
TB Meningitis	**Recommended investigation** • Rapid HIV test • Lumbar puncture • Laboratory tests on cerebrospinal fluid (CSF) including Gram stain, GeneXpert MTB/RIF Ultra, differential cell count, protein and glucose in CSF, Cryptococci CSF antigen (CRAG) or India ink **Finding suggestive of TB** • GeneXpert MTB/RIF Ultra positive • CSF of 100-500 cells/mm3 with lymphocyte predominance • CSF with high protein and low glucose • India ink and/or cryptococcal antigen negative • Evidence of TB in another part of the body **Non-suggestive of TB** • Rapid onset • Very high opening CSF pressure (more likely cryptococcal) • CSF cloudy or with neutrophilic predominance (more likely bacterial) • India ink or CRAG test positive (although dual infection possible)

Type of TB	Investigation, finding suggestive of TB
Disseminated TB	**Recommended investigation** • Rapid HIV test • Sputum smear or Xpert MTB/RIF • CXR and or ultrasound • LAM tests (if CD4 <200 cells/mm3) **Finding suggestive of TB** • Abnormal CXR including "miliary" pattern • Large spleen and/or liver, lymphadenopathy and spleen micro-abscesses **Non-suggestive of TB** • Shock/sepsis (very low BP) • Other pathogen from blood culture

Table 4.2-2 Different forms of Extrapulmonary TB cases

4.2.2. Histopathological Examination

Pathology plays a complementary role in confirming the diagnosis of TB. Multiplication of tubercle bacilli in any site of the human body causes a specific type of inflammation, with the formation of a characteristic granuloma that can be found on histopathological examination.

4.2.3. Chest radiography

Radiography-based examinations are crucial in a variety of medical settings and at all major levels of health care. Chest radiography, or chest x-ray (CXR) is an essential tool for early detection of TB, and therefore fundamental to achieving the targets set out in WHO's End TB Strategy. CXR is a rapid imaging tool that allows for easy identification of lung abnormalities. It has high sensitivity, but limited specificity for the diagnosis of pulmonary TB. It is therefore especially suitable for screening and triaging. Recommendations for CXR are included in several WHO policies, summarized below.

Classic radiographic findings suggestive of TB, particularly in patients who are not immunocompromised, include (*see sample **image 1** in the link below*):

- Upper lobe infiltrates
- Cavitary lesions
- Effusion may be present

In patients with primary PTB and HIV infection, the x-ray findings can be quite different. These include (*see sample **image 2** in the link below*):

- Lower lobe infiltrates
- Hilar and/or para-tracheal lymphadenopathy
- Effusion may be present
- Miliary or "scattered seed"-like pattern (*see sample **image 3** in the link below*)

CXR is a sensitive tool for screening for active TB. It has a much higher sensitivity for pulmonary TB than screening for TB symptoms and can be used as a supplementary diagnostic tool, although the specificity is low. While a bacteriologically confirmed diagnosis is always preferable, an abnormal CXR is an indication for full diagnostic evaluation. *(For more details refer to radiology tests or CXR manuals, e.g., the "Lighthouse CXR training manual": https://www.mwlighthouse.org/resources/light-house-training-materials).*

Key messages in screening and diagnosis of TB

- While a bacteriologically confirmed diagnosis is always preferable, an abnormal CXR is an indication for full diagnostic evaluation as diagnosis of tuberculosis by using X-ray alone is nonspecific as any abnormalities seen on a chest X-ray may be mimicked by a variety of other conditions
- Chest X-ray has a limited role in confirming the diagnosis of pulmonary tuberculosis. The decision to start anti-TB treatment on patients should not be based solely on abnormal CXR findings
- All efforts should be made to perform a bacteriological examination for confirmation of TB disease.
- If microbiological tests are negative, then chest X-ray findings may be substantiated with a thorough history, clinical examination, and other available tests
- Chest X-rays may also be used at the end of the treatment to assess the extent of lung damage and to detect any residual complications like bronchiectasis, fibrosis, pleural thickening, and lung collapse
- CXR is an important tool in the diagnosis of pulmonary and extrapulmonary TB in children, in combination with history, evidence of TB infection, and microbiological testing
- CXR can improve the efficiency of using the Xpert MTB/Rif assay. CXR and further clinical assessment can be used to triage who should be tested with Xpert MTB/Rif to reduce the number of individuals to be tested with Xpert MTB/Rif
- CXR can assist in the diagnosis of TB among PLHIV. It is particularly useful to rule out TB disease before the provision of treatment for latent TB, as symptom screening and CXR can be done to exclude active TB before initiating treatment of latent TB infection
- CXR is also an essential technology for TB prevalence surveys

4.2.4. FASH ultrasound (Focused Assessment with Sonography for HIV-associated TB)

FASH is implemented in central and selected district hospitals to improve TB diagnosis among high-risk groups. FASH ultrasound should be considered for all patients with a high clinical probability of disseminated and extra-pulmonary TB. Patients with HIV infection especially patients with low CD4 counts and severe immunosuppression are at the highest risk. The patient should be screened for clinical symptoms of TB (weight loss, night sweats). Frequently, clinical (and sonographic) findings of disseminated TB become apparent a few weeks after HIV-infected patients start antiretroviral therapy (ART) and the immune reaction improves, a phenomenon known as “demasking IRIS” (immune reconstitution inflammatory syndrome).

Key points and interpretation

- Pericardial effusion, (unilateral) pleural effusions and, to a lesser extent, ascites can be signs of extra-pulmonary TB
- Enlarged abdominal lymph nodes and focal micro-abscesses in the spleen are frequently seen in disseminated TB
- In the resource-poor high-prevalence setting many FASH findings are often specific enough to initiate empiric TB treatment especially if other conditions (like Kaposi’s sarcoma) are unlikely

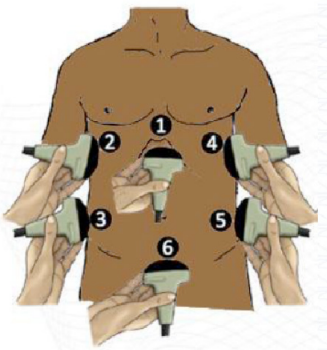
Probe position	No.	Localization	Possible FASH Findings
	1	Epigastric angle	-Pericardial effusion -Abdominal lymph nodes
	2	Right axillary line thorax	-Pleural effusion
	3	Right axillary line abdomen	-Focal liver lesions -Ascites in the pouch of Morison
	4	Left axillary line thorax	-Pleural effusion
	5	Left axillary line abdomen	-Focal spleen lesions -Ascites in spleno-renal pouch
	6	Suprapubic pelvis	-Ascites in the puch of Douglas

Figure 4.2-1 FASH exam: Probe position and possible FASH findings

4.3. Laboratory diagnosis of TB

Whenever possible, bacteriological confirmation of TB by one of the laboratory methods described below should be used to make a definitive diagnosis of TB disease. A bacteriological test refers to using smear, culture or newer WHO-approved rapid diagnostic tests to definitively identify TB.

The laboratory diagnosis of TB begins with the collection of a high-quality specimen which in most cases is a sputum. However, other specimens such as urine from people living with HIV (PLHIV), stool in children, pleural fluids, lymph nodes biopsies among others are also collected when extrapulmonary TB is suspected. Specimens such as sputum, stool and urine are easy to collect in adult patients compared to in children, whereas other techniques such as bronchoalveolar lavage and biopsies for pulmonary and extrapulmonary TB suspects respectively are invasive and patient care is needed during sample collection.

4.3.1. Sputum Collection

4.3.1.1. Specimen Collection Container

An essential prerequisite for the safe collection of satisfactory specimens is a leak-proof, clean container. Containers must be combustible, and rigid to avoid crushing in transit and must possess a water-tight wide-mouthed screw top to prevent leakage and contamination. Specimens should be collected in clean containers that are free from paraffin and other waxes and oils. These materials may appear as acid-fast artefacts or may react with other bacteria and cause them to appear as acid-fast.

4.3.1.2. Specifications are recommended for choosing a suitable container

- Wide-mouthed so that the patient can expectorate easily into the container without contaminating the outside
- Volume capacity of at least 50ml
- Made of transparent material to observe specimen quality and volume without opening the container
- Made of a single-use combustible material to facilitate disposal
- Screw cupped to obtain a watertight seal to reduce the risk of leakage during transportation
- Easily labelled walls that will allow permanent identification

4.3.1.3. Time interval of sputum Sample collection

- Only two sputum specimens should be collected using the two-sample spot + spot approach
- The first sputum specimen should be collected from a designated place (cough booth) within the health facility
- Use a well-labelled container at the time when the patient presents to a facility or when in contact with the health care provider
- A second labelled sputum container should be given to the patient and/ or guardian so that his or her sputum can be collected later in the day, preferably 45 minutes to an hour after the first sample has been collected

4.3.1.4. Before collecting sputum

- Patients should be well informed about the diagnostic process and the reason for collecting sputum
- Sputum collection should be done in a designated area in the open air (or ventilated room) away from other people to avoid infecting them
- Patients should be told to clean their mouths if they have been eating to prevent artefacts in the specimen
- A health worker should demonstrate how to cough out sputum and how to open and close the sputum container

- The laboratory request form should be filled out accurately and completely
- Clearly label the sputum container with the patient's name and the date of collection. Label the container itself, not the lid. The labelling should also include sample number in order of sample collection time, whether sample 1 or sample 2
- Make sure that the patient's details have been recorded in the presumptive TB register

4.3.1.5. How to collect good quality sputum

- Tell the patient that the best specimens come from deep inside the lungs after coughing, not from saliva
- Demonstrate how to cough deeply
- Ensure that no one is standing in front of a patient producing sputum
- Instruct the patient to Inhale deeply 2 to 3 times and to breathe out hard each time, followed by a deep inspiration and COUGH deeply from the chest, Place the open container close to the mouth to collect the sputum, and screw the lid tightly
- Avoid contaminating the outside of the sputum container with sputum. If the outside is contaminated, discard the container in an appropriate waste container, and repeat the collection with a new container
- The volume of the sputum should be 3-5 ml

4.3.1.6. After collecting a sputum specimen

- Double check to ensure that the container is labelled properly
- Ensure that the container is firmly closed and wash your hands with soap and clean water
- The two sputum specimens should be sent to a microscopy or GeneXpert site within 24 hours of sample collection
- Store sputum specimens for culture, preferably in a refrigerator at 2-8 degrees Celsius or in a cool, safe, and dark place while awaiting transportation
- Sputum specimens for culture should be received by the culture laboratory within 4 days of collection
- Do not use laboratory request forms for wrapping specimens
- All delivered samples to the testing laboratory should accompany properly filled-in laboratory request forms, that match with details of the patient on the sample bottle

4.3.1.7. Who should collect sputum specimens

- It is the responsibility of health workers and community volunteers to collect sputum specimens from presumptive TB cases
- For in-patients, the ward nurse should check with the patient and/or guardian each morning to encourage sputum production and to collect samples for submission to the laboratory
- At health centre and community levels, health surveillance assistants (HSAs) and community volunteers should follow up with presumptive TB cases to ensure sputum specimens are collected
- Should the patient not return after submission of the first spot specimen, the HSA, community volunteer or DTO must follow up with the patient immediately

4.3.1.8. Packaging and transportation of sputum specimen

- Every health worker is responsible for sending TB specimens to the laboratory as soon as possible to ensure examination is done and results received within 24-48 hours of collection. However, should this be impossible, a maximum allowance of 4 days is awarded where the sample is kept under refrigeration before it is transported and tested at a testing facility.

- Every effort should be made to ensure that samples reach the lab within the recommended time of not more than 4 days from the date of collection to preserve the sample quality
- All samples from health facilities shall be transported by an integrated specimen referral system through designated third-party providers that transport samples to microscopy or GeneXpert sites and specimens from districts to NTRL and two Regional TB Culture laboratories (Mzuzu and Zomba Central Hospitals)
- To improve service coverage and enhance efficiency, there is a need to improve sample referral by ensuring service coverage to all the districts reducing sample transit TAT, and implementing a demand referral system
- Specimens must be packaged to withstand shocks and pressure changes and contain any leakage. Impact-resistant cooler boxes and ice packs should be used for the transport of sputum specimens
- Each specimen should be packed in an individual zip-lock bag to avoid contamination of the cooler box in case of leakage. The cooler box lid should be securely fastened during transportation, the box must be kept as cool as possible and away from direct sunlight
- Request forms should be placed in a plastic zip lock bag separate from the specimen container
- Before dispatch, the sending health facility must verify the following:
    - The number of specimen containers in the box corresponds to those on the accompanying list
    - Patient information or identification number on each specimen container that corresponds to the information or identification number of the laboratory request forms
    - The necessary data for each patient has been filled accordingly on the laboratory request forms that will accompany the samples

4.3.2. Sputum Smear Microscopy

Sputum smear microscopy allows rapid detection of the most infectious cases of pulmonary TB. It is a cheaper, simple, and rapid procedure with reliable test results. Two staining methods can be used to identify Acid-Fast Bacilli (AFB)

Principle for Ziel-Neelsen (ZN) staining or fluorescent auramine staining (LED FM)

The property of acid–fastness of mycobacterial is based on the presence of mycolic acid in the cell wall. Primary stain (Auramine-O/Carbolfuchsin) binds to mycolic acid.

Intense decolorization (Strong acids) does not release primary stain from the cell wall easily and AFBs keep the fluorescent bright yellow colour of Auramine-O and red colour of Carbolfuchsin.

Counterstain (Methylene Blue) provides a contrasting background. Fluorescent stains are usually organic substances that absorb ultraviolet light and reemit part of the energy as light of a longer wavelength which can be observed through eyepieces as fluorescence. When exposed to ultraviolet light, the fluorescent bacilli are perceived as brightly coloured organisms against a dark background.

Advantages	Disadvantages	Limitation
• Sputum specimens from patients with PTB, especially those with cavitary disease, often contain sufficiently large numbers of AFB to be detected by microscopy. • suitable for peripheral-level and higher-level laboratories. • Can be done safely in a laboratory that has implemented only a low level of precautions to mitigate the risk of laboratory-acquired TB infection. • Essential for treatment monitoring for patients with DS-TB. • LED FM provides additional advantages over ZN as it requires less time for slide preparation and reading. It has better sensitivity (around an additional 10%) over ZN to identify bacilli.	• Direct sputum-smear microscopy is relatively insensitive: at least 5,000 bacilli per ml of sputum are required for a positive result. • The sensitivity is further reduced in patients with EPTB, children, and PLHIV. • A comprehensive quality assurance programme is necessary; although this may be challenging to implement, it is necessary to ensure high-quality test results.	• AFB cannot distinguish Mycobacterium tuberculosis complex (MTB) from non-tuberculous mycobacteria. • Cannot distinguish viable from non-viable organisms and drug-susceptible strains from drug-resistant strains. • Smears stained with auramine need to be re-stained if they are to be rechecked as part of an EQA program. • ZN microscopy has low sensitivity (40-60%) and requires at least 5000-10,000 bacilli per ml of sputum to give positive results.

Table 4.3-1 Advantages, disadvantages, and limitations of TB microscopy techniques

The Laboratory personnel report results based on the number of TB bacilli seen when evaluating areas visualised under the microscope called “fields” (see Table 4.3-2).

IUATLD scale (100 x field- HPPF* Grade	Ziehl Neelsen (ZN) microscopy (1000 x magnification: 1 length = 2cm =100HPF)	LED-Fluorescence microscopy (400 x magnification: 1 length=40 fields=200HPF)
Negative	Zero AFB/1 Length	Zero AFB/1 Length
Positive		
Scanty	1-9 AFB/1 length or 100HPF	1-19 AFB/1 length or 100HPF
1+ Grade	10-99 AFB/ 1 Length or 100HPF	20-199 AFB/ 1 Length
2+ Grade	1-10AFB/1HPF on average	5-50 AFB/1HPF on average
3+ Grade	>10AFB/1HPF on average	>50 AFB/1HPF on average

Table 4.3-2 Reporting laboratory results for AFB Microscopy examination

***The number of AFB indicates how infectious the patient is. It is important to record exactly what you see. Finding of < 3 bacilli in 100 fields does not correlate well with culture positivity.*

4.3.3. Sputum culture Examination

This is a bacteriologic confirmatory test and a definitive diagnosis of TB. It is primarily used for monitoring MDR-TB patient's response to therapy through Drug Susceptibility Testing (DST).

Culture is a highly sensitive technique that can detect as few as 100 viable bacilli per ml of sputum.

Solid culture media: (Lowenstein-Jensen) is a culture media that has several advantages over liquid media, including ease of preparation, low cost, and low contamination rate. However, the length of time it takes to culture and conduct drug susceptibility testing (DST) as well as the turnaround time for results limits its use in peripheral laboratories.

Liquid culture media: (MGIT 960/320 system) is a specially enriched culture media developed to shorten the time required for bacillary growth to 5-15 days. It has an additional 10% sensitivity over LJ solid media. However, the method is prone to a higher contamination rate.

Note: Because culture facilities are located centrally, the time between collection and processing should be four days or less when kept in a cold chain (2-8°C).

ADVANTAGES AND LIMITATIONS OF MTB CULTURE TECHNIQUES

Advantages of MTB culture	Limitations of MTB culture
• Detects small numbers of organisms (as few as 10 bacilli) • Is often 30-50% more sensitive than smear microscopy in diagnosing TB • Allows species identification and drug susceptibility testing • Recommended for monitoring the treatment response of drug-resistant TB patients	• TB culture results can take 4-8 weeks for a negative solid and up to 6 weeks for a negative liquid culture to be issued • High installation and maintenance costs. • High biosafety level requirement • Requires well-trained personnel • Requires an efficient sample transportation system

Table 4.3-3 Advantages and Limitations of MTB culture techniques

4.3.4. GeneXpert MTB/RIF (Ultra) Assay

This assay is a Point of care test that takes 2 hours to deliver results and is indicated for the diagnosis of MTB and to screen for rifampicin resistance (RR) in sputum samples. In Malawi, Genexpert MTB RIF ultra is used as a primary test to diagnose TB for priority groups of people. Its biosafety level (BSL-2) is the same as for direct microscopy, making it feasible for peripheral laboratories.

Priority population group for GeneXpert test

- People who live in urban slums, Refugees, internally displaced people, Miners, and Ex-miners
- HCWs and community health volunteers with presumptive TB
- Mobile and cross border populations, People working in congregate settings and Prison inmates
- Hospitalized patients, undernourished People (BMI <18.5K/M2),
- PLHIV, People with cancer/ undergoing immunosuppressive therapy and People who have diabetes
- Presumptive TB among Children and Elderly over 65 years

The GeneXpert MTB/RIF (Ultra) assay simultaneously detects MTB and RR in less than 2 hours, with a sensitivity

for detection that is like that of liquid culture (88% when compared with liquid culture as a standard).
The superior performance of Gene Xpert MTB/RIF (Ultra) in detecting TB over that of microscopy makes it a particularly useful tool for case-finding among PLHIV. As a tool for detecting RR, Xpert MTB/ RIF has a sensitivity of 95% and a specificity of 98%.

ADVANTAGES AND LIMITATIONS OF GENEXPERT MTB/RIF TEST

Advantages of Xpert MTB/RIF	Limitations of Xpert MTB/RIF
• Allow simultaneous detection of both MTB and RR. • High sensitivity (68%) and specificity (99%) for MTB detection even in smear-negative cases. • Produces results in two hours. • Minimal technical training is required to run the assay. • Does not require sophisticated biosafety precautions. • GeneXpert platforms provide an opportunity to strengthen other activities such as Intensive TB case findings (ICF) and Integration of HIV, HBV, SARS COV-2, and TB activities	• It cannot be used for monitoring of TB treatment. • It requires a continuous electricity supply. • It does not inform susceptibility to isoniazid (INH).

Table 4.3-4 Advantages and limitations of GeneXpert MTB/RIF test

Interpretation of GeneXpert results

The results are interpreted by the GeneXpert DX System from measured fluorescent signals, and embedded calculation algorithms and will be displayed in the "View Results" window.

- MTB Detected - MTB target DNA is detected, and the MTB result will be displayed as High, Medium, Low, or Very Low
- For MTB RIF/Ultra it includes Trace results, depending on the Ct value of the MTB target present in the sample
- MTB Not Detected - MTB target DNA is not detected
- MTB invalid – presence or absence of MTB DNA cannot be determined, repeat testing is needed in this scenario
- Error/No result - MTB – NO RESULT repeat testing is needed in this scenario

4.3.5. Truenat™ MTB or MTB Plus Assay

The Truenat™ MTB or MTB Plus rapidly detects Mycobacterium tuberculosis complex bacteria (MTBC) and rifampicin resistance. The testing system uses portable, battery-operated devices resulting in the semi-quantitative detection of MTBC. The system is designed to be operated in peripheral laboratories with minimal infrastructure and therefore complements other molecular point-of-care tests for TB and smear microscopy or conventional culture.

Advantages of Truenat™ MTB or MTB Plus Assay

- Minimal power requirement hence uses battery
- Operate under ambient use room temperature stable reagents
- Designed to be operated in peripheral laboratories with minimal infrastructure
- Truena t can be positioned in laboratories as low as microscopy center level given
- In-built batteries allow for testing without power for up to 8 hours. Note that power is still required to charge batteries as well as to potentially cool the storage room for test chips (storage at ≤ 30°C)
- Equipment can be used at relatively high room temperatures: ≤ 40°C (for reference, GeneXpert operating temperature: ≤ 30°C; TB-LAMP HumaLoop: ≤ 40°C)
- Equipment can be used in humid settings (relative humidity: 10-80%)

- Equipment can be used in dusty settings (PCR analyzer does not require air intake)
- Need for minimal biosafety precautions, like microscopy, Xpert or LAMP
- A carrying case is also available, allowing for portability for active case finding purposes
- Long shelf-life: All test reagents: 2 years
- Use of Truenat with sputum specimens as a replacement for smear microscopy for detecting TB among people being evaluated for pulmonary
- Shorting TAT of 35 mins per test

Disadvantages of Truenat™ MTB or MTB Plus Assay

- Unknown for use cases in testing children or people living with HIV
- Able to store Truenat chips and Sample Pre-treatment Pack and Prep Kit at 2 - 30°C and 2 - 40°C respectively

4.3.6. Line Probe Assay

LPA is a rapid and accurate test to identify both first-line (INH and RR) and second-line DST, strains of the MTB complex. It can be performed either directly from smear-positive sputum samples or culture isolates.

- If a patient with TB is smear-positive, the sputum contains enough bacilli to perform an LPA directly on the sputum and DR-TB can be confirmed within two days
- If the sputum is smear-negative, growth of bacilli should be demonstrated on culture first (preferably on liquid medium) and then, LPA can be performed on the isolates to check for sensitivity for INH and rifampicin
- LPA can also be performed to screen for resistance to other second-line TB drugs, although these results would need careful interpretation

Advantages of LPA

- Can be performed directly on positive sputum samples
- Can also be performed on bacillary isolates from culture
- Highly sensitive (98%) and specific (99%)
- Rapid test
- Capacity to perform large numbers of tests per day

Disadvantages of LPA

- Requires well-trained staff
- Requires at least three rooms for the different steps
- Infection control precautions require sophisticated biosafety levels (BSL-3)

4.3.7. Next-generation sequencing for mycobacterium TB

Next-generation sequencing (NGS) is one of the methods for rapidly diagnosing drug-resistant tuberculosis (DR-TB) which will be adopted by NTLEP. The NGS will overcome many of the significant challenges associated with other methods by providing rapid, detailed sequence information for multiple gene regions or whole genomes of interest.

Advantages

- NGS characterises MTBC resistance mutations to the major anti-TB drug compounds
- Provides detailed sequence information for multiple gene regions or whole genomes of interest compared to conventional and other molecular assays
- Has the ability to detect novel type of mutations

Disadvantages

- High demands costs
- Demand for integration into existing laboratory workflows
- Requires technical training and skill requirements for utilisation of the technology
- Needs expert guidance on management and clinical interpretation of sequencing data.

4.3.8. Lateral Flow Lipoarabinomannan Assay (LF-LAM)

LF-LAM is a component of the cell wall of M. tuberculosis. It is released from metabolically active or degenerating bacterial cells, and disseminated TB with renal involvement can result in LAM in the urine.

A LF-TB LAM is a point-of-care rapid antigen test mainly used in HIV and advanced immunodeficiency patients that do not have respiratory TB symptoms and/or are unable to produce sputum. For all the patients who test LF-LAM positive, sputum samples are also collected, and perform Genexpert test to rule out **pulmonary TB**.

Some priority population group for LF-LAM test

- PLHIV with CD4 < 200 cells/ml before ART initiation / while on ART. However, CD4 test results are not required for urine LAM if other criteria are met
- Advanced HIV disease (AHD) with WHO stage 3 or 4 before ART initiation
- Seriously ill" PLHIV
- All PLHIV admitted as in-patient
- HIV infected patients with any of the following danger signs:
  - Adults: ≥30 breaths/min; heart rate ≥120 beats/min; unable to walk unaided; ≥39°C
  - Children: lethargy; unconsciousness; convulsions; unable to drink or breastfeed; repeated vomiting; fever ≥39°C; tachycardia; tachypnoea

Sample collection and storage

- Early morning and fresh midstream urine are the mostly preferred sample type
- When feasible testing should be done immediately just after collection
- If immediate testing is not possible, urine can be stored at room temperature for a maximum of 8 hours or at 2–8 C for a maximum of 3 days

Advantages

- Bedside- rapid antigen test –takers 15 minutes to get results.
- Performed by non –laboratory staff
- No electricity required
- Does not require sophisticated equipment and infrastructure
- Urine sample is easy to collect

Disadvantages

- Does not differentiate between the various species of Mycobacterium, such as M. tuberculosis, M. leprae, and M. avium
- Not used for monitoring TB treatment
- Does not detect any resistance to anti-TB drugs
- Low sensitivity and specificity compared to other TB diagnostic methods
- Does not allow the use of samples other than urine (e.g., sputum, serum, plasma, CSF, or other body fluids) or pooled urine

4.3.9. Drug Susceptibility Testing

DST is required to make a definitive diagnosis of MDR- and XDR-TB. It can be done by using either phenotypic assays (e.g., conventional proportion method) or genotypic techniques (e.g., the line probe assay (LPA) or Xpert MTB/RIF/Ultra) and Xpert MTB/XDR techniques.

- Phenotypic DST: can be performed by either observation of growth or by metabolic inhibition of the bacilli in a culture medium containing anti-TB drugs. It is considered the gold standard technique to test susceptibility to various TB drugs. However, the technique can only be performed on MTB isolates grown on culture media. Currently, there are two main phenotypic DST methods used in Malawi, namely solid (Lowenstein Jensen) and liquid-MGIT (Mycobacteria Growth Indicator Tube)
  - Phenotypic DST (pDST) is reliable and reproducible for RIF, INH and Lfx
  - There is a capacity for Linezolid, Bedaquiine, and Delamanid
  - Mfx: there is a need for critical concentrations to be re-evaluated
  - EMB, Eto/Pto, Cs, PZA: pDST is not reliable
- Molecular DST techniques: are DNA PCR technologies that are specifically designed to detect/confirm genetic mutations associated with resistance to TB drugs. They can produce rapid results. Their role is limited to diagnostic/screening purposes and cannot be used to monitor treatment response as they do not distinguish between live and dead bacilli. At present, Xpert MTB/RIF and LPA are the two (genotypic) techniques recommended in Malawi

4.3.10. Xpert MTB/XDR Assay

- This a 10-colour reflex assay or test intended to detect resistance or mutations associated with both first-line and second-line anti-TB drugs namely, isoniazid (INH), fluoroquinolones (FLQ), ethionamide (ETH), and second-line injectable drugs (SLIDs)
- The type of patient sample is like GeneXpert MTB/RIF (Ultra) such as unprocessed sputum samples and concentrated sputum sediments. However, only those that are positive for Mycobacterium tuberculosis
- Results can be obtained in under 90 minutes using 10-color GeneXpert modules

4.4. External Quality Assurance in TB Diagnostic Network

A process to assess laboratory performance that allows participating laboratories to assess their capabilities by comparing their results with those in other laboratories in the network. It helps to identify errors, motivate staff, solve problems, and is used to improve performance across the laboratory network.

There are three main methods used in EQA activities across the TB network, namely:

1. **On-site supervision** - The assessment of laboratory capability in terms of space, equipment, laboratory safety, SOPs, performance of QCs, and adequacy of supplies to perform TB diagnosis. This is done by the central unit (NTLEP/NTRL) and district health team covering microscopy and GeneXpert and QMS activities
2. **Blinded rechecking** - The process of blinded re-reading TB slides from a participating laboratory to assess whether that laboratory has an accepted level of performance. This is also done by the central unit (NTLEP/NTRL now an accredited ISO 15189 laboratory) and district health team
3. **Panel testing** - Examination of panel samples with known results to scheme providers to determine the competence of laboratory personnel in TB techniques for GeneXpert and microscopy services. The EQA services across the NTLEP network is provided by PT schemes below:
   - National Health Laboratory Service (NHLS)- culture, GeneXpert and microscopy
   - CDC Atlanta- GeneXpert
   - Supra Reference Laboratory (SRL) Uganda-culture, DST, Gene Xpert, and microscopy

NTRL with technical support from SRL-Uganda and other CDC funded partners has currently embarked on microscopy, GeneXpert and LF-LAM local PT scheme implementation accreditation under ISO 17043.

4.4.1. Laboratory equipment maintenance, calibration, and validation

There is a Service Level Agreement (SLA) for major equipment, namely, GeneXpert, Air Handling units, MGIT machines and cold room (for TB culture laboratories), and Biosafety Cabinets across the entire TB network. Some major equipment lacks service contracts e.g. iLED microscopes.

Reporting of laboratory test results

Reporting of test results is done either through a paper-based or electronic system. For a paper-based system, the same laboratory request form that bares the patient information is used for documenting patient test results before final documentation in the laboratory registers. Currently, GxAlert/ASPECT, emails, and TB-LIS are the electronic data reporting systems for TB, EID/VL, HBV, and SARS Cov-2 test results. GxAlert/ASPECT is also under a service contract.

4.5. TB Diagnostic Pathways

Early identification of TB cases and putting patients on effective treatment is important for TB control and reducing TB-related mortality. Particularly, in TB/HIV co-infected patients whose immune system may be compromised.

- Diagnosis of TB depends on the identification of the tubercle bacilli in sputum by microscopy, culture, or newer molecular tests OR a strong suspicion of TB based on sound clinical judgment
- The overall diagnosis of TB starts with TB screening which was presented in the previous section
- Once a presumptive TB client is identified, the decision for further diagnostics will be made as per information on the Risk of MDR TB, HIV test result, Age, and Association with another risk group

The revised national algorithm for TB diagnosis, drug susceptibility testing, and management of the patients is based on the results of recommended tests.

- All individuals who present with symptoms of PTB should have a bacteriological confirmation either with Xpert MTB/RIF or sputum microscopy
- Use of rapid screening tests, such as Xpert or LPA, is recommended for screening of drug-resistant TB in nationally prioritized patients' groups
- Supportive evidence from X-ray abnormalities or histopathological examinations may be used to investigate patients for whom the clinician has a high suspicion of TB despite the negative results from confirmatory tests
- Interpretation of test results and the decision to treat for TB should be made carefully to avoid patient mismanagement

The choice of microscopy and Xpert MTB/RIF or Truenat MTB Plus assay as a primary test for TB depends on the age, HIV status, increased risk of TB, risk of harbouring drug-resistant TB, and the anatomic site of presumptive TB disease.

The following algorithms are intended to guide the management of presumptive TB cases based on the assessment of risk conditions, availability of diagnostics, and patient conditions.

- Overall approach to presumptive TB case (Figure 4.5-1)

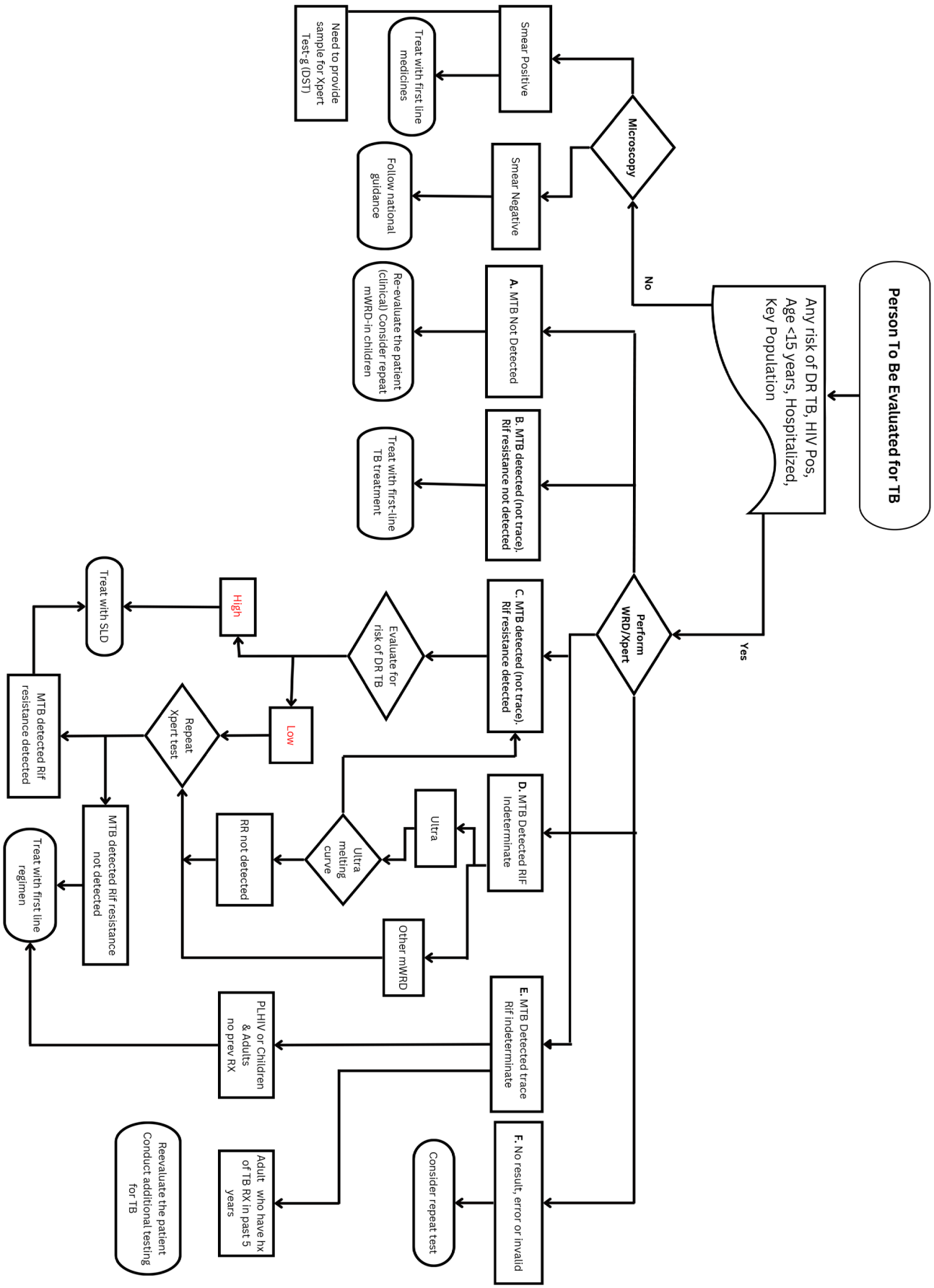


Figure 4.5-1 General diagnostic approach to presumptive TB cases in Malawi.

For all Smear-positive patients and those clinically diagnosed TB patients, the health worker is required to conduct Xpert Ultra. Patients diagnosed with Extrapulmonary TB need to be tested for Rif resistance.

Wherever rif resistance TB is detected, the clinician needs to conduct a risk assessment immediately. The laboratory technologist /technician needs to alert and discuss with the clinician in charge in the facility.

The clinician is expected to use the following criteria and clinical judgment to determine if the patient is high-risk or low-risk. Once the patient is determined low-risk, the repeat test needs to be conducted.

Patients at high risk for DR-TB include **previously treated patients**, including those who had been lost to follow-up, relapsed, or failed a treatment regimen; **non-converters (smear-positive at end of intensive phase)**; household or close contacts of DR TB patients; s**ymptomatic contacts of a patient who died while on directly observed TB treatment**; health care workers; prisoners; immigrants from settings with a high prevalence of DR-TB;

Another group of people to be considered as high-risk DR-TB because of the paucibacillary nature of their samples or high risk of unfavorable treatment outcomes if the repeat test is false negative, are people living with HIV; EPTB samples; children; people with comorbidities like diabetics, patients with danger signs and older people (55 years and above).

LF-LAM is a component of the cell wall of M. tuberculosis. It is released from metabolically active or degenerating bacterial cells, disseminated TB with renal involvement can result in LAM in the urine.

The following are population group for LF-LAM test.

- PLHIV with CD4 < 200 cells/ml before ART initiation/while on ART. However, CD4 test results are not required for urine LAM if other criteria are met.
- Advanced HIV disease (AHD) with WHO stage 3 or 4 before ART initiation.
- Seriously ill" PLHIV

5. Tuberculosis Management and Monitoring

5.1. Treatment of TB

The goals of TB treatment are to cure the patient and restore their quality of life, to prevent death from TB, to reduce transmission of TB in the community and to prevent the development and spread of drug-resistance.

5.1.1. Directly Observed Treatment (DOT)

- The treatment supervisor watches the patient swallow the tablets throughout the whole course of treatment. DOT ensures that the TB patient takes the right drugs, in the right doses at the right times. Supervisors or "treatment supporters," can be health workers, volunteers, trained members of the community, or guardians.
- A patient-centered approach with proper communication between the patient and treatment supporter promotes patient education, good adherence, and early identification of challenges with treatment (including side-effects and clinical worsening).
- All treatment supporters should be chosen together and should be acceptable to the patient.
- The need for good adherence and follow-up should always be reinforced.
- Patients should be reminded about the duration of treatment and common side effects.

5.1.2. Treatment of susceptible TB

- Susceptible TB is treated with first-line drugs: Rifampicin (R), Isoniazid (H), Ethambutol (E), Pyrazinamide (Z) and Streptomycin (S). The first four oral drugs (RHZE) come as an FDC tablet. Streptomycin (S) is a first-line injectable drug used for TB meningitis.
- Patients should not be admitted in the ward or hospital for administration of TB drugs except where they are too sick.
- TB drugs should be provided on ambulatory basis in all facilities.

	Initial phase 2 months	Continuation phase 4 months
Body weight in kg	**[RHZE] [R150/H75/Z400/E275] Number of tablets**	**[RH] [R150/H75]**
25-29	2	2
30-37	2	2
38-54	3	3
55-74	4	4
75 and over	5	5

Table 5.1-1 Dosages of FDC formulations of first-line anti-TB drugs for adults

KEY FACTS

- Patient weight should be monitored each month, and doses adjusted if weight changes from one weight band to another are observed during the treatment.
- If the patient continues to lose weight while on treatment, they should undergo a detailed review by a clinician.
- New smear-positive PTB patients treated with first-line drugs should submit a sputum sample for smear microscopy on completion of the intensive phase.

Xpert MTB/RIF should not be used to monitor response to treatment in TB patients.

KEY FACTS RELATED TO CHILDHOOD TB

- Globally 27.5% of the estimated 0-4yrs and 44.6% of 5-14yrs are detected
- Globally only 11% of the target of DR TB in children is achieved
- Children can present with TB at any age, but most commonly between the ages of 1 & 4 years in high burden settings
- Infants and children under 2 years are at higher risk of developing disseminated disease and tuberculosis meningitis
- Adolescents with TB usually present with infectious TB disease

5.1.3. Sputum monitoring by smear microscopy in new PTB patients

New bacteriologically confirmed Pulmonary TB patients should submit sputum samples at 2, 5, and 6 months.

Month of treatment					
1	2	3	4	5	6
Intensive Phase		Continuation Phase			
	If smear-positive, repeat in month 3	If smear-positive, obtain culture and DST		If smear-positive, obtain culture and DST	If smear-positive, obtain culture and DST

Table 5.1-2 Schedule for smear monitoring in new smear-positive TB cases

Smear or culture positive at month 5 or later is defined as treatment failure and requires:

- Re-registration of patient as a treatment failure
- Change to retreatment regimen.
- Send sputum for Xpert MTB/RIF

5.1.3.1. Interpretation of follow-up AFB microscopy results

For new patients

- If AFB results at the end of the intensive phase:
  - Is **negative**, start continuation phase of treatment.

- Remains **positive, initiate continuation phase** and repeat AFB at the end of 3rd month and if the result remains positive do rapid DST to decide on next action.

- If DST shows resistance at least to rifampicin:
  - **Stop treatment.**
- If AFB results at the end of month 5 (or later) of treatment:
  - Is **negative,** continue with the same treatment.
  - Is **positive**, assign "**Treatment failure**" as the final outcome. Re-evaluate the patient as a previously treated case and perform rapid DST.
- If AFB results at the end of month 6 of treatment:
  - Is **negative**, declare the outcome as "**Cured**" or "**Completed**".
  - Is **positive**, declare the outcome as "**Treatment failure**". Re-evaluate the patient as a previously treated case and perform rapid DST.

5.1.4. TB meningitis

The regimen for TBM is 2RHZE/7RH, i.e., the treatment is longer than in pulmonary TB. Corticosteroids should be given with anti-TB drugs as they have been shown to significantly reduce the risk of death in patients with TB meningitis (see 7.1.9).

5.1.5. Treatment regimens for patients previously treated for TB.

Patients eligible for retreatment should be referred for a rapid molecular test for drug **susceptibility testing** to determine at least rifampicin resistance, and preferably also isoniazid resistance status and other available second-line DST.

On the basics of the drug susceptibility profile, a standard first-line treatment regimen (2HRZE/4HR) can be repeated if no resistance is documented; and if rifampicin resistance is present, a DR-TB regimen should be prescribed according to WHO's recent drug-resistant TB treatment guidelines.

5.1.6. Clinical Monitoring of TB Patients

Patients with extra-pulmonary TB or those who were diagnosed on clinical grounds without bacteriological confirmation of TB should be monitored clinically throughout treatment. Weight is a useful indicator of clinical improvement and should be monitored monthly. If there is a poor response to treatment, alternative diagnoses and the possibility of drug resistance must be considered.

Sputum AFB results for smear-negative patients may be done if the patient later develops a cough or shows clinical deterioration. If the smear microscopy turns positive before reporting the case on case finding, the patient should be re-classified the patient as a bacteriologically confirmed TB case and the recommendations for monitoring, as described above, should be followed.

5.1.7. Common side effects and use of anti-tuberculosis drugs in special situations

Side effect	Drug responsible	Management
Orange or red discoloration of urine (and other body fluids)	RIF	Reassure patient and continue drug
Peripheral neuropathy	INH	Ensure patient is taking pyridoxine. Pyridoxine can be increased to 50 - 75 - 100 mg daily.
Joint pain, gout	PZA	Give NSAID, usually PZA can be continued
Visual impairment, esp. colour vision	EMB	Stop EMB, do not re-challenge
Skin rash	RIF, INH, PZA	Depends on severity of the skin rash: • Mild, itching rash (no blistering, no mucosal involvement and no other systemic symptoms) => give antihistamine • Petechial rash - usually rifampicin. Check platelet count. If platelet count < 60.000 => stop rifampicin • Rash with blistering, mucosal involvement, possibly fever and hepatitis (Stevens Johnsons syndrome) => stop all drug
Jaundice/hepatotoxicity	RIF, INH, PZA	Do liver function tests. Exclude other causes. Stop and re-challenge

Table 5.1-3 Common side effects of TB drugs and management

The following situations require special considerations and adjustment of standardized TB regimens.

5.1.7.1. Pregnancy

- Streptomycin is potentially ototoxic and may cause deafness in infants.
- Streptomycin should not be given in pregnancy.
- Isoniazid, rifampicin, pyrazinamide, and ethambutol are safe in pregnancy
- Pyridoxine supplementation is recommended for all pregnant and breastfeeding women receiving isoniazid

5.1.7.2. Oral contraceptives

- Rifampicin reduces the effectiveness of the oral contraceptive pill
- Health workers should advise patients on TB treatment to use barrier contraception like male or female condoms while on rifampicin

5.1.7.3. Renal impairment and renal failure

- RHZE are not nephrotoxic, but ethambutol and pyrazinamide are cleared by the kidneys and may accumulate during the intensive treatment in renal failure and cause other side effects
- Intensive phase: Calculate creatinine clearance (CreaCl) => If CreaCl < 50 ml/min give RHZE tablets alternating with RH tablets
- Continuation phase: RH can be given normally as both drugs are cleared through the liver
- Streptomycin should be avoided in patients with renal failure, or, if it must be used, the frequency should be reduced

Drug	Dose	Normal frequency	Frequency in renal failure
Pyrazinamide (Z)	25 mg/kg	Daily	3x/week
Ethambutol (E)	15 mg/kg	Daily	3x/week

Table 5.1-4 Recommended dosages in patients with renal failure

5.1.7.4. Liver impairment and liver failure

- Isoniazid, rifampicin and pyrazinamide are recognized to be hepatotoxic
- In case of suspected liver toxicity refer patient for LFTs, HBsAg, and liver ultrasound. If ALT >200 IU/L and/or total bilirubin > 3 mg/dl -> discuss with NTP program
- Consider to start liver-sparing **TB background regimen** as follows:
  - **Levofloxacin (15-20mg/kg daily, max 1000mg) + ethambutol (800-1200mg daily) + linezolid (600mg daily)**
  - Avoid linezolid if Hb<8. Cycloserine is also an option if any of the above are contra-indicated/unavailable
- Once ALT has decreased to < 100 U/L and bilirubin is normal isoniazid, rifampicin, and pyrazinamide can be reintroduced stepwise. Check with NTP for advice

5.1.7.5. Epilepsy

- Rifampicin induces liver enzymes that reduce levels of anticonvulsant medications (phenobarbital and phenytoin) in the blood
- Increase the dose of the anticonvulsant and monitor the patient closely for increasing seizure frequency

5.1.7.6. TB/HIV and taking ART

- Rifampicin induces liver enzymes that reduce levels of some ARTs e.g., dolutegravir (DTG) in blood. The dose of DTG must be increased to 50 mg bd
- Patients taking protease-inhibitors should only receive boosted-lopinavir (LPV/r) in double doses. Atazanavir (ATV/r) and darunavir (DRV) cannot be combined with RIF
- Other drugs (efavirenz (EFV), tenofovir (TDF), zidovudine (AZT), abacavir (ABC), lamivudine (3TC)) have no drug-drug interactions with RHZE and co-administration is not problematic

5.1.8. Management of hospitalised TB patients

- Hospitalised TB patients merit a DAILY ward round like any other patient
- Daily ward rounds should assess patient symptoms, vital signs, response to therapy, side effects, and complications of TB (e.g., anaemia, pleural effusion, respiratory failure, renal failure, hearing loss, cachexia/malnutrition, IRIS)
- Patients with tachypnoea (respiratory rate >20 breaths per minute) and hypoxemia (oxygen saturation <90%) due to PTB, TB pericarditis, or pleural TB may require prolonged oxygen therapy until improvement in respiratory status is achieved

5.1.9. Corticosteroids and tuberculosis

- Corticosteroids in conjunction with anti-TB drugs reduce the risk of death in TBM and of constrictive pericarditis in TB pericarditis. Patients with TBM or TB pericarditis should be given corticosteroids for an initial period of 4 weeks tapered over 2 weeks
- Prednisolone (or the equipotent does of dexamethasone) should be used

Patient Category	Week 1-4	Week 5	Week 6
Adults	60 mg	30 mg	15 mg
Children	1 mg/kg	0.5 mg/kg	0.25 mg/kg

Table 5.1-5 Prednisolone dosing in TBM and TB pericarditis

5.1.10. Default tracking action

- At initial registration, the health worker should record and confirm the patient's address, other relevant addresses (such as those of family members), and, if possible, the patient's or a family member's mobile phone number in case the need to contact or track the patient arises
- Should a TB patient miss a scheduled appointment, action must be taken within three days of the date the patient was due for the appointment or drug collection
- It is the responsibility of the District TB Officer (DTO) to ensure a sound default-tracking plan is in place and implemented at the district level
- The DTO may call upon HSAs, community volunteers, and/or other health workers to locate a patient who has defaulted

5.1.11. Managing transfer-out and transfer-in patients

- When a patient transfers out to another treatment facility, it should be indicated in the facility TB register
- The date of transfer-out and the new treatment facility must be indicated. Transfer-out forms must accompany the patient and must be sent to the new treatment facility
- A copy of each transfer-out form must be sent to the DTO in the receiving district
- A copy of each transfer-out form must be kept at the original treatment unit in a special Transfer-out folder
- **TB patients being transferred out MUST carry their drugs for the remaining period of treatment**
- When patients transfer in from another facility, they should be registered in the **Transfer-in register**
- The patient's treatment outcome must be entered in the transfer-in register; and results must be communicated to the original treatment unit. Transfer-in registers must be properly completed
- TB officers must indicate when quarters start and finish. All transfer-in forms must be kept in a special Transfer-in folder

5.1.12. Recording TB treatment results

It is vital, for assessing programme performance, that accurate recording of treatment outcome results is entered in the TB registers and treatment cards for ALL patients. Treatment cards for patients who have completed treatment died or defaulted must be collected from health centres. These treatment cards must be kept safely and in chronological order in the TB office.

At the end of treatment, the results of chemotherapy should be recorded as per treatment outcomes.

Duration of interruption	Recommended Action	Results	Recommended intervention
Interrupted treatment for less than 1 month	1) Establish the cause for treatment interruption and address the problem or concerns	No lab investigation required	Continue treatment and add the missed doses. • If the interruption occurred **during the intensive phase**, the duration of this phase must be extended by the number of missed days. • If the interruption occurred **during the continuation phase**, the duration of this phase must be extended by the number of missed days
Interrupted treatment for 1-2 months	1. Establish the cause for treatment interruption and address the problem or concerns 2. Collect sputum for Xpert MTB/Rif 3. Continue same treatmen	Xpert MTB positive and rifampicin sensitive	Continue treatment and add the missed doses at the end of the treatment phase
		Xpert MTB positive and rifampicin resistant	Stop current treatment Register patient as "RR-TB" and refer to the MDR-TB treatment site for further management
		Xpert detects no MTB / no Xpert result	Continue same regimen • Arrange sputum sample for culture and DST and decide on next action based on DST result
Interrupted treatment for two months or more (lost to follow-up)	1. Establish the cause for treatment interruption and address the problem or concerns 2. Collect sputum for Xpert MTB/Rif 3. Stop treatment	Xpert MTB positive and rifampicin sensitive	Register patient "Treatment after loss to follow-up" Restart same regimen again
		Xpert MTB positive and rifampicin resistant	Register patient as "RR-TB" and refer to the MDR-TB treatment site for further management
		Xpert detects no MTB / no Xpert result	Register patient "Treatment after loss to follow-up" Restart same regimen again • Arrange sputum sample for culture and DST and decide on next action based on DST result

Table 5.1-6 Management of New TB treatment interrupters

6. Treatment of latent TB infection

6.1. Background

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation by Mycobacterium tuberculosis (MTB) antigens with no evidence of clinically manifest active TB.

It is estimated that about a quarter of the world's population is infected with TB. The immune response to TB infection can be ascertained using a Tuberculin Skin Test (TST) or an Interferon Gamma Release Assay (IGRA).

Following infection, MTB can overcome the body's immune system and cause active TB disease. On the other hand, the body's immune system can overcome MTB, and prevent it from causing TB disease rendering MTB inactive. The inactive MTB bacteria are not killed in the process but rather remain in a dormant form which is called Latent TB Infection (LTBI).

An individual with LTBI can live a healthy life without any symptoms, cannot transmit TB to others, and is not sick. At any point in time when conditions become favourable for MTB such that the body's immune system is weakened.

Recognizing this risk of progression from LTBI to active TB disease, the NTLEP has adopted Tuberculosis Preventive Therapy (TPT) which is a strategy that uses anti-TB medication to target LTBI. Screening for Active TB Disease

Active TB disease MUST be ruled out before prescribing TB preventive Therapy (TPT).

Make sure all attempts to rule out active TB have been made to a high degree of satisfaction before prescribing any form of TB preventive therapy. Symptomatic TB screening alone can be used to rule out active TB.

Note: PLHIV and Children may not have the classic symptoms for active TB and may have Extrapulmonary TB and therefore may warrant a thorough physical examination to rule out active TB. (Refer to the EPTB section).

6.1.1. Target Populations

Any contact with a bacteriologically confirmed Pulmonary TB patient has a risk of acquiring MTB. The Malawi National TB and Leprosy Elimination Program therefore has identified the following target groups for TPT.

- All Under-five children who are household contacts of bacteriologically confirmed pulmonary TB cases regardless of HIV status & previous TB treatment or Previous TB Preventive Therapy
- Household contacts for bacteriologically confirmed pulmonary TB >5 years (children, adolescents and adults who are HIV-negative or HIV positive), regardless of previous TB treatment or Previous TB Preventive Therapy (excluding women who are pregnant or postpartum period (<3month old)
- People living with HIV as per HIV guideline. (Clinical managment of HIV in Children & Adults ,Malawi integrated Guideline and Standard Operating Procedures for providing HIV services , 2022)

6.2. Key steps in ruling out active TB and considering TPT

Screening of TB	Household or close contact of bacteriologically confirmed TB patients			
Screening tools	Adults and adolescents living with HIV	Children living with HIV	HIV-Negative Household or close contact	Clinical at-risk populations
	Clinical symptom-based screening	Current cough, fever, weight loss or night sweats	Absence or poor weight gain, fever or current cough or history of contact with a case of TB, reduced playfulness, night sweats	Cough, fever, weight loss or night sweats for 2 weeks or more
Frequency of symptom screening	At every visit to a health facility or contact with a health worker			
Chest radiography	Chest X-ray is not mandatory although desirable. It may be considered among PLHIV on ART, Asymptomatic adolescents and adult contacts, and clinical at-risk groups where X-ray is available and human resources and health system capacity permits			
Diagnostic testing for TB if screen test is positive	Rapid diagnostics (such as Xpert MTB/Rif, Stool SOS, urine lipoarabinomannan assay among seriously ill PLHIV) as per national guidelines			
Test for TB infection (TST or IGRA)	Not recommended under programmatic condition, but can be used under operational research			

Table 6.2-1 Key steps in ruling out TB and Considering TPT

6H & 3HP & 3HR	3HP and 3HR (only)
• Suspected Or Confirmed TB • Prior Adverse Events or Hypersensitivity to INH • Active Hepatis, Hepatitis Surface antigen positive, Liver damage, Heavy alcohol use. • Peripheral Neuropathy	• PI and NNRTI based regimens must not be combined Rifapentine or Rifampicin based TPT regimens. • Prior Adverse Events or Hypersensitivity to INH, Rifapentine or Rifampicin

Table 6.2-2 Contra-indication for TPT

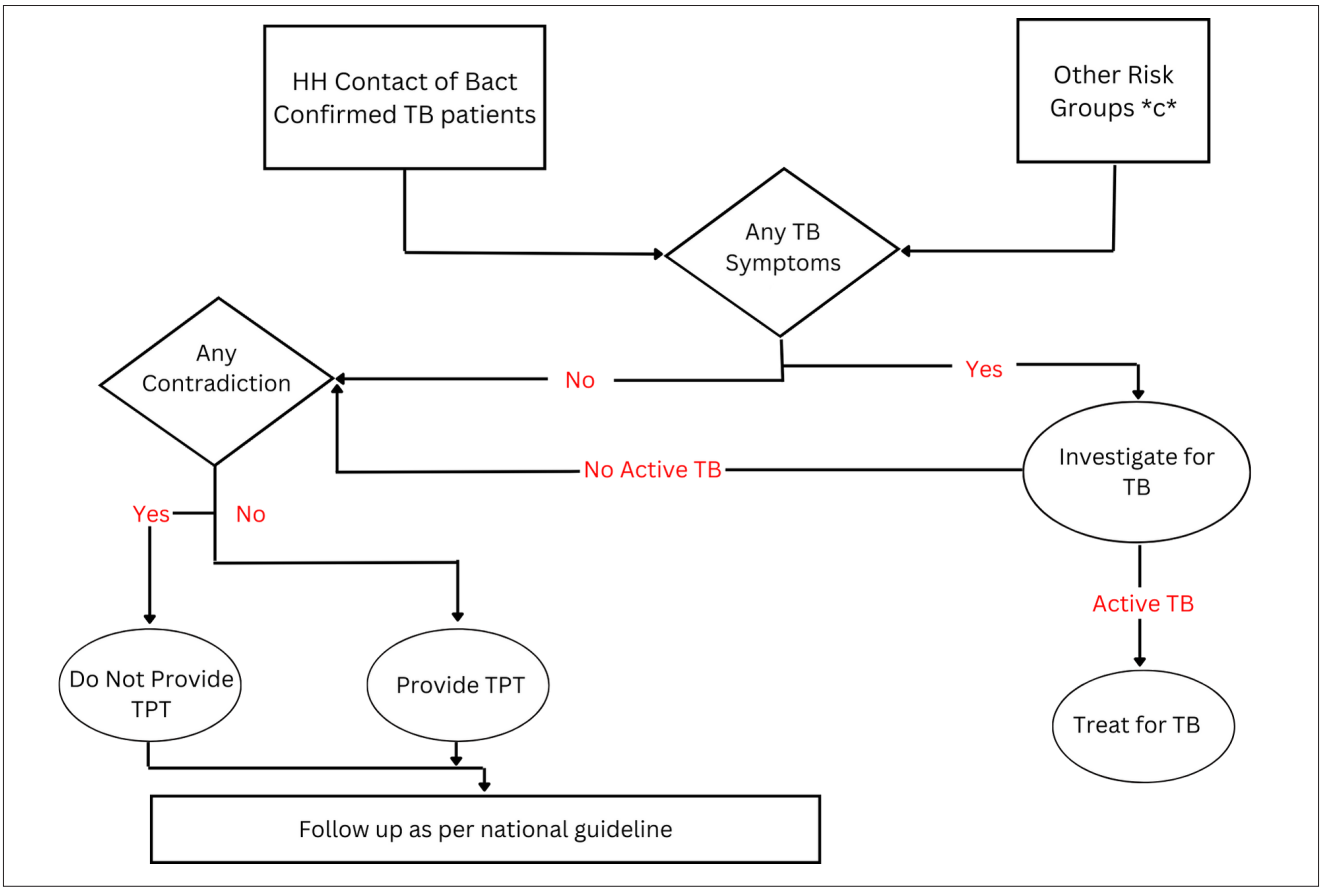


Figure 6.2-1 TPT Algorithm

1. If less than 5 years, any one of current cough or fever or history of contact with TB or reported weight loss or confirmed weight loss >5% since last growth curve flattening or weight for age < -2 Z-scores. Chest Radiography (CXR) may be used in PLHIV on ART before starting TPT.
2. Anyone with cough, fever, night sweats, or weight loss. In children <5 years, absence of playfulness, and failure to thrive. For HIV-negative adult contacts, cough, fever, and drenching night sweats should persist for 2 weeks. (see screening criteria section)
3. Silicosis, dialysis, anti-TNF agent treatment, preparation for transplantation, or other risks. People in group c should also have TB disease ruled out if they have suggestive clinical manifestations.

6.3. TPT Regimens

The following three alternative TPT regimens may be used in Malawi and are similarly effective:

Regimen	Recommendation
3HP: 3-month course of weekly isoniazid + rifapentine	This is a preferred regimen for all contacts above 25 Kg regardless of HIV status unless contraindicated
3RH: 3 months of daily Rifampicin and Isoniazid	Suitable for all age groups who are contacts of bacteriologically confirmed pulmonary TB contacts
6H: 6-month course of daily dose of isoniazid	Preferred regimen for all children under 5 years old and can be combined with all ART regimens. An alternative regimen for those patients contraindicated to 3HP.

Table 6.3-1 Alternate TPT regimens

Notes:

- TPT is well tolerated by most patients. Most side effects are mild and disappear with time. Serious side effects are rare: hypersensitivity, neuropathy, and severe hepatitis
- Document all serious side effects on the yellow pharmacovigilance forms and submit to PMRA
- Stop TPT if any of the following are seen:
  - If signs and symptoms of active TB
  - Nausea, vomiting, loss of appetite
  - Pellagra-type skin rash in sun-exposed areas and other severe skin rashes
  - Yellow eyes
  - Dizziness/confusion/convulsions
  - Moderate numbness/burning pain and muscular weakness of legs and/or arms
  - Flu-like symptoms, syncope.

DO NOT RESTART TPT if any significant side effect is experienced.

6.3.1. 3HP

- Preferred regimen in all age groups >5 years regardless of HIV status
- 3HP is easier to complete due to its short duration and fewer side effects
- Is not suitable for patients on PI and NNRTI-based ART regimens
- Use drug interaction job aid in case any new drugs are started in persons on 3HP
- Give weekly doses of Rifapentine/Isoniazid for 12 weeks based on weight
- Give 1 daily tablet of Pyridoxine 24-hourly for 12 weeks. Adults: 25 or 50mg. Children <20kg: about 1 mg/kg
- Review patients at months 1, 2, and 3 after starting 3HP for any side effects and monitor adherence. Match visits with ART refills

Medicine/Weight Band	25-29 Kg	30-34.9 Kg	35-39.9 Kg	40-49.9 Kg	>50Kg
Isoniazid 300mg	1.5	1.5	2	2	3
Rifapentine 150mg	4	5	5	5	6
Rifapentine 300mg/ Isoniazid 300mg (FDC)	N/A	3	3	3	3

Table 6.3-2 3HP dosing

6.3.2. 3RH

- 3 months of daily Rifampicin and Isoniazid
- Preferred Regimen in HIV Negative Children <5 years
- Can be given as TPT option for all age groups including <2-year-olds unlike 3HP.
- 3RH is a dual therapy TPT option unlike 6H monotherapy
- Child-friendly fixed-dose combinations (FDCs) are already available since RH is used for the treatment of drug-susceptible TB in children during the continuation phase
- Rifampicin has drug-drug interactions with protease inhibitors (PIs) e.g. Lopinavir/Ritonavir and integrase non-strand Inhibitors (INSTI) e.g. Dolutegravir/Raltegravir. Therefore, do not combine with 3RH
- Dosing (Single dosing)
  - Rifampicin

- Age 10 years & older: 10 mg/kg/day
- Age < 10 years: 15 mg/kg/day (range, 10–20 mg)

○ Isoniazid

- Age 10 years & older: 5 mg/kg/day
- Age < 10 years: 10 mg/kg/day (range, 7–15 mg)

Weight Band	4-7 kg	8-11 kg	12-15 kg	16-24 kg	25 kg +
RH 75/50 mg (FDC)	1	2	3	4	Use adult formulation

Table 6.3-3 Dosing for 3HR Fixed Dose Combination

6.3.3. 6H (6 Months Isoniazid)

- Preferred regimen for HIV positive <5 years
- All child household contacts of bacteriologically confirmed pulmonary TB patients who are 5 years and below should receive 6H
- Adult ART clients who have **contraindications to 3HP** can be provided 6H as an alternative TPT regimen to 3HP
- All household contacts of bacteriologically confirmed pulmonary TB above the age of 5 years who have contraindications to 3HP should be given 6H
- Give 1 daily dose of INH and Pyridoxine for 6 months (cumulative total of at least 168 daily doses). For children, use weight-based dosing charts
- Give 1 daily tablet of Pyridoxine 24-hourly. **Adults**: 25 or 50mg. **Children <20kg**: about 1 mg/kg
- Review patients every month for the duration of treatment and monitor for any side effects and adherence. For HIV positive children and adults, match visits with ART refill

Medicine/ Weight band	3-5.9 Kg	6-9.9 Kg	10-13.9 kg	14-19.9 kg	20-24.9 Kg	25-29.9 Kg	30-34.9 Kg	35-39.9 Kg	40-49.9 Kg	50Kg+
Isoniazid 100mg	0.5	1	1.5	2	2.5	N/A	N/A	N/A	N/A	N/A
Isoniazid 300mg	N/A	N/A	N/A	N/A	N/A	1	1	1	1	1

Table 6.3-4 6H Dosing

Regimen	Dosing (mg/kg/day)	Frequency	Duration of treatment	Target population	FDC	Pediatric dispersible formulation
3HP	Adult: 900mg INH/ 900mg RPT Weight-banded pediatric dosing for 10 kg – 40 kg	Once weekly	12 weeks 12 doses	All household contacts of pulmonary TB patients (Adults and children > 5 years) regardless of HIV status	YES	*NO
3RH	Weight-banded pediatric dosing. Preventive treatment requires the same dosing as recommended for treatment of drug-sensitive TB:< 25kg: Pediatric FDC (RH 75/50mg)> 25 kg: adult FDC (RH)xix	Once daily	12 weeks 90 doses	Under 5 HIV negative children	YES	YES (RH 75/50mg)
6H		Once daily	6 months 180 doses	Under 5 children on ART	Single formul-ation	YES (INH 100 mg)

Overview of key characteristics of 3HP and 3RH regimens

** Due to unavailability of child-friendly formulation, 3HP not recommended in children below 25 kg weight 3RH and 6H preferred regimens for that age category.*

TPT Regimen	Pros and Cons
3HP	Shorter regimen, better adherence, cost-effective.
	Potential drug-drug interactions with some antiretroviral drugs (e.g., lopinavir-ritonavir and nevirapine), higher cost, FDC and child-friendly formulation still in development phase
3RH (for pediatric population)	Shorter regimen, better adherence, availability of a child-friendly FDC, wide availability
	Potential drug-drug interactions with some ARV (lopinavir-ritonavir, dolutegravir, nevirapine), marginal price increase compared to IPT
6 months INH	Low cost, effective, compatible with most ART regimens
	Poor adherence, low uptake, more side effects than rifamycin-based regimens (3HP and 3RH)

Table 6.3-5 Overview of pros and cons for TPT Regimens

6.3.4. Special Situations in TPT Provision

6.3.4.1. Contacts of drug resistant TB

- Household contacts for patients with DR-TB or isoniazid mono-resistance are at a higher risk of TB infection than contacts exposed to drug-susceptible TB
- Currently, the Malawi National TB and Leprosy Elimination Program (NTLEP) does not recommend any form of TPT for Drug Resistant TB (DRTB) contacts

Management of babies born to mothers with active TB disease

- Assess the newborn. If the newborn is not well, refer to the next level of care
- Ensure the mother receives effective treatment so that she is no longer infectious
- Ensure basic TB infection control measures at the home or hospital (e.g. ventilation, use of masks)
- If the new-born is well (absence of any signs and symptoms of presumptive TB), provide TPT and delay BCG vaccination until TPT is complete. Administer pyridoxine at 5-10mg/day
- If the infant is HIV exposed (mother HIV positive) and on nevirapine, IPT should be started
- At the end of TPT (6 months), give BCG
- If the infant is HIV positive, delay BCG vaccination until ART has been started and the infant confirmed to be clinically and immunologically stable
- If the mother is taking anti-TB medicines, she can safely continue breastfeeding. Mother and baby should stay together, and the baby may be breastfed while on TPT
- Infant breastfeeding from a mother either on TPT or TB treatment should receive pyridoxine for the duration of the mother's treatment

6.3.4.2. Pregnant and Postpartum women

- Do not give TPT to pregnant women until 3 months postpartum
- Supplement Pyridoxine to all breastfeeding infants whose mothers are taking TPT

6.3.4.3. PLHIV (TPT-DTG Interactions)

- Rifampicin based regimens have drug-drug interactions with DTG based ART regimens
- Rifampicin interacts with DTG reducing DTG therapeutic levels necessitating doubling the dose of DTG
- However, Rifapentine, when administered once weekly, does not have significant interactions with DTG to warrant a dose adjustment for DTG
- Therefore, there is no need to "boost" DTG when co-administering with once-weekly Rifapentine

6.3.4.4. 3HP/3RH and Malaria Treatment

- Rifamycins (e.g., Rifampicin and Rifapentine), are known to interact with Artemisinin Combination therapy, (ACTs- Artesunate and Lumefantrine Artemether, LA) and Quinine
- Rifamycin lowers therapeutic levels of these anti-malaria
- If a person is diagnosed with Malaria but is not yet on Rifamycin based TPT e.g. (3HP/3RH), the Episode of Malaria should be prioritised and treated first. Hold Initiation of 3HP/3RH. Start TPT after the Malaria episode has resolved
- If a person is diagnosed with Malaria while on a rifamycin-based TPT (3HP/3RH), Hold TPT, and Treat for Malaria according to national guidelines. Continue TPT after the Malaria Episode has resolved
- If a person has Malaria recurrence while on Rifamycin based TPT (3HP/3RH), Hold TPT and prioritise Malaria treatment. Continue TPT after the Malaria Episode has resolved.

6.3.4.5. Women receiving oral or Hormonal contraception.

- Rifampicin and Rifapentine interact with Oral and Hormonal contraceptives potentially decreasing their contraceptive efficacy.
- Women receiving Oral or Hormonal contraceptives while taking Rifampicin or Rifapentine should use:
  - Barrier methods of contraception
    - Male or female condoms
  - Intrauterine Contraceptive devices (IUDs)

        - Copper IUD, or Levonorgestrel IUD (Mirena)
    - Two monthly Depo Medroxyprogesterone Acetate

6.3.4.6. Liver Disease

- Rifampicin/Rifapentine and Isoniazid are associated with hepatic damage
- Do not prescribe 3HP or 6H in clients with either acute or chronic Hepatitis until hepatitis has resolved.

6.3.4.7. Hepatitis C

- Rifamycin interacts with medications used to treat Hepatitis C effectively reducing their concentration to subtherapeutic levels.
- Do not give 3HP to clients with active hepatitis C or on medications used to treat hepatitis C.
- Offer 6H to clients on Hepatitis C medicines without active Hepatitis.

6.3.4.8. Renal Failure

- Rifampicin/Rifapentine/Isoniazid are excreted from the body by the liver, kidney function or renal failure therefore has no effect on 3HP and INH concentrations in the human body.
- Both 3HP and 6H can be given at normal standard doses in the presence of renal failure

6.3.5. TPT completion and management of interruption

- Document all clients started on TPT in the TB TPT register
- Provide adherence support for clients to complete the TPT course
- A complete course of 3HP takes 12 weeks. A patient who misses doses for:
    - Less than a month – proceed with the course but up to 16 weeks
    - More than a month – restart the whole course of 3HP
- A complete course of 6H takes at least 146 doses with no more than 2 months of interruption in doses. All doses should be completed within 8 months
    - Repeat the 6H course if there is more than 2 months' treatment interruption
- A complete course of 3RH is 84 doses, prescribed as 1 dose daily, and amounts to 84 days (3 TB Months). When interrupted the maximum allowed time to completion is 120 days
    - Interruption for < 2 weeks (14 days)
        - Where a client missed doses of 3HR for less than 14 days, continue TPT till 84 doses. This means the next appointment will be delayed by an extra number of days
    - Interruption >2 weeks (14 days).
        - If the client took 3HP for more than 14 days and the remaining doses can be taken within 120 days to reach 84 doses (total of 84 days), then continue treatment.
        - If the client interrupted treatment for more than 14 days such that 84 doses cannot be completed within 120 days, restart 3RH.

	Total Duration (Months)	Expected Number of Doses	Minimum Number of doses required to Complete Treatment	Maximum Time for TPT completion (days)
6H (Daily Isoniazid)	6 Months	182	146	239
3HP (once weekly Isoniazid + Rifapentine)	3 Months	12	11	120
3RH (Rifampicin + Isoniazid)	3 Months	84	68	120

Table 6.3-6 Preventive TB treatment Completion

7. TB and HIV

7.1. HIV infection

Infection with HIV leads to the destruction of the body's immune system. Persons who are infected with HIV are therefore more prone to TB disease than those without HIV infection. When recognized opportunistic diseases accompany HIV infection, the affected person is said to have acquired immunodeficiency syndrome (AIDS).

7.1.1. The interaction between TB and HIV

A strong immune system usually prevents the development of TB disease following infection with TB bacilli. HIV reduces the protection provided by the immune system and enables TB bacilli to multiply uncontrolled, facilitating rapid progression to active TB disease. For WHO African Region HIV prevalence among TB patients is approximately 20%, while in Malawi about 47% of TB patients are HIV-positive (2022[1]). HIV-related tuberculosis is associated with poor TB treatment outcomes. It is therefore imperative to rapidly identify and treat TB cases among PLHIV.

7.1.2. Impact of HIV on TB

- High HIV prevalence is associated with an increase in the number of new TB cases. HIV infection increases susceptibility to new TB infections and accelerates the progression from LTBI to active TB disease. HIV is associated with an increase in smear negative and EPTB cases
- HIV infection increases TB-associated morbidity and mortality. HIV-positive TB patients have a higher case fatality during TB treatment compared with HIV-negative patients. HIV-positive, smear-negative patients and EPTB patients have worse treatment outcomes than smear-positive TB patients. Adverse reactions to anti-TB drugs are more frequent in PLHIV compared to the general population, leading to interruptions of treatment and poor outcomes
- TB recurrence rates are higher in HIV-positive patients than in HIV-negative patients. Recurrence of TB may be from reactivation of persistent organisms not killed by previous anti-TB treatment or re-infection due to re-exposure to another infectious person
- MDR-TB has been reported amongst patients with HIV in Malawi. HIV does not cause MDR-TB, but it can increase the spread of this condition by increasing susceptibility to infection and accelerating the progression from infection to disease

7.2. Collaboration and coordination between the TB and HIV programmes

Controlling TB/HIV requires collaboration and coordination between the TB and HIV programmes at all levels. Service integration can include referral of patients and presumptive TB cases between TB and HIV services, partial provision of joint TB/HIV services, or full integration of the TB and HIV/AIDS clinics ("one-stop shop" or "all services under one roof").

Examples of integrated TB/HIV services include:

- PITC of TB patients;
- Provision of CPT;
- Early initiation of ART in HIV-infected patients with TB,
- Offering of anti-TB drugs and ART in the same room by the same person ("one-stop shop"),
- Screening of all HIV-positive persons for active TB, and

1 Annual TB report, 2015. National Tuberculosis Control Programme, MOH. Malawi

- Provision of IPT to PLHIV who do not have evidence of active TB.

7.2.1. PITC for TB patients

- All presumptive TB cases and patients should be offered HIV testing and counselling by health workers
- HIV testing should be carried out if HIV status is unknown, was previously reported as negative in the past 3 months, or was refused or opted out of during the patient's previous visit
- If a patient reports having been previously tested for HIV but has no documented evidence of this fact, the test should be repeated. All HIV-positive TB patients are entitled to quality HIV treatment, care, and support services

7.2.2. Provision of ART in co-infected TB patients

- Regardless of CD4 count, all TB/HIV co-infected patients should be started on ART within the first 2 weeks of TB treatment
- If the TB/HIV co-infected patient is clinically stable, ART and TB treatment may be started concurrently on the same day. ART should be started at least within 14 days of diagnosis
- The ART regimen for TB patients initiating ART is a combination of tenofovir/lamivudine/dolutegravir [TDF/3TC/DTG + extra DTG 50 (Regimen 13A+DTG 50)]. Extra DTG 50 mg is required whenever Rifampicin is contained in the TB regimen (refer to the 2022 Integrated National PMTCT/ ART Guidelines for additional details)

7.2.3. Provision of CPT

All HIV-positive TB patients should be started on CPT to reduce the risk of death and the occurrence of opportunistic infections. If possible, CPT should be started on the same day that the patient's HIV-positive status is determined. Once CPT is started, it should be given for life.

The following are contraindications to cotrimoxazole:

- Known severe drug reaction to sulpha-containing drugs,
- Severe megaloblastic anaemia or pancytopenia,
- End-stage renal disease.

7.2.4. Management of HIV-positive patients with active TB

Management of TB in HIV co-infected patients may present challenges related to TB diagnosis, drug-drug interactions, medication side effects, and IRIS. The response to treatment may be slow in HIV-positive TB patients, especially when the patients are severely immunocompromised.

7.2.5. Immune reconstitution inflammatory syndrome

- An HIV-positive patient's condition could worsen within the first 6 months of starting ART because of IRIS. IRIS is a result of the recovery of the body's immune system. Two forms exist:
  - An unmasking IRIS of a previously not known opportunistic infection
  - A paradoxical IRIS with relapse or worsening of symptoms of an infection that seemed diagnosed and treated successfully

KEY POINTS ON IRIS

- Occasionally an HIV/TB co-infected patient may experience a temporary worsening of TB symptoms soon after beginning ART and TB treatment. IRIS should be considered as a potential cause of such clinical worsening
- Clinical worsening. Signs and symptoms include: high fever, lymphadenopathy, and worsening CXR findings.
- Other causes of clinical worsening should be ruled out before making a diagnosis of IRIS; these include undiagnosed TB disease, cryptococcal meningitis and Kaposi Sarcoma
- Patients with advanced AIDS who start ART late are at the greatest risk of developing IRIS

7.2.5.1. Management of TB-related IRIS

- Before starting ART, counsel TB patients about the possibility of a temporary worsening of symptoms
- If a patient develops IRIS while on anti-TB treatment and ART, seek the advice of a senior ART provider or medical specialist
- There is no need to stop or change TB or ARV treatment
- Confirm that the patient is adhering to their medication regimen as prescribed. Admit severe cases to the hospital
- Treat with:
  - prednisolone, 1 mg/kg body weight (once daily) for 14-21 days
  - or dexamethasone, 16 mg/day (divided into twice daily dosing)
  - After 14-21 days, rapidly taper the steroids over a 10 to 14-day period while monitoring for recurrence and/or worsening of symptoms
- Consider TB treatment failure or MDR-TB if the patient worsens despite having received one or more months of anti-TB treatment

7.2.5.2. Overlapping ARV and TB drug side effects

- Concurrent use of ARVs and TB drugs has the potential for added toxicity
- The most common causes of skin rashes are pyrazinamide, isoniazid, and rifampicin
- ARVs such as nevirapine and efavirenz can also cause skin rashes
- These overlapping side effects make it difficult to identify the causative drug when a patient is receiving treatment for both TB and HIV concurrently
- Patients on both treatments need a thorough history and clinical assessment to establish which drug is responsible for the side effects

Drug	Isoniazid	Rifampicin	Ethambutol	Pyrazinamide
TDF	OK	OK	OK	OK
AZT	OK	OK	OK	OK
3TC	OK	OK	OK	OK
DTG	OK	Major dose adaptation	OK	OK
EFV	OK	OK	OK	Hepatitis
NVP	Skin Rash	Hepatitis	OK	Hepatitis
ABC	OK	OK	OK	OK
ATV/r	OK	No experience, do not combine	OK	OK
DRV	OK	No experience, do not combine	OK	OK
LPV/r	OK	Major dose adaptation	OK	OK

Table 7.2-1 Drug interactions between ARVs and TB drugs

Major Issue Follow up

8. Management of Tuberculosis in children and adolescents

8.1. TB screening and contact investigation

Screening criteria

- TB screening serves to identify children and adolescents who may have the disease (presumptive TB) and who need further evaluation
- Children and adolescents living with HIV should systematically be screened for TB disease at each visit to the health facility

- Screening child contacts of people with bacteriologically confirmed TB
  - Symptom screening
    - Cough >2 weeks.
    - Fever more than 2 weeks
    - Poor weight gain or weight loss in the past 3 months
    - Young children, reduced playfulness or lethargy should be included
  - Chest X-RAY
    - Sensitivity for TB of “any abnormality” as reported on CXR in close contacts aged under 15 years is 84%, and specificity is 91% [2]
    - Abnormalities caused by TB seen on CXR in children may differ widely from those in adults.
    - Older children may have adult-type disease presentation, such as lung cavities, but changes in CXR associated with TB disease in younger children may be subtle and hard to see if the quality is not optimal.
  - Screening of children and adolescents living with HIV
    - Screening for symptoms and contacts
    - Other screening tests
  - Screening criteria
    - Cough
    - Fever
    - Night sweats
    - Poor weight gain/ Unexplained weight loss Failure to thrive and/or malnutrition
    - Chest radiography
    - History of close contact with a TB case within the past year
    - Decreased appetite, often with weight loss;
    - Features of increased intracranial pressure such as vomiting without diarrhoea, early morning headache, irritability.
    - Drowsiness/lethargy and convulsions, especially focal seizures.
    - Behavioural changes (irritability, confusion, or agitation).

Contact investigation (refer contact investigation section)

- Index cases
- Household contacts

2 Childhood TB

- Approach for contact investigation

The diagnosis of TB in children relies on a thorough assessment of all the evidence derived from a careful history of exposure, clinical examination, and relevant investigations. The recommended approach to diagnosing TB in children includes:

- Gathering a detailed patient history, including history of TB contacts, BCG status and symptoms consistent with TB;
- Clinical examination including growth assessment;
- HIV testing: provider initiated testing and counselling (PITC);
- Sputum microscopy, Gene Xpert and culture when possible.

All children with symptoms suggestive of TB should be investigated. Children can present with TB at any age, but it is most common in the under-5 age group and during adolescence.

8.2. Diagnosing TB in Children and Adolescents

KEY FACTS PERTAINING DIAGNOSING TB IN CHILDREN AND ADOLESCENTS

- All Children and adolescents who screen positive during contact investigation and/or at a health facility must be evaluated further for TB disease
- The diagnosis of TB disease should be made based on a careful clinical history and assessment, supported by relevant tests and investigations
- Most young children with TB have relatively few TB bacilli. As a result, diagnostic tests that detect TB bacilli are not as sensitive in young children as in older adolescents and adults with TB
- Young children cannot easily produce sputum. Therefore, alternative sample types should be used A stool sample should be prioritized but nasopharyngeal or gastric aspirates can be used where feasible to collect
- In children with signs and symptoms of PTB, Xpert Ultra should be used as the initial diagnostic test for TB and detection of rifampicin resistance on sputum, stool or the other specimens
- In children (aged <10 years) presumed to have PTB attending health care facilities, integrated treatment decision algorithms may be used to diagnose PTB. See section 9.2 for details
- PTB is the most common type of TB in children and adolescents. TB in children usually involves the intrathoracic lymph nodes, but in adolescents, it more commonly resembles adult-type disease with cavities in the upper lobes of the lungs
- A trial of treatment with TB medicines is not recommended as a method of diagnosing TB in children.
- CXR is useful to support the clinical diagnosis of PTB when TB is suspected, and bacteriological testing is negative
- Histopathological examination should be done for children with EPTB whenever possible.
- Routine HTS should be offered to all children and adolescents completing evaluation for exposure to TB, with presumptive TB or diagnosed with TB
- Avoid using sputum smear for microscopy to diagnose TB in children. All samples from children for the diagnosis of TB should be tested on GeneXpert Platform

Diagnosing TB in children and adolescents relies on a combination of:

- Careful history, including any TB contact (especially in the past 12 months), previous TB treatment, and signs and symptoms consistent with TB;
- Clinical examination, including growth assessment.
- HIV testing if status unknown;

- Bacteriological testing
- CXR (preferably AP and lateral in children aged under 5 years and PA in older children and adolescents);
- Investigations relevant for presumed EPTB

Children aged <5 years have a higher risk of developing TB compared with older age groups. Risk of TB disease is more pronounced among children and adolescents who:

- Are in a household or other close contact with a person with PTB
- Are aged <5 years
- Are HIV infected (CLHIV);
- Have severe acute malnutrition (SAM);
- Are hospitalized with pneumonia, especially if not responding to antibiotic treatment

A decision to start TB treatment based on clinical parameters (clinical diagnosis) should not be delayed if the necessary investigations are not available, particularly for children at higher risk of developing severe disease, such as those aged <2 years, CLHIV, with SAM, or hospitalized with pneumonia (not responding to first-line treatment for pneumonia).

Atypical clinical presentations of children with pulmonary TB

TB may present in atypical ways, such as acute severe pneumonia (more common in children aged <2 years and CLHIV) or fixed airway wheezing (more common in children aged <5 years).

PTB should be suspected if there is a poor response to antibiotics, and/or a positive TB contact history. In CLHIV, other HIV-related lung diseases such as *Pneumocystis jirovecii* pneumonia should also be suspected.

Wheezing can be caused by airway compression due to enlarged intrathoracic TB lymph nodes.

PTB should be suspected when a wheeze is asymmetrical, persistent and monophonic, not responsive to bronchodilator therapy, and associated with other typical features of TB (e.g. poor weight gain, persistent fever).

Note: Wheezing due to asthma is usually recurrent and variable rather than persistent, and responsive to inhaled bronchodilators.

Bacteriological confirmation

Despite challenges with bacteriological confirmation of paucibacillary TB in young children, every effort should be made to establish bacteriological confirmation. In adolescents, who usually have adult-type disease, bacteriological confirmation is common.

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

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

Sample types

Recommended clinical samples for the diagnosis of PTB in children and adolescents using Xpert MTB/RIF or Ultra include sputum (expectorated or induced), stool, gastric, and nasopharyngeal aspirates.

Each of these specimen types has advantages and disadvantages

Each of the samples requires a specific standard operating procedure for sample collection methods. Urine for LF-LAM should be considered in eligible CLHIV.

Sputum collection by spontaneous expectoration is often possible in older children and adolescents, usually from 8 years but sometimes in younger children.

The choice of specimen type depends on

- Acceptability for the child, parents, HCWs, and other stakeholders;
- Feasibility of collecting and preparing specimens in the local context;
- Local test availability.

In Malawi, we recommend that **expectorated sputum** be prioritized at all healthcare levels and that stool should be the primary alternative (especially in younger children) to maximize the number of children able to submit samples for bacteriological confirmation of TB and RR. **Urine in eligible CLHIV** should be considered.

Both expectorated sputum and stool are non-invasive and highly acceptable by caregivers. Induced sputum, gastric, and nasopharyngeal aspirates can be collected where resources allow and only when expectorated sputum and stool are not feasible or there is a need to assess RR after a trace result.

Sample type	Advantages	Disadvantages	Caregiver acceptability
Expectorated sputum	Low cost Non-invasive	Not feasible in young children	High
Induced sputum	Non-invasive (if followed by spontaneous expectoration)	Requires several pieces of equipment, electricity, hypertonic saline and trained personnel May require additional nasopharyngeal aspiration in young children Aerosolized transmission risk to HCWs and others	Moderate
Gastric aspirate	Feasible in young children	Invasive High level of discomfort Requires fasting Requires consumables and trained personnel	Low
Nasopharyngeal aspirate (NPA)	Feasible in young children Less invasive than gastric aspirate	Invasive Requires equipment and trained personnel Aerosolized transmission risk to HCWs and others (lower than for induced sputum)	Moderate
Stool	Non-invasive	Requires additional laboratory processing, depending on processing method Must wait for bowel movement	High

Table 8.2-1 Sputum sample methods of collection

WHO-recommended rapid diagnostic tests

Xpert MTB/RIF Ultra – Primary Diagnostic Test

- Use Xpert MTB/RIF Ultra as an **initial diagnostic** test for TB and detection of RR rather than smear microscopy/culture

- Appropriate specimens from suspected sites of involvement should be collected for rapid testing using Xpert MTB/RIF Ultra
- The Xpert MTB/RIF Ultra assay uses the same GeneXpert platform, and a new enhanced cartridge developed to improve the sensitivity and reliability of detection of M. tuberculosis complex and RR
- Xpert MTB/RIF Ultra can be used on various respiratory (sputum, NPA, gastric aspirates, stool) and non-respiratory (CSF, lymph node tissue) specimens
- For children (both HIV infected and HIV negative) being evaluated for PTB and EPTB, the "M. tuberculosis complex detected trace" Ultra result is considered bacteriological confirmation of TB
- However, "trace results" have an indeterminate result for RR – therefore, alternative specimens may need to be collected for Xpert Ultra processing in children likely or suspected to have DR-TB

Xpert MTB/XDR can further diagnose resistance towards isoniazid (INH), fluoroquinolones (FLQ), second-line injectable drug (SLID) (amikacin, kanamycin, capreomycin) and ethionamide (ETH)

Urine Lateral Flow Lipoarabinomannan (LF-LAM)

- Urine LF-LAM detects the mycobacterial LAM antigen in urine, and can be used in CLHIV with advanced HIV

Patient groups with advanced HIV are the following:

- All children <5 years old are considered to have advanced HIV disease until they are clinically stable with a suppressed VL on ART
- CD4 < 200 cells/ml before ART initiation/while on ART

> Note that a CD4 test result is not required to conduct urine LAM and CrAg testing if other criteria (see below) are met.

- WHO stage 3 or 4
- Every ART experienced patient with viral load 1000+ (on ART for > 1 year)
- "Seriously ill" PLHIV:
  - All PLHIV admitted as in-patient
  - HIV infected patients with any of the following danger signs:
    - Adults: ≥30 breaths/min; heart rate ≥120 beats/min; unable to walk unaided; ≥39°C
    - Children: lethargy; unconsciousness; convulsions; unable to drink or breastfeed;
      - Repeated vomiting; fever ≥39°C; tachycardia; tachypnoea

Using the Chest X-ray

- CXR remains an important tool in the diagnosis of TB in children, especially those with a clinical diagnosis of PTB, or negative bacteriological tests or where bacteriological testing is not available
- Most children with PTB have radiographic changes suggestive of TB. If possible, AP and lateral films should be obtained in children aged <5 years, and PA films in older children and adolescents
- Abnormalities on CXR suggestive of PTB include:
  - Enlarged perihilar or paratracheal lymph nodes
  - Dense alveolar opacification in a child who is not acutely ill
  - Military pattern of opacification
  - Cavitation (more frequent in adolescents;
  - Pleural or pericardial effusion
- Adolescents with TB usually have radiographic changes similar to those seen in adults, with apical infiltrates with or without cavity formation or unilateral large pleural effusions being the most common forms of presentation

Integrated treatment decision algorithms for pulmonary TB in children

- In children with presumptive PTB attending health care facilities, integrated treatment decision algorithms may be used to diagnose PTB
- New integrated treatment decision algorithms for specific populations and settings have been developed and internally validated
- The algorithms cover the **diagnosis of PTB in children aged <10 years**, including those with intrathoracic lymphadenopathy
- The algorithms are not suitable for the diagnosis of EPTB
- These algorithms for use in settings with and without CXR were developed based on diagnostic and treatment outcome data in children aged <10 years presenting for evaluation of pulmonary TB in high TB burden settings

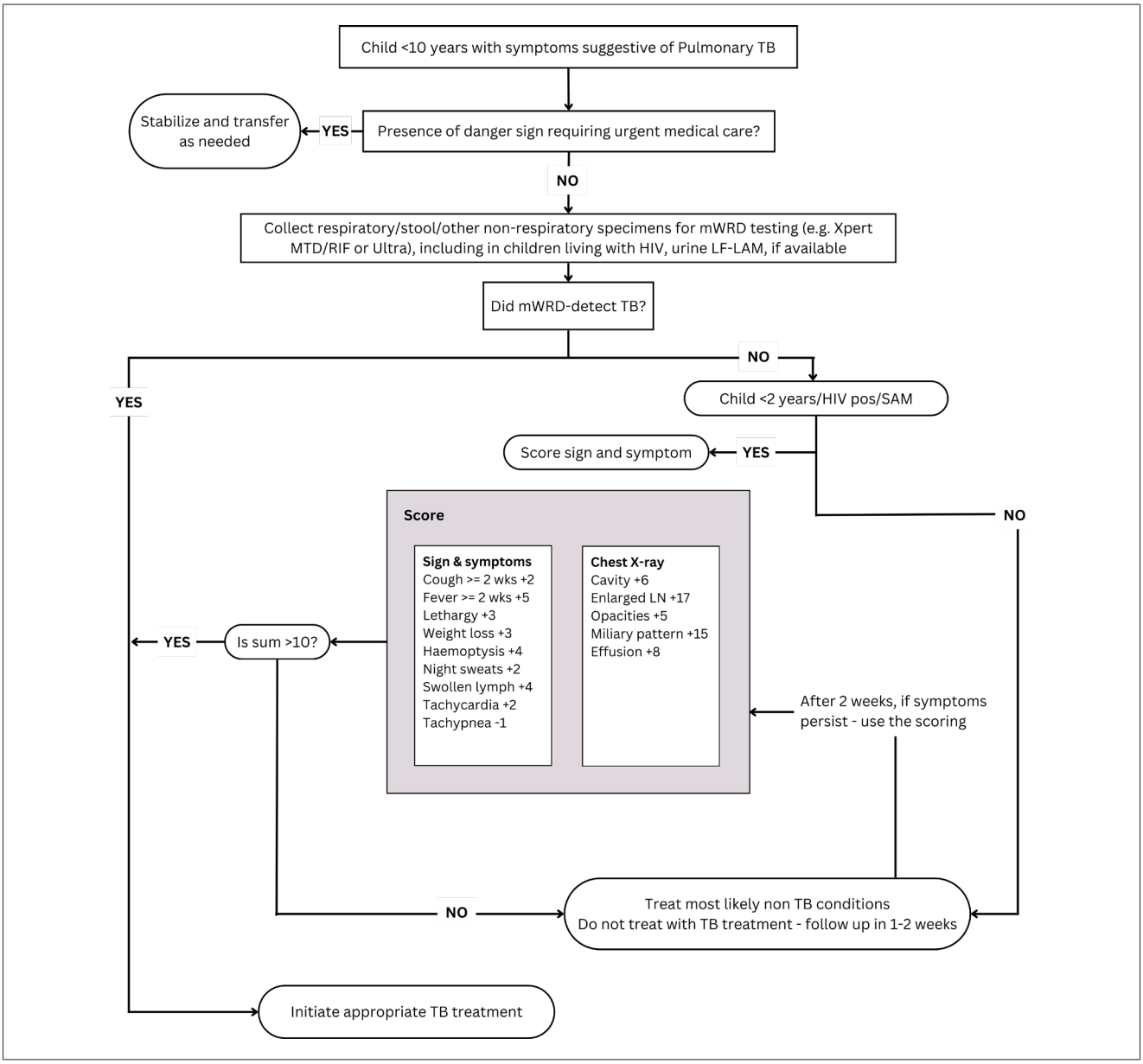


Figure 8.2-1 Integrated treatment algorithm for children

Diagnosing Extrapulmonary TB (EPTB)

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

Note: Intrathoracic lymphadenopathy in children is now classified as PTB.

- EPTB is a common CLHIV
  - Symptoms of EPTB vary, depending on the site of the disease. They are usually persistent and progressive and may be associated with weight loss, poor weight gain and fever.
  - Clinical assessment in all presumed cases of EPTB should consider:
    - History of TB contact
    - Collection of appropriate specimens from an affected site (including CSF, lymph node aspirate, lymph node biopsy, pleural fluid, peritoneal fluid, pericardial fluid, synovial fluid or urine specimens) for confirmatory tests, including mWRDs (and histology where appropriate and available)
    - Collection of respiratory samples (stool, sputum, gastric aspirate or NPA sample) to evaluate for PTB (as the child may have both PTB and EPTB)
    - CXR and other imaging, depending on the affected site
    - HIV testing
  - Since it is more challenging to diagnose, children with presumed EPTB should be urgently evaluated or referred for further evaluation and diagnostic workup
- All children diagnosed with EPTB should be started on appropriate TB treatment immediately

8.3. TB case finding strategies among paediatric TB patients

8.3.1. Systematic TB screening in OPD including IMNCI clinics

- Screen all patients using screening criteria for TB
- All presumptive TB patients should be tested using WRD
- A diagnostic criterion for children needs to be used for these groups

8.3.2. Systematic TB screening paediatric wards

- All paediatric presumptive TB cases need to be screened for TB
- Screening criteria and tests need to be review
- A screening register to monitor coverage of screening, yield will be made available

8.3.3. Systematic TB screening in HIV clinics

- TB screening regularly using symptomatic TB screening at each visit
- All identified presumptive TB cases need to be tested using WRD
- Patients with positive TB test result need to be referred for treatment initiation

8.4. TB prevention

8.4.1. BCG vaccination

- BCG is a live attenuated bacterial vaccine derived from Mycobacterium bovis that was originally isolated in 1902 from a tuberculous cow
- BCG has demonstrated significant effectiveness, but protection has not been consistent against all forms of TB in all age groups
- BCG has also shown effectiveness in preventing leprosy (caused by Mycobacterium leprae) and Buruli ulcer

(caused by Mycobacterium ulcerans)

- BCG provides good (up to 90%) protection against severe forms of TB, including TBM and miliary TB, if given during the neonatal period.
- Although neonatal vaccination also provides protection against pulmonary TB, it mainly prevents progression to disseminated forms of TB.
- BCG-vaccinated children exposed to people with infectious TB had 19% less TB infection than unvaccinated children (95% confidence interval (CI) 8-29%).
- BCG may also have nonspecific beneficial effects on all-cause mortality.

Recommendations

BCG in children living with HIV

- Children known to be **living with HIV** should not receive BCG vaccination because they are at increased risk of developing disseminated BCG disease
    - However, if they are receiving ART, and are clinically well and immunologically stable they should be vaccinated. Immunologically stable children have a CD4% over 25% (children aged under 5 years) or a CD4 count of 200/mm3 or higher (children aged over 5 years)

In settings without access to CD4 testing, immunological stability may be assessed clinically, based on the absence of new opportunistic infections and any other symptoms.

BCG in Neonates

- Neonates born to women with **unknown HIV status** should receive BCG vaccination.
- Neonates with unknown HIV status born to women living with HIV should be vaccinated, provided they have **no clinical evidence suggestive of HIV infection**, irrespective of the mother's ART status
- Neonates diagnosed with HIV infection, as confirmed by early virological testing, should not receive BCG at birth
    - Vaccination should be delayed until ART has been started and the infant is confirmed to be immunologically stable (CD4% over 25% in children aged under 5 years; CD4 count of 200/mm3 or higher in children aged over 5 years)
- Neonates born to women with **bacteriologically confirmed PTB** who do not have TB symptoms should receive TPT after exclusion of TB disease
- The infant should be regularly followed up and monitored for the development of symptoms and signs suggestive of TB. If the infant remains asymptomatic and is HIV-negative, BCG vaccination should be provided using a normal infant dose 2 weeks after completion of the full course of TPT
- Contraindication for BCG
    - Pregnancy;
    - People living with HIV but not on ART, or on ART but not immunologically stable;
    - People with other forms of immunosuppression (e.g. candidates for organ transplants, people on immunosuppressive therapy)

8.4.2. TB prevention treatment

KEY FACTS

- TB infection is defined as a state of persistent immune response to stimulation by M. tuberculosis antigens without evidence of TB disease
- The number of people worldwide estimated to have M. tuberculosis infection is 1.7 billion
- 7.5 million children aged under 15 years are estimated to be infected with TB every year
- On average, 5-10% of people with TB infection develop TB disease over the course of their lives, usually within the first 5 years after initial infection
- The risk for TB disease after infection is particularly increased among young children
- The efficacy of currently available TPT regimens ranges from 60% to 90%
- The potential benefit of TPT needs to be balanced against the risk for drug-related adverse events
- For people with TB infection in population groups with a high risk for progression to TB disease, the benefits of TPT are greater than the potential harms
- Children and adolescents with increased likelihood of exposure to TB, including household contacts of people with bacteriologically confirmed TB and those living or working in institutional or crowded settings

Infants' children and adolescents living with HIV:

- Adults and adolescents living with HIV who are unlikely to have active TB should receive TB preventive treatment as part of a comprehensive package of HIV care. Treatment should be given to those on antiretroviral treatment, to pregnant women, and to those who have previously been treated for TB, irrespective of the degree of immunosuppression and even if LTBI testing is unavailable. (**Strong recommendation, high certainty in the estimates of effect**)
- Infants aged under 12 months living with HIV who are in contact with a person with TB and who are unlikely to have TB disease on an appropriate clinical evaluation or according to national guidelines should receive TB Preventive Treatment (**strong recommendation, moderate certainty in the estimates of effect**)
- Children aged 12 months and over living with HIV who are considered unlikely to have TB disease on an appropriate clinical evaluation or according to national guidelines should be offered TPT as part of a comprehensive package of HIV prevention and care if they live in a setting with high TB transmission, regardless of contact with TB (**strong recommendation, low certainty in the estimates of effect**)
- All children living with HIV who have successfully completed treatment for TB disease may receive TPT (**conditional recommendation, low certainty in the estimates of effect**)
- Household contacts (regardless of HIV status): Children aged under 5 years who are household contacts of people with bacteriologically confirmed PTB and who are found not to have TB disease on an appropriate clinical evaluation or according to national guidelines should be given TPT, even if TB infection testing is unavailable (**strong recommendation, high certainty in the estimates of effect**)
- Children aged 5 years and over and adolescents who are household contacts of people with bacteriologically confirmed PTB who are found not to have TB disease by an appropriate clinical evaluation or according to national guidelines may be given TPT (**conditional recommendation, low certainty in the estimates of effect**)
- In selected high-risk household contacts of people with MDR-TB, TPT may be considered based on individualized risk assessment and a sound clinical justification (**conditional recommendation, very low certainty in the estimates of effect**)

Note:

1. Malawi does not recommend TPT for contacts of Drug Resistant TB under any circumstances
2. All TB contacts should be evaluated for TPT regardless of previous TPT or TB treatment

Household contacts

- Children aged under 5 years who are **household contacts of people with bacteriologically confirmed TB** have a significantly higher risk of acquiring TB infection and progressing rapidly to TB disease.
- Children aged under 2 years are also at particularly high risk for severe and disseminated forms of TB with a very high risk of morbidity and mortality.
- TPT is strongly recommended in all TB household contacts aged under 5 years once TB disease is ruled out.
- Other household contacts are also at increased risk of acquiring TB infection compared with the general population and should be considered for the programmatic management of TPT.
- TPT should be considered only **after TB disease has been ruled out by a clinical evaluation or according to national guidelines and after a careful risk assessment**, including intensity of exposure, certainty of the source of disease, reliable information on the drug resistance pattern of the source case, and potential adverse drug reactions.

Children aged < 5 years who are household contacts of people with **bacteriologically confirmed pulmonary TB** and who are found not to have active TB on an appropriate clinical evaluation or according to national guidelines should be given TB preventive treatment even if LTBI testing is unavailable. (**Strong recommendation, high certainty in the estimates of effect**)

Children aged ≥ 5 years, adolescents and adults who are household contacts of people with **bacteriologically confirmed pulmonary TB** who are found not to have active TB by an appropriate clinical evaluation or according to national guidelines may be given TB preventive treatment. (**Conditional recommendation, low certainty in the estimates of effect**)

Ruling out TB

- Adults and adolescents living with HIV should be screened for TB according to a clinical algorithm
- Those who do not report any of the symptoms of current cough, fever, weight loss or night sweats are unlikely to have TB disease and should be offered preventive treatment, regardless of their antiretroviral therapy status (**strong recommendation, moderate certainty in the estimates of effect**)
- Adults and adolescents living with HIV who are screened for TB according to a clinical algorithm and who report any of the symptoms of current cough, fever, weight loss or night sweats may have TB disease and should be evaluated for TB and other diseases and offered preventive treatment if TB disease is excluded (**strong recommendation, moderate certainty in the estimates of effect**).

  Chest X-ray may be offered to people living with HIV and on antiretroviral therapy and preventive treatment given to those with no abnormal radiographic findings (conditional recommendation, low certainty in the estimates of effect).
- Infants and children living with HIV who have poor weight gain, fever, or current cough or who have a history of contact with a person with TB should be evaluated for TB disease and other diseases that cause such symptoms. If TB disease is excluded after an appropriate clinical evaluation or according to national guidelines, these children should be offered preventive treatment, regardless of their age (strong recommendation, low certainty in the estimates of effect)
- The absence of any symptoms of TB and the absence of abnormal CXR findings may be used to rule out TB disease among HIV-negative household contacts aged 5 years and over and other at-risk groups before preventive treatment (conditional recommendation, very low certainty in the estimates of effect)
- **HIV-negative household and close contacts of a person with pulmonary TB:**
  Infants and children aged under 5 years Children aged under 5 years who are household contacts of a person with bacteriologically confirmed PTB are usually identified through contact investigation or visits to health care facilities
- They should be screened for TB symptoms (current cough, fever, not eating well or anorexia, weight loss or failure to thrive, fatigue, reduced playfulness, decreased activity)

- Those with any one of the symptoms should be evaluated for TB disease, while those who are asymptomatic should be offered TPT. **HIV-negative household and close contacts of a person with pulmonary TB**: children and adolescents aged 5 years and over

Target group	Preferred regimen	Alternative regimen	Notes
HIV-negative children aged ≤2 year	3HR if paediatric fixed-dose combination (FDC) an available	If paediatric FDC not available, use 6H (preferably dispersible tablets) There is a lack of data on appropriate doses of rifapentine to allow use of 3HP in children aged <2 years	There is a lack of data on appropriate doses of rifapentine to allow use of 3HP in children aged
HIV-negative children aged ≥2 years and ≤25 kg body weigh	3HP if Child-friendly formulation is available	If paediatric FDC not available, use 3RH or 6H	A child-friendly rifapentine is available and can be used with isoniazid to form 3HP paediatric FDC for rifapentine and isoniazid is not planned for development
Children living with HIV>2 years	3HP using dispersible formulations	Invasive High level of discomfort Requires fasting Requires consumables and trained personnel	For more details on TPT regimens to use with ART, see Section 7.1 Data on 3HP in children on DTG are not yet available
Adolescents living with HIV	3HP if on TDF, EFV, DTG or RALbased ART	1HP (age ≥13 years) if on TDF, EFV, DTG or RAL-based ART 6H	For more details on TPT regimens to use with ART, see Section 7.1 (including dose adjustments for 1HP with DTG or RAL)

Table 8.4-1 TB preventive treatment options

8.5. Treatment of Paediatric Tuberculosis

8.5.1. Treatment of Drug-susceptible pulmonary TB in children

PRINCIPLES OF TREATMENT

- 2-month intensive phase should be followed by a continuation phase of 2-4months
- Non-severe TB is defined by WHO as peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion or paucibacillary, non-cavitary disease confined to one lobe of the lungs and without a miliary pattern
- Children and adolescents with severe TB should be treated with a standard treatment regimen (2HRZE/4HR)
- Infants 0-3months with suspected or confirmed pulmonary TB should be treated with 6-month regimen (2HRZE/4HR)
- Children gain weight while on TB treatment and dosages need to be adjusted

Age and severity of TB	Intensive Phase	Continuation Phase
Infants aged < 3 mo or weight < 3kg	2 HRZE	4 HR
Children 3 mo to 12 years	2 HRZE	2 HR
Adolescents 12-<16 years	2 HRZE	2 HR
Adolescents age 16-20	2 HRZE	4 HR

Table 8.5-1 Treatment of Drug-Susceptible Non-Severe Pulmonary TB

Eligibility Criteria For 4-month regimens in children/adolescents 3 months-16 years

- (non-severe TB determination will be done where there is a capacity for Xray and ability to differentiate severe/non-severe TB & this will be determined by the program periodically)
- Chest x-ray with non-severe TB
  - Intrathoracic lymph node TB w/o significant airway obstruction
  - PTM in one lobe, no cavities or miliary pattern
  - uncomplicated pleural effusion (no pneumothorax or empyema)
  - TB that is negative, trace, very low or low using Xpert MTB/RIF or Ultra, or sputum smear-negative (if Xpert MTB/RIF or Ultra not available)
- Mild TB symptoms not requiring hospitalization

*In settings without access to CXR, a 4-month treatment regimen should be implemented in children and adolescents meeting all of the following three criteria:

TB that is negative or smear-negative, trace, very low or low by Xpert MTB/RIF or Ultra.

Age and severity of TB	Intensive Phase	Continuation Phase
Infants aged < 3 mo or weight < 3kg	2 HRZE	4 HR
Children 3 mo to < 12 years	2 HRZE	4 HR
Adolescents 12-15 years	2 HRZE	4 HR
Adolescents age 16-20	2 HRZE	4 HR

Table 8.5-2 Pulmonary TB Treatment of Severe Disease

8.5.1.1. Treatment of Drug-Susceptible Extrapulmonary TB in Children and Adolescents

Age	Intensive Phase	Continuation Phase
Infants aged < 3 mo or weight < 3kg	2 HRZE	4 HR
Children 3 mo to 16 years	2 HRZE	2 HR
Children and adolescents age>16	2 HRZE	4 HR

Table 8.5-3 Treatment of Drug-Susceptible Peripheral Lymph Node TB

TREATMENT OF TB MENINGITIS AND OSTEOARTICULAR DISEASES

Age	Intensive Phase	Continuation Phase	Condition
Children and adolescents 0-19 years	2 HRZE	10 HR	TB meningitis
*Alternative	6HRZE		TB meningitis
Children and adolescents 0-19 years	2 HRZE	10 HR	Osteoarticular disease

Table 8.5-4 Regimen for TB meninges and Osteoarticular diseases

- The alternative regimen could be considered in children with no drug resistance or low likelihood of resistant TB and who are HIV negative
- Children under 2 years with miliary TB should be evaluated for TB meningitis regardless of CNS symptoms
- If children under 2 years are not evaluated for TB meningitis, consider extension of treatment for 12 months

Medicine	Dose (mg/kg)	Range (mg/kg), max dose
Isoniazid (H)	10	7-15
Rifampin (R)	15	10-20
Pyrazinamide (Z)	35	30-40
Ethambutol (E)	20	15-25

Table 8.5-5 Paediatric TB Drug Dosing Recommendations for children and young adults 0-14 years (excluding the alternative 6-month intensive TB meningitis treatment)

Medicine	Recommended dose range in the interim dosing strategy (mg/kg body weight)
Isoniazid (H)	15–20 a
Rifampicin (R)	22.5–30
Pyrazinamide (Z)	35–45
Ethionamide (Eto)	17.5–22.5

Table 8.5-6 Recommended interim dosing for the 6-month intensive regimen (6HRZEto) to treat drug-susceptible TB meningitis in children and adolescents.

Weight (Kg)	Intensive Phase (R50/H75/Z150mg)	Ethambutol (E) 100 mg	Continuation Phase (HR) 50/75mg
4-<8	1	1	1
8–<12	2	2	2
12–<16	3	3	3
16–<25	4	4	4
≥25 Adult dosages recommended**			

Table 8.5-7 Fixed Dosed Combination for first line TB

Pyridoxine Supplementation

- Pyridoxine (vitamin B6) supplementation is recommended for all children and adolescents on TB treatment or IPT.
- Supplementation with B6 is to prevent pyridoxine deficiency which can be present as peripheral neuropathy.
- Children with HIV and severe malnutrition are especially vulnerable.
  - Dose 0.5-1mg/kg/day
  - 0-25kg ½ 25 mg tablet or ¼ 50mg tablet
  - Pyridoxine doses can be increased to 2-5mg/kg/day if peripheral neuropathy develops.

Recommendations for use of Corticosteroids in TB Meningitis and TB Pericarditis

- Steroids are recommended for use in all children with TBM
- Steroids should be tapered over 6-8 weeks

Drug	Dose Range (mg/kg/day)	Maximum Dose (mg)
Prednisolone	2-4 mg/kg	60 mg
Dexamethasone (alternative)	0.3-.0.6 mg/kg	2

Table 8.5-8 Steroid for TB meningitis and pericarditis

8.5.1.2. Management of Adverse Events from Drugs Used to Treat Drug-Susceptible TB

Monitoring TB Treatment

- Monitor for resolution of TB symptoms and side-effects of medications
- Measure weight and adjust dosages accordingly
- Assess adherence with patient and caregivers/treatment supporters
- **Follow-up smear microscopy 2 months after the start of treatment in children with Xpert MTB/RIF-positive, Xpert Ultra-positive, smear-positive, or culture-positive at diagnosis**
- If the follow-up smear is positive, investigate for drug resistance
- **For children that can provide sputum, a follow-up specimen at the end of treatment is not needed if a 2-month sample at 2 months is negative**
- Symptomatic improvement and weight gain may be more valuable markers of improvement

Return to school

- Most children with TB are not infectious and can return to school when they are on treatment and feeling better
- Older children and adolescents and younger children with positive bacteriological tests should not attend school until they have been on TB treatment for at least 2 weeks, adherence is confirmed and there is clinical improvement

Treatment Failure

Definition: when TB treatment is permanently stopped or changed to a new regimen.

Potential reasons for failure:

- No clinical or bacteriologic response
- Adverse drug reactions
- Evidence of resistance to the medications

Reasons to suspect failure:

- Child has no symptom resolution or worsening of symptoms
- Continued weight-loss
- Child is smear-positive at 2-month follow-up
- Is the dosage correct?
- Is the child or adolescent taking the medicines as prescribed (good adherence)?
- Is it possible that the child or adolescent has poor gastrointestinal absorption of the medicine?
- Does the child or adolescent have medicine toxicity?
- Is the child or adolescent living with HIV? If so, has the child or adolescent developed IRIS or other opportunistic infections?
- Is the child or adolescent severely malnourished, and is SAM managed appropriately?
- Is there a reason to suspect DR-TB (index patient has DR-TB or is not responding to treatment)?
- Is there a reason for the illness, other than or in addition to TB?

8.5.2. Treatment Interruption

Treatment Failure and Retreatment

Potential Side Effects with Drug-Susceptible TB Treatment

- Adverse events caused by TB medications occur left often in children than adults
- Hepatoxicity can be caused by isoniazid, rifampicin, or pyrazinamide is the most important adverse event to monitor for
- Children preventing with liver tenderness, hepatomegaly, persistent nausea, vomiting, loss of appetite, jaundice should have ALT, AST, and TB drawn when possible.

When to stop TB therapy:

- When liver enzymes (ALT, AST) are more than five times the upper limit of normal or more than 3 times the upper limit of normal with symptoms of hepatitis
- After liver function tests ALT and total bilirubin are less than 2 times the upper limit of normal, ethambutol and rifampicin can be reintroduced
- If there is no worsening of liver function tests isoniazid can be added, with repeating of liver function tests in 3-7 days
- Pyrazinamide should not be reintroduced. Treatment with isoniazid, rifampicin, and ethambutol should be continued for a total of 9 months.
- If liver hepatoxicity occurs in the continuation phase, NTP should be notified for further consultation.

Peripheral Neuropathy:

- In young children, this could present as failure to walk or gait change
- See the section on pyridoxine supplementation for treatment

Optic Neuritis:

- If a patient develops optic neuritis on ethambutol- ethambutol should be stopped for the remainder of the regimen

Retreatment of TB in Children

- Children requiring TB retreatment, category II regimen should no longer be used
- Children with relapse or reinfection should have a rapid molecular test to evaluate for rifampicin resistance

8.5.3. Treatment of Multi-drug Resistant and Rifampicin Resistant TB

Identify which children should be treated for MDR-TB:

- Children with a bacteriologic diagnosis of MDR-TB should be started on WHO-recommended treatment regimen
- Children can be diagnosed with MDR-TB clinically if the child had a clinical diagnosis of TB and either exposure to a known case of MDR/RR-TB or the presence of other risk factors for MDR/RR-TB (child previously treated for TB or exposed to a source case who died from TB or failed TB treatment)
- Children with clinically diagnosed MDR/RR-TB should be started on treatment without delay and efforts to confirm diagnosis bacteriologically should be made
- Treatment of children and adolescents with clinically diagnosed MDR/RR-TB should be guided by the DST results and the history of exposure to TB medicines of the most likely MDR/RR-TB source case
- If a child or adolescent has a positive culture for M. tuberculosis MDR/RR-TB they should be treated based on the DST of the isolate

Drug resistant TB management in children

- Children with drug-resistant TB generally have initial resistance transmitted from a primary case with drug-resistant TB. The treatment of culture-negative children with clinical evidence of active TB disease and a contact with a documented case of drug-resistant TB should be guided by the results of DST and the history of the contact's exposure to anti-TB drugs.
- Monthly weights should be taken and dosage adjustment of medications should take place based on weight Dosing of DR-TB drugs in paediatric and adolescents is given.
- There should be special attention to adherence and psychosocial support for children and adolescents on DR-TB treatment regardless of regimen selection.
- Decisions on treatment duration in children, if unable to be determined from bacteriologic results, should be based on clinical improvement or standard durations.

Use of Bedaquiline in children

In children with MDR/RR-TB, an all-oral treatment regimen containing Bedaquiline may be used for shorter (9-month) and longer regimens containing Bedaquiline.

- All-oral modified Bedaquiline-containing regimen of 9–12 months duration is recommended in eligible patients with confirmed multidrug- or rifampicin-resistant tuberculosis (MDR/RR-TB)
  - Who have not been exposed to treatment with second-line TB medicines used in this regimen for more than 1 month, and in whom resistance to fluoroquinolones has been excluded
- Bedaquiline can therefore be used in children of all ages to treat MDR/RR-TB

Use of delamanid in children

- In children with MDR/RR-TB aged below 3 years Delamanid may be used as part of longer regimens
- Delamanid may be included in the treatment of MDR/RR-TB patients aged 3 years or more on longer regimens
- A modified 9-month all oral treatment regimen with Delamanid is an option of choice for children of less than 6 years of age depending on eligibility (i.e drug-drug interaction) and avoidance of pill burden in Bedaquiline based 9-month treatment regimen
- Refer to Section 10 - page 89 for an understanding on the delamanid based regimens

Longer individualized regimens for children with multidrug-resistant and rifampicin-resistant TB who are not eligible for the standardized all-oral treatment regimens. Also refer to Section 10 - page 89 for an understanding on individualized regimens.

- These children should be treated with longer, individualized regimens

PRACTICAL APPROACH TO DESIGNING INDIVIDUALIZED MULTIDRUG-RESISTANT AND RIFAMPICIN-RESISTANT TB TREATMENT REGIMENS

FQ Susceptibility	Regimen	Additional Medicines
FQ-Susceptible	Bdq–Lfx–Lzd–Cfz-(Cs)	Cs, Dlm, PAS, Eto, (E, Z)
FQ-Resistant	Bdq–Lzd–Cfz–Cs– (Dlm) e	Dlm e, PAS, Eto,(E, Z)
FQ-resistant and bedaquiline- (+/-) clofazimine resistant	Lzd–Cs–Dlm e–E–Z d	Mpm/Clav, Eto, PAS

Table 8.5-9 Possible individualized multidrug-resistant and rifampicin-resistant TB treatment regimens for children of all ages and adolescents, by fluoroquinolone resistance and disease severity

Bdq: Bedaquiline; Cfz: clofazimine; Cs: Cycloserine; Dlm: delamanid; E:ethambutol; Eto: ethionamide; FQ: fluoroquinolone; Lfx: levofloxacin; Lzd: linezolid; Mpm/Clav: meropenem–clavulanate; PAS: P-aminosalicylic acid; Z: pyrazinamide.

Special Considerations: TB Meningitis in MDR/RR-TB

- Children/adolescents with severe forms of EP MDR/RR-TB are not eligible for short all-oral Bedaquiline-containing regimen as in adults.
- Treatment of MDR/RR-TBM should be guided by the ability of the medicines to cross the blood–brain barrier and resulting CSF concentrations, where this is known (Table 8.5-10).

Medicine	CSF penetration
Levofloxacin, moxifloxacin, linezolid, cycloserine, ethionamide, meropenem, pyrazinamide	Good penetration
Isoniazid in presence of isoniazid resistance, P-aminosalicylic acid, amikacin	Poor penetration, except in presence of meningeal inflammation
Ethambutol	Poor penetration
Bedaquiline, delamanid, clofazimine	Limited data available

Table 8.5-10 Cerebrospinal fluid penetration of TB medicines used for the treatment of multidrug-resistant and rifampicin-resistant TB

8.5.4. TB/HIV Coinfection in treatment of MDR/RR TB Treatment

- A similar approach to designing MDR/RR_TB regimens should be used for all children regardless of HIV status.
- All potential drug-drug interactions should be avoided
- The most significant drug-drug interaction with ART is with Bedaquiline
- ART regimens with integrase inhibitors such as DTG are the best option for children living with HIV receiving Bedaquiline, as clinically significant drug–drug interactions are not expected
- ART regimens that contain EFV should be avoided in children and adolescents while they are on Bedaquiline, as EFV substantially lowers the concentrations of Bedaquiline. If EFV based regimen cannot be avoided then Delamanid should be used instead of Bedaquiline
- Other options for children living with HIV on ART receiving Bedaquiline are:
  - LPV/r – co-treatment with LPV/r may result in elevated Bedaquiline exposures, but experience has not shown this to result in an increase in adverse effects, so this may be considered with careful monitoring
  - NVP – the reduced efficacy of NVP-containing regimens means this is not an ideal choice when other

options are available and as, indicated above, substitution with EFV is not an option

- Triple nucleoside reverse-transcriptase inhibitor (NRTI) regimen – this is not recommended routinely if there are other options, especially if the viral load is high, as this regimen has reduced potency

Monitoring of children and adolescents on multidrug-resistant and rifampicin-resistant TB treatment

- Children/adolescents should be monitored regularly to treatment failure, adverse events, adherence/ psychosocial support/financial support

Once on MDR/RR-TB treatment, children and adolescents must be monitored regularly to evaluate their response to treatment; identify treatment failure early; monitor for adverse events; and provide adherence, psychosocial and financial support to children and their caregivers.

8.5.5. Treatment of TB in children and adolescents living with HIV

- Children living in settings where the prevalence of HIV is high or who are living with HIV should be treated for TB with a four-medicine regimen (isoniazid, rifampicin, pyrazinamide and ethambutol) for 2 months followed by a two-medicine regimen (isoniazid and rifampicin) for 4 months or 2 months (for non-severe TB) at standard dosages given daily
- The child should be assessed 2 weeks after the start of TB treatment and then reviewed monthly with clinical monitoring, which should include symptom assessment, weight measurement, assessment of adherence to treatment, and inquiry about any adverse events. Dosages of TB medicines should be adjusted to account for any weight gain

Co-trimoxazole preventive therapy

- Co-trimoxazole is a broad-spectrum antimicrobial medicine that prevents a range of secondary bacterial and parasitic infections in eligible people living with HIV.
- Daily prophylaxis with CPT prolongs survival and reduces the incidence of comorbidities in children living with HIV.
- It also reduces the risk of coinfections such as pneumocystis pneumonia in infants exposed to HIV.
- CPT is recommended for all HIV-exposed infants and children living with HIV, including those with TB

Antiretroviral therapy: Timing of antiretroviral therapy

- ART should be started as soon as possible within two weeks of initiating TB treatment, regardless of CD4 count, among adolescents and children living with HIV (except when signs and symptoms of meningitis are present)
- In children and adolescents living with HIV with TBM, ART should be delayed at least 4 weeks after treatment for TBM is initiated and initiated 4–8 weeks after starting TB treatment
- The recommendation on the use of adjuvant corticosteroid therapy with dexamethasone or prednisolone (tapered over 6–8 weeks) also applies to children and adolescents living with HIV with TBM

Age	Preferred first-line regimen, including initiation while on TB treatment	Alternative first-line regimen	Special circumstances
Neonates	AZT + 3TC + RAL b	AZT + 3TC + NVP	AZT + 3TC + LPV/r c
Children	ABC + 3TC + DTG d	ABC + 3TC + LPV/r TAF + 3TC (or FTC) + DTG e	ABC + 3TC + EFV (or NVP) ABC + 3TC + RAL f AZT + 3TC + EFV g (or NVP) AZT + 3TC + LPV/r (or RAL)
Adolescents	TDF + 3TC (or FTC) + DTG h	TDF + 3TC + EFV 400 mg i	TDF + 3TC (or FTC) + EFV 600 mg i AZT + 3TC + EFV 600 mg i TDF + 3TC (or FTC) + PI/r i TDF + 3TC (or FTC) + RAL TAF j + 3TC (or FTC) + DTG ABC + 3TC + DTG h

Table 8.5-11 Preferred and alternative first-line antiretroviral therapy regimens for neonates, children and adolescents on TB treatment

Adjustments to antiretroviral therapy regimens with TB treatment

In people with TB/HIV coinfection, the dose of DTG needs to be doubled by giving it twice instead of once a day because of drug–drug interactions with rifampicin.

This extra dose of DTG is well tolerated, with equivalent efficacy in viral suppression and recovery of CD4 cell count compared with EFV

8.5.6. Management of asymptomatic neonates of mothers with TB

- TB disease should be excluded in neonates born to women with presumptive or confirmed TB.
- The level of infectiousness and drug susceptibility in the mother should be determined.
- Breastfeeding should be continued, and the mother advised to wear a surgical mask when close to the baby
- While screening for TB disease or TB infection is ongoing, BCG should be postponed in neonates exposed to TB;
- Neonates born to women with bacteriologically confirmed PTB and who are well should receive preventive treatment once TB disease has been excluded. BCG vaccination should be delayed until after completion of TPT
- 3HR using the child-friendly HR 50/75 mg FDC is a good option for infants who have not been exposed to HIV, but consultation with a neonatal specialist is advised
    - If the infant has been exposed to HIV and is on NVP, IPT should be started. Infants on TPT should receive pyridoxine 5–10 mg/day
- They should be regularly followed up and monitored for the development of symptoms and signs suggestive of TB. If the infant remains asymptomatic after completion of TPT If TST or IGRA is negative or not available, and the infant is HIV-negative
    - BCG vaccination should be provided using a normal infant dose, 2 weeks after completion of the full course of TPT
- If the mother is non-infectious, the infant should be screened for TB. If there is no evidence of TB disease, the infant should be followed up regularly to ensure TB disease does not develop, and TPT should be considered

9. TB Infection Control

9.1. Introduction

Nosocomial transmission of TB is a major problem in healthcare facilities. This is because persons with undiagnosed and potentially infectious TB mix with others, including those with HIV infection.

Persons with HIV-associated immunosuppression may become infected or re-infected with TB if they are exposed to someone with infectious TB disease and they can progress rapidly from TB infection to disease. Healthcare workers and other staff are also at particularly high risk of infection with TB when frequently exposed to patients with infectious TB disease. It is therefore important to reduce the risk of TB transmission in healthcare facilities by applying control measures.

The interventions described below should not be implemented individually or in a way that dissociates them from other administrative and environmental controls, and personal protection; rather, they must be considered as an integrated package of IPC interventions to prevent M. tuberculosis transmission.

Effective IPC measures are a critical part of the quality of health service delivery to achieve people-centered, integrated universal health coverage.

9.2. Managerial activities

- These activities serve to achieve the first objective to strengthen coordination of implementing, and monitoring appropriate TB infection prevention and control (IPC) measures and standards
- Each healthcare facility must have a functioning multidisciplinary IPC committee. TB-IPC measures fall under this committee. As a minimum requirement, at least one member must have a TB background and training on TB-IPC. These guidelines do not attempt to create a parallel programme exclusively dedicated to TB IPC; instead, they emphasize the importance of building integrated, well-coordinated, multisectoral action toward TB infection control across all levels of care
- Training of staff on standard precautions and transmission-based precautions is essential

Training on airborne precautions should include the following:

- Basic concepts of TB transmission and pathogenesis, i.e. the difference between infection and disease;
- Risk of TB transmission to HCW;
- Symptoms and signs of TB;
- Impact of HIV infection on increasing risk of developing TB disease and the importance of TB as a major cause of disease and death in PLHIV;
- Importance of the facility IPC plan and the responsibility that each staff member must implement and maintain TB-IPC practices;
- Specific TB-IPC measures, standards, procedures, and SOPs that reduce the likelihood of transmitting TB;
- Specific checklists to monitor compliance with TB-IPC standards
- Renovating buildings or rearranging the use of available spaces and placement of furniture to optimise the implementation of TB-IPC measures is also crucial

9.3. Administrative controls

Administrative control measures serve as the first line of defence against the spread of TB. These key measures comprise specific interventions aimed at reducing exposure and therefore reducing transmission of M. tuberculosis.

They include triage and patient separation systems (i.e. management of patient flows to promptly identify and separate presumptive TB cases), prompt initiation of effective treatment, and respiratory hygiene.

Early identification of patients with presumptive or bacteriologically confirmed infectious TB disease (triage) is the first in administrative control.

- A healthcare worker should be assigned to screen patients with a cough of two weeks or more immediately after they arrive at the facility and before they enter an enclosed space
- After triaging, patients with chronic cough (>2 weeks) should be educated on cough etiquette
- Education on proper cough etiquette should be given routinely to patients with presumptive or confirmed TB. Respiratory hygiene has been encouraged to reduce the dispersal of respiratory secretions that may contain infectious particles and has been used as an additional measure to prevent M. tuberculosis transmission
- Face masks should be provided to patients with chronic cough
- All patients with presumptive pulmonary TB should be fast-tracked (to avoid queuing), separated (to avoid mixing with other patients in crowded, poorly ventilated enclosed areas), placed near a window for good ventilation or separated/isolated from other patients without respiratory symptoms at a separate outdoor waiting area or part in the ward, or referred to a higher-level health care facility

9.4. Environmental controls

To reduce the risk of transmission of M. tuberculosis, air can be made less infectious through the use of three principles: dilution, filtration, and disinfection. Environmental controls are aimed at reducing the concentration of infectious droplet nuclei in the air.

Environmental control measures include the following:

Ventilation (natural, mixed-mode, and mechanical) systems;

- Natural ventilation relies on open doors and windows to bring in air from the outside. Natural ventilation will help to dilute the concentration of contaminated air in a room.
- This implies that IEC materials such as posters and window stickers are displayed as reminders and daily checks (up-to-date log books) are in place to make sure doors and windows are maintained in an open position to enhance ventilation.
- Unrestricted openings (that cannot be closed) on opposite sides of the room provide the most effective natural (cross) ventilation. Ideally, the unrestricted opening area should be 20% of the floor area.
- Electrical fans and wind-driven roof turbines – **"Whirlybirds"** – used for mixed-mode ventilation systems may assist, not only in providing comfort but also in mixing the air and controlling the direction of airflow.

Mechanical ventilation systems;

- These may be useful in specialized, identified high-risk TB containment laboratories where liquid culture procedures and drug susceptibility testing are conducted.

Filtration;

- Highly Efficient Particulate Air (HEPA) filter units are applied in mechanical ventilation systems and bio-safety cabinets (BSC) filtering out infectious particles.

GUV (Germicidal ultraviolet) systems

- In high-risk settings where optimal ventilation cannot be achieved through natural or mechanically-aided means, properly designed, placed, and maintained shielded GUV units should be considered as an effective control measure. Upper-room germicidal ultraviolet (GUV) systems are recommended to reduce M. tuberculosis transmission.

Personal Protective Equipment (PPE)

- Respiratory protection controls are designed to further reduce the risk of exposure to M. tuberculosis (and other airborne pathogens) for health workers in special areas and circumstances. The recommendations given here are aimed at strengthening these controls and preventing the inadequate implementation of respiratory protection programmes that may lead to a false sense of security and therefore increase the risk to healthcare staff
- Respirators are the last line of defence against TB infection. These are recommended for healthcare workers when caring for patients with presumptive or confirmed infectious TB. Respiratory protection is particularly needed during the performance of specific aerosol-generating procedures, to supply the desired level of safety
- The main limitation of respirators is that they may not be practical to always wear, and they are often not used when unsuspected (untreated) TB patients are being seen. Personal protective equipment is aimed at reducing the risk of inhaling infectious MTB containing particles
- Respiratory protection controls refer to the selection, fit testing, training, and use of respirators. Respirators protect HCWs from inhaling MTB. Supervisors should reinforce compliance with their correct use and should ensure that they are always available, as per TB-IPC facility assessment and plan (refer to SOP on use of respirator)

10. Drug resistant tuberculosis

10.1. Introduction to drug-resistant TB

The main reasons for the development of DR-TB under programmatic conditions are:

- On-going transmission of resistant strains from person to person
- Inadequate treatment leading to direct or indirect monotherapy
  - The potential causes of inadequate treatment can be categorized in to:
    - Health care factors (Provider and program related factors)
    - Drug related factors (Expired drugs and poorly stored drugs)
    - Patient related factors (Poor drug adherence and rate of drug denaturation)

There are four principal ways to prevent drug-resistant TB:

1. Early detection and high-quality treatment of drug-susceptible and drug resistant TB;
2. Good TB infection control measures to minimise the risk of TB transmission within populations;
3. Health system strengthening, regulation and access to TB diagnostics and drugs;
4. Addressing underlying risk factors and social determinants of TB.

10.2. Overall services arrangement for programmatic management of drug-resistant TB

10.2.1. DR-TB service arrangement

- **DR-TB referral centres:** These are central referral hospitals (where available) responsible for managing of complicated RR-/MDR-/XDR-TB patients. The referring facilities should call those centres notifying them of those complicated cases before referring the patients.
- **DR-TB registration sites (treatment initiating centres):** These are district hospitals which are responsible for initiating second-line TB treatment services for DR-TB for ambulatory patients. They are also responsible to report the DR-TB data to the appropriate department.
- **DR-TB treatment follow-up sites:** These are health facilities located close to the homes of the DR-TB patients that provide such services.
- **Community volunteers:** During home visits, community volunteers are responsible for referring family members of confirmed drug-resistant TB patients' health facilities for contact investigation.
- **Culture /DST facilities:** These are responsible for receiving and processing DR-TB sputum from peripheral sites and providing the results to the referring health facilities as per the specified turnaround time. They also provide follow-up culture tests for confirmed DR-TB patients enrolled on second-line treatment.
- **TB microscopy centres:** responsible for performing monthly follow-up sputum microscopy for DR-TB patients on treatment.
- **Health facilities with Xpert services:** Xpert sites are responsible for processing samples received from sites where Xpert MTB/RIF technology is not yet available and providing the results to the requesting facility as per the specified turnaround time.

10.2.2. Minimum requirements for health facilities for RR-/MDR-TB treatment

Criteria	DR-TB referral site	DR-TB registration and treatment site	DR-TB treatment follow up site
DR-TB team: Programmatic management of drug-resistant TB (PMDT) training	1 medical doctor, 2 clinical officers, 2-3 DR-TB nurses, 1 lab personnel, 1 pharmacy personnel, 1 environmental health officer (EHO), radiology personnel, eye clinician and data officer.	1 medical doctor, 1 clinical officer, 1 nurse, 1 TB officer, 1 lab personnel, 1 pharmacy personnel, 1 environmental health officer (EHO), eye clinician and data officer.	1 clinical officer or medical assistant, 1 nurse, 1 TB officer, 11 lab personnel, 1 pharmacy personnel, 1 H S A or AEHO, DOT supporters
DR-TB outpatient services	2 exam rooms, 1 DOT clinic, dispensary and sample processing area	1 exam room, 1 nutrition and psychosocial assessment room, one DOT clinic and sample collection area	1 DOT clinic integrated with drug susceptible TB and with minimum infection control requirements
DR-TB inpatient service	Separate male and female DR TB wards with isolation room for management of severely ill patients	Short-term separate male and female admission rooms to stabilise and monitor patients in the medical ward	N/A
Designated patient waiting area	Separate waiting area for DR-TB patients/cases	Separate waiting area for DR-TB patients	Required
Respirator	At least N-95 respirators per person, surgical masks per patient.	At least N-95 respirators per person, and surgical masks per patient.	At least N-95 respirators per person, and surgical masks per patient.
Xpert MTB/RIF Ultra or MTB/XDR	Required	Required	Required
Laboratory monitoring tests	ZN/FM, FBC, chemistry, electrolytes test, blood sugar level, pregnancy test.	ZN/FM, FBC, chemistry, electrolytes test, blood sugar level, and pregnancy test.	ZN/FM
Patient Clinical review/ Clinical mentoring support	Every month organized by DRTB team at the hospital Visual acuity and color discrimination screening X-ray machine ECG machine Mentoring support to follow-up site every quarter by representatives from DR-TB team	Every month organized by DRTB team at the hospital Visual acuity and color discrimination screening X-ray machine ECG machine Mentoring support to follow-up site every quarter by representatives from DR-TB team	Participate in the clinical review seminar and discuss patient management and challenge Receive mentorship from DR-TB registration and treatment site.

Criteria	DR-TB referral site	DR-TB registration and treatment site	DR-TB treatment follow up site
Clinical review meeting monthly.	Present clinical cases of special interest; share knowledge on case management	Present clinical cases of special interest; share knowledge on case management	Participate in the clinical review meeting and discuss patient management and challenge
Clinical review meeting bimonthly.	Present clinical cases of special interest; share knowledge on case management	Present clinical cases of special interest; share knowledge on case management	Participate in the clinical review meeting and discuss patient management and challenge

Table 10.2-1 Minimum requirements for health facilities for DR-TB treatment

10.2.3. Site level Program Management and Support

10.2.3.1. DR-TB management team (clinical panel team)

All district hospitals need to establish a DR-TB management team to assist the smooth implementation of the DR-TB program and provide appropriate patient care. The DR-TB team should be composed of at least one or more DR-TB clinicians, one or more DR-TB nurses, one laboratory technician, a district TB officer, and a pharmacy technician.

The DR-TB clinical team is responsible for:

- Deciding on treatment initiation and starting regimen;
- Arranging social support for eligible patients;
- Defining treatment outcomes for DR-TB patients
- Providing technical support for treatment follow-up centres regularly;
- Monitoring and managing the adverse effects of drugs;
- Conducting contact tracing and evaluation;
- Providing training to health care workers on DR-TB;
- Timely ordering of second line and ancillary drugs

10.3. Drug-resistant TB case finding strategy

The aim of the drug-resistant TB case finding strategy is to diagnose patients early, initiate them on effective treatment and interrupt the chain of TB transmission in the general population. Due to limitations in resources, universal access to DST is not feasible in TB patients in Malawi.

10.3.1. Presumptive DR-TB /risk groups

According to the national drug resistance survey[3], previously treated patients are 3 times more likely to have DR-TB than new patients. Presumptive DR-TB patients are defined as the following risk groups:

- All patients, who remain smear-positive after 2 months of therapy with first-line drugs;[4]

3 Abouyannis et al. 2014. Drug resistance of Mycobacterium tuberculosis in Malawi: a cross-sectional survey. Bull WHO; 92:798-806. http://www.who.int/bulletin/volumes/92/11/13-126532/en/ Accessed 7 April 2017.

4 WHO. WHO treatment guidelines for drug-resistant tuberculosis.2016 Updates. Accessed on June 13,2017.

- Patients who have had contact with a known DR-TB patient;
- Failure of new TB regimen;
- Symptomatic contacts of a DR-TB patient who died while on directly observed treatment;
- New patients coming from areas with high prevalence of DR-TB;
- Health care workers in hospital/health facility setting;
- Previously treated TB patients
- TB patients returning after loss to follow-up;
- Any TB patients in whom there is significant clinical concern for acquired resistance.

Patients are assigned to a registration group based on the most recent treatment history at the time of collecting the biological specimen that was used to confirm DR-TB. All confirmed drug-resistant TB patients should be treated as per the national guidelines.

	Groups for DST	Remarks
1	Failure of retreatment regimens with first-line anti-TB drugs (HREZ) - (previously known as chronic TB patients)	Patients who are still sputum smear-positive at the end of a retreatment regimen have the highest DR-TB rates of any group, often approaching 90%.
2	Exposure to a known drug-resistant TB patient	Most studies have shown that close contacts of DR-TB patients have very high rates of DR-TB
3	Failure of new TB regimens (HREZ)	Patients who, while on treatment, are sputum smear-positive at month 5 or later are at elevated risk of drug-resistant TB. Not all patients in whom a regimen fails have drug-resistant TB, and the percentage may depend on several factors, including whether rifampicin was used in the continuation phase and whether directly observed therapy was used throughout treatment.
4	Relapse and return after loss to follow-up, without recent treatment failure	Evidence suggests that most relapse patients and those that return after loss to follow-up (without recent treatment failure) do not have drug-resistant TB. However, certain patient histories may point more strongly to possible drug-resistant TB; for example, erratic drug use or early relapses.
5	Exposure in institutions that have drug-resistant TB outbreaks or a high drug-resistant TB prevalence	Patients who frequent homeless shelters, prisoners, and health care workers in clinics, laboratories, and hospitals can have a high risk of drug-resistant TB.
6	Residence in areas with high drug-resistant TB prevalence	Drug-resistant TB rates in some areas can be high enough to justify routine DST in all new TB patients.
7	History of using anti-TB drugs of poor or unknown quality	The percentage of drug-resistant TB caused by use of poor-quality drugs is unknown but considered significant.
8	Treatment in poorly-run programmes (especially with recent and/or frequent drug stock-outs)	These are usually programmes with poor drug management and/or distribution systems.

Table 10.3-1 Priority target groups for DST (DR TB detection)

10.3.2. Diagnosis of drug-resistant TB

- The diagnosis of drug-resistant TB (DR-TB) is done by Sputum on Xpert MTB/Rif, & Xpert Ultra, LPA, DST, Xpert MTB/XDR. Lack of culture conversion by the end of the fourth month of the standardized regimen
- Bacteriological reversion in the continuation phase after conversion to negative among DR-TB patients on second-line drugs
- Evidence of DR-TB treatment failure
- DR-TB patients who return after being lost to follow up

10.3.2.1. TB DR Diagnostic approaches

- All presumptive drug resistant patients are bacteriologically confirmed using either phenotypic or genotypic methods
- The methods of choice for DR-TB are divided into two patterns: Sample qualities and sample flow and feedback (refer to lab section)

Algorithms

NTP has developed algorithms to diagnose drug-resistant TB for health centres, hospitals and reference laboratories. (refer to figure)

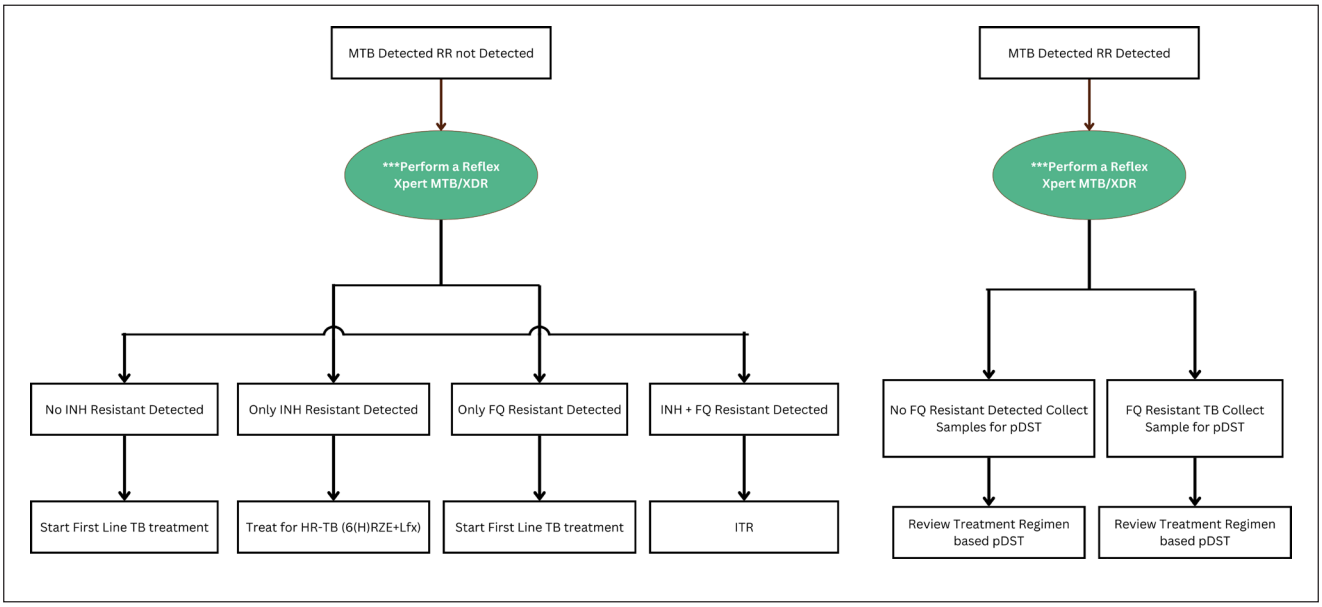


Figure 10.3-1 DR TB diagnosis algorithm using 10 colour Gene-xpert machines

10.3.2.2. Communication of results from culture and DST laboratory

All efforts must be made to deliver the culture and DST results to referring health facilities as soon as available. The laboratory unit and TB officer should arrange reliable and fast mechanisms to return results to the providers. All confirmed drug-resistant TB patients should be linked to the designated treatment centre without delay once the DST results are received from the diagnostic centre. Patients should be provided with the following key information:

- Interpretation of the laboratory results and next action
- Need for clinical evaluation of household and close contacts of the confirmed patient
- Infection control measures at home and community

- Basic information on the nature of the disease
- Treatment modality and duration of treatment
- Treatment sites and mechanism of follow up of treatment
- Expected follow-up visits including necessary laboratory monitoring examinations.

10.3.3. Drug-resistant TB patient classification and definition of terms

WHO recently developed standardized definitions, classification, registration and reporting systems to facilitate uniform communication of concepts related to drug-resistant TB. In general, strains of TB can either be susceptible or resistant to anti-TB drugs:

- Susceptible TB refers to a tuberculosis strain that is not resistant to any anti-TB drugs
- Drug-resistant TB is confirmed through laboratory tests that show the infecting isolates of MTB grow in vitro in the presence of one or more anti-TB drugs. (can also be confirmed by molecular test as Xpert MTB/RIF or Xpert Ultra, Xpert MTB/XDR, LPA or Phenotypic DST

10.3.3.1. Patterns of drug resistance

A diagnosis of drug resistance is primarily a laboratory-based diagnosis. There are two broad methods in use in Malawi;

- **Phenotypic:** (Liquid and solid culture)
- **Genotypic:** (Xpert MTB/Rif & Xpert Ultra, LPA, Xpert MTB/XDR, Truenat, genomic sequencing techniques)

10.3.3.2. Classification based on drug resistance pattern

Patients with TB can either be bacteriologically confirmed or clinically diagnosed. Bacteriological confirmation can either be through molecular methods, culture or smear microscopy.

Bacteriologically confirmed patients are further classified based on resistance to the main drugs, based on laboratory diagnosis by genotypic and/or phenotypic Drug Susceptibility Tests as follow:

- **Mono-resistant TB:** Resistance to one first-line anti-TB drug
- Poly-resistant TB: Resistant to more than one first-line anti-TB drug other than R and INH
- **Rifampicin Resistant TB (RR–TB):** Resistance to Rifampicin using genotypic or phenotypic methods regardless of whether there is documented resistance to other first- or second-line anti TB agents.
- **Multi-drug resistant TB (MDR-TB):** Resistance to rifampicin and INH
- **Pre-XDR-TB:** TB caused by Mycobacterium tuberculosis (M. tuberculosis) strains that fulfill the definition of MDR/RR-TB and that are also resistant to any fluoroquinolones
- **XDR-TB:** TB caused by Mycobacterium tuberculosis (M. tuberculosis) strains that fulfill the definition of MDR/RR-TB and that are also resistant to any fluoroquinolones and at least one additional Group A drug
- Any patient who falls into one of the above listed types of drug-resistance is considered a drug-resistant TB patient.

10.3.3.3. Classification of drug-resistant TB based on laboratory confirmation

10.3.3.3.1. Registration group based on history of anti-TB treatment

All RR-/MDR-TB patients must be registered as per the history of anti-TB treatment. Patients should be classified in two ways:

1. Classification as per the history of anti-TB treatment is used mainly to assign the appropriate treatment regimen. Registration groups are:
   - **New:** A patient who has received no or less than one month of anti-tuberculosis treatment
   - **Previously treated with first-line drugs:** a patient who has received first-line anti-TB treatment for four weeks or more
   - **Previously treated with second-line drugs:** a patient who has received second-line anti-TB treatment for four weeks or more
2. Classification is determined by the history of treatment at the time of collection of the sample that was used to confirm DR-TB. Previous history refers to the outcome of the latest TB treatment of the patient. Registration groups are:
   - **New:** A patient who has received no or less than one month of anti-tuberculosis treatment
   - **Relapse:** A patient who was previously treated for TB and whose most recent treatment outcome was "cured" or "treatment completed", and who is subsequently diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection), either bacteriologically confirmed or clinically diagnosed
   - **Treatment after being lost to follow-up:** A patient who had previously been treated for TB and was declared lost to follow-up at the end of the most recent course of treatment
   - **After failure of first treatment with first-line drugs:** A patient who has received first-line drug treatment for TB and in whom treatment has failed
   - **After failure of retreatment regimen with first-line drugs:** A previously treated TB patient who has received a retreatment regimen with first-line drugs and in whom the retreatment has failed
   - **Transfer-in:** A patient who has been transferred from another DR-TB registration site to continue DR-TB treatment
   - **Other previously treated:** refers to any DR-TB patient who does not fit into any of the above categories

10.4. Treatment of Drug Resistance TB in Malawi

10.4.1. Treatment Approach

Treatment of patients with DR-TB involves second-line drugs. They are much more expensive, less effective and have more side effects than first-line TB drugs.

10.4.1.1. Groups of Anti-TB Drugs

The anti-TB drugs have traditionally been divided into first- and second-line anti-TB drugs with isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin being the primary first-line anti-TB drugs. In 2018, WHO regrouped medicines for treating Rifampicin resistance and MDR-TB into three categories and ranked based on the latest evidence about the balance of effectiveness to safety as follows:

- Group A: Medicines to be prioritised
- Group B: Medicines to be added next (second priority). This does not mean that Group A and B medicines have to be initiated at different times. It only means that the most effective regimen is one that has most medicines from Group A and less from Group B
- Group C: Medicines to be included to complete the regimens and when agents from Groups A and B cannot be used

Groups	Medicine	
Group A	Levofloxacin/Moxifloxacin Bedaquiline Linezolid	Lfx/Mfx Bdq Lzd
Group B	Clofazimine Cycloserine/Terizidone	Cfz Cs/Trd
Group C	Ethambutol Delamanid Pyrazimamide	E Dlm Z

Table 10.4-1 Grouping of second line anti-TB drugs

10.4.1.2. Treating mono and poly-drug resistant TB

When a decision has been made to treat mono or poly-drug resistant TB, the most effective regimen should be chosen from the start to maximize the likelihood of cure; effective drugs should not be withheld for later use.

The recommendations for treating patients with mono- and poly-resistant strains are outlined in table below:

Drug resistance pattern	Suggested regimen	Comments
RIF mono- or poly-drug resistance	MDR/RR-TB regimen	The patient should be started on either a shorter or individualized MDR/RR-TB regimen depending on eligibility criteria
INH poly-drug resistance susceptible to RIF (e.g. INH + EMB and/or S resistance)	MDR/RR-TB regimen	Treat as MDR/RR-TB. Caution should be taken when interpreting these DST results, as many patients with DST results suggesting poly-drug resistance actually have MDR-TB. Determine the patient's treatment history. If in doubt, consult with the clinical expert committee.
INH mono-resistance	6(H)RZE + Levofloxacin*	Patient with no previous treatment of TB, no risk of amplification of resistance, and no risk of unfavourable outcome: consider treatment with levofloxacin + (H)REZ for 6 months.
		Patients with history of previous TB treatment, risk of amplification of resistance, or risk of unfavourable outcome (extensive disease) treat with either a shorter or an individualised MDR/RR-TB treatment regimen depending on eligibility criteria.

** When fixed-dose combination (FDC) formulations are used, isoniazid is included but it is not obligatory for the regimen. If levofloxacin cannot be used because there is fluoroquinolone resistance or intolerance or other contraindications to the use of fluoroquinolone, then 6(H)RZE may be prescribed daily for 6 months.*

Table 10.4-2 Suggested regimens for mono- and poly-drug resistance

H = Isoniazid; R = Rifampicin; E = Ethambutol; Z = Pyrazinamide; S = Streptomycin

Care should be taken to evaluate the medical history for possible amplification of resistance which may have developed but may not be apparent from the laboratory results. As such, treatment for mono and poly-drug resistant TB should never rely solely on DST results.

It is important to assess history of previous TB treatment, contact history, risk of amplification of resistance, extension of the disease and patient condition.

10.4.1.3. Type of resistance and suggested drug to be used

Type of resistance	Drugs/regimen used
Sensitive TB	H, R, E, Z
R - resistance	6-BPaLM, 6-9-BPaL, 9-mSTR, 18-20-LAOTR or ITR
H, R - resistance	
H, R, S	
H, R, Bdq	To reconsider Pre XDR and XDR regimens (ITR). Generally, the backbone is Dlm, Cfz and linezolid.
H, R, Lzd	To reconsider Pre XDR and XDR regimens. Generally, the backbone is Bdq and/ or Dlm, and Cfz
H, R, FQ	To reconsider Pre XDR and XDR regimens. Generally, the backbone is Bdq and/ or Dlm, Cfz and linezolid.

Type of resistance and suggested drug to be used

10.4.1.4. Treatment of poly-resistance patients

Combine the maximum possible number of available anti-TB drugs that act upon different targets in the micro-organisms.

Note: Pyrazinamide has low risk of resistance in the first-line regimen. All TB patients can be cured with at least 3 drugs that have never been used by the patient or for which no drug resistance exists. Rifampicin can be substituted with Rifabutin in an HIV positive patient who needs protease inhibitor therapy.

Standardised / Conventional Treatment of DR-TB cases

Drug resistance survey data from representative patient populations are used to base regimen design in the absence of individual DST in which all patients in a defined group or category receive the same regimen as per national guidance.

Empiric treatment regimen

Initiation of treatment prior to determination of a firm diagnosis of drug-resistance TB based patient's risk for drug resistance. Empiric regimen is mainly reserved for children in whom DST confirmation is unlikely or pending. And needs to be considered in HIV patients or EPTB patients where confirmation is not possible or difficult.

Standardised treatment regimens for DR-TB

This approach requires that all patients initiated on standardised regimen will be based on the result of full DST while on treatment. Hence, samples should be sent for full DST upon treatment initiation for all confirmed DR-TB patients.

Advantages of choosing standardised regimen

- Simpler implementation
- Simpler drug supply management
- Easy to train health care workers

- Reduces chance of error in regimen construction
- Minimises the need for sophisticated culture and DST laboratories

Standardised regimen for MDR/RR-TB

The following treatment regimens for MDR/RR-TB can be applied under programmatic conditions:

Option A: The 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM) regimen or 6-month bedaquiline, pretomanid and linezolid (BPaL)

The BPaLM regimen includes four components – bedaquiline, pretomanid, linezolid and moxifloxacin. In the BPaLM regimen, pretomanid is administered at 200 mg once daily. Bedaquiline is dosed at 400 mg once daily for 2 weeks, then 200 mg three times per week afterwards. Linezolid dosing is 600 mg once daily and moxifloxacin 400 mg once daily.

For MDR/RR-TB with Fluoroquinolone Resistant

6-9 months of Bedaquiline, Pretomanid and Linezolid

- This regimen may be used without moxifloxacin (BPaL) in the case of documented resistance to fluoroquinolones (in patients with pre-XDR-TB). Drug susceptibility testing (DST) to fluoroquinolones is strongly encouraged, but DST should not delay treatment initiation.
- Patients with susceptibility to fluoroquinolones can be started on the BPaLM regimen for 6 months (26 weeks). In the case of resistance to fluoroquinolones, identified after treatment initiation, moxifloxacin may be discontinued, and the regimen can be continued as BPaL.
- When the regimen is BPaL from the start or is changed to BPaL, it can be extended to a total of 9 months (39 weeks) (continuing from the start of the therapy with BPaLM/BPaL). This extension of the BPaL regimen can occur in cases where there is a lack of culture conversion or clinical response (based on the clinical judgment of the treating physician) between months 4 and 6. Treatment interruption up to 1 month can be added to the overall treatment duration if there is a need to make up the missed doses.
- Individuals who switch from BPaLM to BPaL should consider their treatment start date the same as the date BPaLM was initiated, because the patient remained on treatment with three effective drugs during the entire treatment period

Eligibility

The BPaLM/BPaL regimen may be offered to patients with MDR/RR-TB in the following situations:

- patient is aged 14 years or older;
- no known allergy to any of the BPaLM component drugs;
- no evidence of resistance to bedaquiline, linezolid, delamanid or pretomanid, or patient has not been previously exposed to any of the component drugs for 4 weeks or longer; when exposure to the component drugs is greater than 4 weeks in duration, the patient may receive the BPaLM regimens if resistance to the specific medicines with such exposure has definitively been ruled out;
- all people regardless of HIV status;
- no XDR-TB according to the up to date WHO definitions; and
- patient is not pregnant or breastfeeding or, if the patient is a premenopausal woman, is willing to use effective contraception.

Exclusion criteria

- Patients with a high risk of treatment failure, such as extensive TB disease
- Patients with extrapulmonary TB, however, patients with TB pleural effusion and children with TB lymphadenitis may be considered for this treatment regimen
- Although bedaquiline, linezolid and fluoroquinolones have been used to treat MDR/RR-TB in children, there are no data about the use of pretomanid in children, and further study is required to expand the use of BPaLM/BPaL to children.
- Pregnant and breastfeeding women. For patients who become pregnant during treatment, it will be necessary to discontinue the BPaLM/ BPaL regimen and prescribe another regimen.

Extensive DR-TB disease

Extensive (or advanced) TB disease in adults is defined as the presence of bilateral cavitary disease or extensive parenchymal damage on chest radiography. In children aged below 15 years, extensive (or advanced) disease is usually defined by the presence of cavities or bilateral disease on chest radiography. This highlights the importance of chest radiography as part of the diagnostic work-up for patients, along with bacteriological tests.

Severe extrapulmonary TB

Severe extrapulmonary TB includes the presence of miliary TB, TB meningitis, osteoarticular TB or pericardial TB. In children aged below 15 years, extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression) are considered severe.

Composition and duration of the regimen

- All medicines in the regimen are to be used throughout the treatment duration, including a potential extension from 26 to 39 weeks (when BPaL is used).
- Ideally, missing doses of all three or four drugs in the regimen should be avoided; however, if doses are missed, any interruption of longer than 7 days should be made up for by extending the treatment duration (for the number of missed doses); therefore, 26 or 39 weeks of prescribed doses should be completed within an overall period of 7 or 10 months, respectively.

Option B: The 9-month modified all oral treatment regimen (mSTR)

The use of modified all-oral shorter MDR-TB regimens was initiated under operational research in October 2022. This is following WHO guide of 2020 and emphasized again in 2022. This recommendation was due to little evidence to support modified all-oral shorter MDR-TB regimens that are designed using the hierarchy of TB medicines.

For MDR/RR-TB with FQ- Sensitive Patients:

The treatment regimen for > 6 years

- 2 months of Bedaquiline, Levofloxacin, Linezolid, Clofazamine, Cycloserine
- 4 months of Bedaquiline, Levofloxacin, Clofazamine, Cycloserine
- 3 months of Levofloxacin, Clofazamine, Cycloserine

2Bdq-Lfx-Lzd-Cfz-Cs/4Bdq-Lfx-Cfz-Cs/3Lfx-Cfz-Cs.

The treatment regimen for children < 6 years

- 2 months of Bedaquiline, Levofloxacin, Linezolid, Clofazamine, Cycloserine
- 4 months of Bedaquiline, Levofloxacin, Clofazamine, Cycloserine
- 3 months of Levofloxacin, Clofazamine, Cycloserine

2Bdq-Lfx-Lzd-Cfz-Cs/4Bdq-Lfx-Cfz-Cs/3Lfx-Cfz-Cs.

Or

- 2 months of Delamanid Levofoxacin, Linezolid, Clofazamine, Cycloserine
- 4 months of Delamanid, Levofoxacin, Clofazamine, Cycloserine
- 3 months of Levofloxacin, Clofazamine, Cycloserine

2Dlm-Lfx-Lzd-Cfz-Cs/4Dlm-Lfx-Cfz-Cs/3Lfx-Cfz-Cs.

The option to choose between Bedaquiline based or Delamanid based among those under 6 years of age will depend on eligibility and avoidance of pill burden.

Eligibility

A patient will be eligible for treatment with a 9-month all-oral shorter MDR/RR-TB treatment regimen, if all the following conditions are satisfied if he/she:

- Has bacteriologically or molecularly confirmed TB with evidence of resistance to at least rifampicin and resistance to fluoroquinolones has been ruled out (or for children likely to be DR-TB based on history of close contact with a confirmed DR-TB case).
- Patients with MDR/RR-TB who have not been previously treated with SLD and with low risk or with DST results excluding resistance to FQ and any of other group A drugs.
- Children, HIV infected patients, patients with EPTB with clinically diagnosed TB who have not been previously treated with SLD and with low risk of resistance to FQ and any of other group A drugs who have been in close contact with patients with documented MDR/RR- TB.

Exclusion criteria

A patient is not eligible for treatment with an all-oral shorter DR-TB treatment regimens if any of the conditions take place if he/she:

- Is unable to take oral medication.
- Must take any medications contraindicated with the medicines in the treatment regimen.
- Has a known allergy to any of the drugs in the DR-TB regimen;
- Has a QTcF interval of ≥ 500 msec; at baseline that does not correct with medical management
- Patients with confirmed resistance to FQ or any other group A drugs by either SL-LPA or phenotypic DST
- Patients with suspected resistance to FQ or any other group A drugs based on contact with patient with this resistance pattern or other risk factor
- Patients with exposure to SLD for >1 month (E.g. Patients already on MDR/RR-TB treatment regimen for more than a month or patients with history of previous treatment with the regimen SLDs)
- Patients with intolerance to any of the medicines in the treatment regimen

- Pregnant women
- Patients with extrapulmonary TB, however, patients with TB pleural effusion and children with TB lymphadenitis may be considered for this treatment regimen
- Patients with high risk of treatment failure, such as extensive TB disease

Note: Presence of any of the above, disqualifies a DR-TB patient from shorter treatment regimen.

If the patient remains smear and/ or culture positive after 6 months, will be declared as treatment failure and switched to an individualized regimen.

Option C: The longer all oral treatment regimens (LAOTR)

Longer all oral treatment regimen (18-20 months)

Longer MDR-TB regimen is used for the treatment of MDR/RR-TB, last at least 18 months and are designed using a hierarchy of recommended medicines. A longer treatment regimen should be proposed mainly when the BpaLM/BpaL or 9-month all-oral regimen cannot be used. Although the total length of treatment is expected to be about 18–20 months in most patients, it may be modified based on the patient's clinical situation and response to treatment

The duration of treatment using longer regimens in children depends on the site and severity of disease, and the extent of resistance. Children with non-severe disease can usually be treated for much less than 18 months. Children with extensive disease may require longer treatment durations, depending on clinical progress or site of the disease.

For MDR/RR-TB with FQ- Sensitive Patients:

The treatment regimen for all age groups (standardized longer regimen 1st option)

- 6 months of Bedaquiline, Levofloxacin, Linezolid, Clofazamine, Cycloserine
- 12 months of Levofloxacin, Linezolid, Clofazamine, Cycloserine

6Bdq-Lfx-Lzd-Cfz-Cs/12Lfx-Lzd-Cfz-Cs

The treatment regimen for all (standardized option for children and or those not eligible for Bedaquiline)

- 6 months of Delamanid, Levofloxacin, Linezolid, Clofazamine, Cycloserine
- 12 months of Levofloxacin, Linezolid, Clofazamine, Cycloserine

6Dlm-Lfx-Lzd-Cfz-Cs/12Lfx-Lzd-Cfz-Cs

Individualized treatment regimen

- This can be designed using a hierarchy of recommended medicines by WHO

Individualising a standardised regimen should be based on:

- Previous exposure for more than one month in a failing regimen suggests the drugs are not effective even if DST results report susceptibility.
- History of previous exposure to first-line and second-line drugs. (Detailed history and review of previous treatment records).
- A sound knowledge of cross-resistance among anti-TB drugs is required.

Principles for designing individualised DR-TB treatment regimens

- The regimen should be designed based on the patient's most recent DST results and history of previous drug use and/or exposure.
- Never add Bdq, Dlm, Cfz or Lzd as a single drug to a failing regimen.
- If the patient is culture negative and the new drugs are being SUBSTITUTED for toxicity reasons, a single drug substitution can be made[5].
- The backbone regimen usually consists of a new drug (Bdq, Dlm, or both), and Lzd
- Dlm should be the new drug of choice for HIV co-infected patients, due to the lack of drug-drug interactions with antiretroviral therapy.
- For patients with limited treatment options (MDR treatment failure, pre-XDR, and XDR-TB), a regimen combining Bdq and Dlm should be designed and approved by the clinical expert committee. Ensure closer monitoring of the QT interval by performing an ECG at baseline, 2 weeks, and monthly until the end of treatment with Bdq or Dlm.
- Bdq or Dlm should be initially given for 6 months; the use of Bdq or Dlm can be extended by the clinical expert committee in patients with highly resistant forms of DR-TB where the remaining regimen is insufficient (less than 3 effective drugs) without Bdq or Dlm and the drug is well tolerated.
- For patients enrolled for treatment with regimens containing new drugs (Bdq or Dlm) informed consent policies should follow local practice for DR-TB in general [11].
- For HIV-infected patients, antiretroviral therapy (ART) should be prescribed within 2-8 weeks of DR-TB treatment initiation, and as soon as possible after DR-TB treatment is tolerated. See Chapter 6 for the treatment of DR-TB/HIV co-infection.
- The QT prolongation that may occur in patients receiving Bdq or Dlm can be monitored in the outpatient setting. There is no reason to admit stable patients to initiate Bdq or Dlm only for cardiac monitoring; Dlm takes 8 weeks to reach its peak concentration, and Bdq up to 16 weeks.

Additional considerations on choice of new drug use (Bdq or Dlm) in individualised regimens:

- Bedaquiline, delamanid, the fluoroquinolones (Mfx more than Lfx), and clofazimine can all cause prolongation of the QT interval (. Patients with DR-TB regimens that contain one of the new drugs, especially when used with additional QT prolonging drugs, should be carefully monitored for clinical signs of an irregular heartbeat, as well as checking regular ECGs.
- Bdq had drug-drug interactions with ART: EFV lowers Bdq serum levels; LPV/r increases Bdq levels.
- When starting Bdq or Dlm, serum electrolytes should be checked and corrected when feasible to reduce the risk of cardiac arrhythmias. Since Dlm is metabolised by albumin, patients with a low BMI and/or low serum albumin should be provided with high-protein dietary foods.
- There is potential cross resistance between Bdq and Cfz; use Dlm if there is a history of prior Cfz use > 2 months for DR-TB (Bdq can be used if there is a history of prior Cfz use for leprosy).
- Bdq has a prolonged terminal elimination half-life of 5 months; if considering the use of Dlm after completion of Bdq (e.g. Bdq treatment failure), patients should be monitored closely given the theoretical risk that the patient will be on 'combination' with both drugs.
- It is not recommended to dose reduce either Bdq or Dlm in the event of adverse events; linezolid, however, may be reduced from 600 mg daily to 300 mg daily if there are serious adverse events at the 600-mg dose (pyridoxine 50 mg should be added as well).

Eligibility

A longer regimen is expected to be used in the following situations:

5 Treatment of Drug-Resistant TB with New and Re-Purposed Medications: A Field Guide. Cleveland, USA. DR-TB STAT; July 2017.

- Extensive TB disease
- Severe extrapulmonary TB;
- Additional resistance to key medicines of the BPaLM/BPaL regimen (except moxifloxacin) or the 9-month all-oral regimen;
- Lack of response to shorter treatment regimens (e.g. treatment failure due to no bacteriological conversion, no clinical response, emerging resistance or loss to follow-up);
- Drug intolerance to the component medicines of the BPaLM/BPaL regimen (except moxifloxacin) or 9 months shorter all-oral treatment regimen; and
- Pregnant and lactating women who could not benefit from the 9-month shorter all-oral regimen owing to certain clinical conditions or children aged below 14 years who could not be treated with BpaLM/BpaL or who, for any reason, cannot opt for a 9-month regimen.

There is limited or no evidence of BpaLM/BpaL use in some patient groups; thus, a longer regimen could also be considered as an option:

- Patients with low BMI (<17 kg/m2),
- Altered hepatic enzymes (3 times greater than the upper limit of normal),
- Baseline anaemia (haemoglobin <8 g/ dL),
- Thrombocytopenia (platelet count <150 000/mm3) or
- Pre-existing peripheral neuropathy of Grade 3–4.

Composition and duration of the regimen

When designing longer regimens, several basic principles need to be respected, in line with the best available evidence on composition of the regimens. The selection of medicines follows a priority order based on the revised classification of regimen components, and a fully oral regimen is preferred. Drugs must be selected, starting from Group A and then from Group B. Group C drugs are usually included in a longer regimen if it cannot be composed with Group A and B agents alone. The choice of drugs from Group C is usually determined by the order in which the medicines are ranked, and by the individual circumstances of the patient and the setting.

Group A

Group A includes fluoroquinolones (levofloxacin and moxifloxacin), bedaquiline and linezolid. These medicines were found to be highly effective in improving treatment outcomes and reducing deaths., and it is strongly recommended that they be included in all longer MDR-TB regimens and used for all MDR/RR-TB patients eligible for longer regimens unless there is a toxicity issue or drug resistance.

Group B

Group B medicines include clofazimine and cycloserine or terizidone, which were found to be effective in improving treatment outcomes but limited in reducing deaths. One or both drugs can be added to ensure that a longer regimen starts with at least four effective medicines.

Group C

Group C comprises both TB and repurposed medicines that are positioned at a lower priority than the Group A and B agents, either because they are less effective (ethambutol, delamanid, pyrazinamide, ethionamide/ prothionamide and p-aminosalicylic acid) or because they are more toxic and cumbersome to administer parenterally (imipenem–cilastatin, meropenem, amikacin and streptomycin). These drugs are usually included in a longer regimen if it cannot be composed with Group A and B agents alone.

Standardised regimen for rifampicin susceptible and isoniazid resistant TB (Hr-TB)

This refers to an Hr-TB treatment regimen that has a duration of 6 months and uses oral agents.

The basic regimen can be summarized as: Hr-TB regimen: 6(H)RZE-Lfx

Eligibility

Hr-TB treatment is expected to be started if either of the following circumstances apply:

- Hr-TB is confirmed, and rifampicin resistance is ruled out before TB treatment is started – in such cases, the 6(H)RZE-Lfx regimen is started immediately
- If the diagnosis is strongly presumed (e.g. close contact of a confirmed Hr-TB source case) but results of DST are still pending, the regimen may be introduced. Should DST results taken at the start eventually show susceptibility to isoniazid, then levofloxacin is stopped, and the patient continues treatment to complete a 2HRZE/4HR regimen
- Hr-TB is discovered after the start of treatment with the 2HRZE/4HR regimen (this includes patients who had undiagnosed isoniazid resistance at the start or who developed isoniazid resistance while on first-line treatment) – in such cases, rapid molecular testing for rifampicin resistance must be undertaken (or repeated). Once rifampicin resistance has been excluded, a full 6-month course of (H)RZE-Lfx is given. The duration is driven by the need to give levofloxacin for 6 months, which usually implies that the companion first-line medicines are taken for longer than 6 months. A report of resistance during treatment presents the clinician with a challenge, because the results may no longer reflect the drug susceptibility of the current bacterial population, given that an inadequate regimen – at times a functional monotherapy – may have favoured the acquisition of additional resistance in the interval. The unexpected discovery of resistance to one agent should prompt the clinician to repeat DST for other agents in the regimen

Composition and duration of the regimen

- The duration of Hr-TB treatment is driven by the need to complete 6 months of a fluoroquinolone containing regimen. This implies that, when Hr-TB is diagnosed after the start of the regimen for treatment of DS-TB, the companion medicines (HRZE) would end up being given for more than 6 months.
- Levofloxacin is included in Hr-TB regimens except in the following instances: when rifampicin resistance cannot be tested for, when there is documented resistance or known intolerance to fluoroquinolones, and when there is pre-existing prolongation of the QT interval and pregnancy. If a fluoroquinolone cannot be used, a patient with Hr-TB can still be treated with 6(H)RZE.
- The inclusion of isoniazid in the regimen has not been shown to lead to substantial benefit or harm to patients; however, isoniazid may increase the hepatotoxicity of pyrazinamide.

Weight based dosing for second line TB medicines

The table below shows the weight based doing or DR-TB medicines for adults

Weight bands in patients older than 14 years										
GRP	**Medicine**	**Weight-based daily dose**	**Formulation**	**Weight bands for patients older than 14 years**					**Usual upper daily dose**	**Comments**
				30-35	**36-45**	**46-55**	**56-70**	**>70**		
				kg	**kg**	**kg**	**kg**	**kg**		
A	Levofloxacin		250 mg tab	3	3	4	4	4	1.5 g	
			500 mg tab							
			750 mg tab							
	Moxifloxacin	Standard dose	400 mg tab	1	1	1	1	1	400 mg	
		High dose	400 mg tab	1 or 1.5	1.5	1.5 or 2	2	2	800 mg	As used in the standardized shorter MDR-TB regimen
	Bedaquiline		100 mg tab	4 tabs od for first 2 weeks; then 2 tabs od 3 times a week for 22 weeks					400 mg	
	Linezolid		600 mg tab	(<15 y)	(<15 y)	1	1	1	1.2 g	
B	Clofazimine		50 mg cap or tab	2	2	2	2	2	100 mg	
			100 mg cap or tab	1	1	1	1	1	100 mg	
	Cycloserine	10-15 mg/kg	250 mg cap	2	2	3	3	3	1 g	
C	Ethambutol	15-25 mg/kg	400 mg tab	2	2	3	3	3		
	Delamanid		50 mg tab	2 bd	2 bd	2 bd	2 bd	2 bd	200 mg	
	Pyrazinamide	20-30 mg/kg	400 mg tab	3	4	4	4	5		
			500 mg tab	2	3	3	3	4		
	Pretomanid		200mg (1 tablet) daily for 26 weeks							

Table 10.4-3 Weight-based dosing or DR-TB medicines for adults

10.4.1.5. Additional tests and equipment required

- The need for LPA or rapid diagnostic test such as Xpert MTB/XDR (Detection of MTB and its resistance to fluoroquinolones)
- ECG monitoring: Bdq, Dlm, Cfz, and Mfx that might lead to cardiac arrhythmias
- Other clinical tests:, CXR, complete blood count, serum creatinine, serum potassium, blood glucose, liver function test, pregnancy test, and visual acuity tests
- Monitoring for effectiveness, relapse, and side effects (active TB drug safety monitoring and management -aDSM). Dosage of medicines to use in the WHO-recommended shorter MDR-TB regimen
- All DR-TB patients are to be tested for resistance to fluoroquinolones before starting any DR-TB treatment.
- The shorter MDR-TB regimen can be used for children younger than 14 years and in people living with HIV, including those who are receiving antiretroviral treatment

10.4.2. Treatment monitoring and the need for modification

10.4.2.1. Switching from the shorter DR-TB regimen to a longer regimen

All the care needs to be taken to select the right patients to receive the shorter MDR-TB regimen. However, fresh information or developments while the patient is on treatment may require that the shorter MDR-TB regimen is stopped and a longer, individualised DR-TB regimen or other treatment is started. This is most likely to happen in the following condition:

- DST results show resistance to medicines in the shorter MDR-TB regimen: this may reflect the actual situation at the start of treatment, which was unknown at that time, or else the acquisition of additional resistance during treatment;
- Lack of response to treatment (e.g. no sputum smear conversion or deterioration of clinical condition despite treatment);
- Patient is treated for more than one month, interrupts treatment and returns after an interval >2 months (i.e. fulfills another exclusion criterion);
- Emergence of another exclusion criterion (e.g. extrapulmonary disease, pregnancy, intolerance to a medicine in the regimen).

10.4.2.2. Management of Patients who are not responding to the BPaLM/BPaL or mSTR and those who interrupt treatment

- Patients on the shorter MDR-TB regimen who do not respond need to be assessed to decide whether they need to be switched to a longer DR-TB regimen.
- No changes should be made to the shorter DR-TB regimen composition if there are signs of impending treatment failure
- If patients miss 2 consecutive months or more of shorter DR-TB treatment, then the episode is classified as “Loss to follow up” and should be managed using the longer regimen
- If a patient has received the shorter MDR-TB regimen for more than one month, and returns for treatment after an interruption of 2 consecutive months or more, the patients should not be restarted on a shorter DR-TB regimen but on a longer DR-TB regimen
- If the interruptions are less than one or just one month (e.g. medical indication in the case of adverse events, patient decision) then the shorter MDR/RR-TB regimen can be continued, and the missed doses added to the rest of the treatment.

10.4.2.3. Monitoring of patients on the shorter MDR/RR-TB treatment regimens

- The treatment outcome definitions and reporting framework are the same as those for longer DR-TB regimens.
- Response to treatment is monitored based on monthly sputum smear microscopy, as well as culture ideally at the same frequency.
- Active TB drug safety monitoring and management (aDSM) with scheduled patient monitoring is thus recommended for the whole duration of treatment.
- Concomitant use of bedaquiline, and moxifloxacin - both of which prolong the QT interval – may make it more important to undertake electrocardiography than for other regimens.
- There is no need to change the Second-line TB treatment register or the Annual treatment outcomes report for MDR/RR-TB when monitoring patients on the shorter MDR/RR-TB regimen.
- The definitions of “Cured” and “Treatment Failed” can be equally applied to shorter MDR/RR-TB regimen
- Patients that are highly likely to have second-line drug (SLD) resistance - those failing MDR-TB treatment, symptomatic close contacts of DR-TB patients with SLD resistance, or patients that have received SLDs for ≥ 1 month in the past - can be started on Bdq or Dlm in the absence of confirmed DST by LPA or culture.

10.4.2.4. DR-TB Regimen Design for Children

The medications used for the treatment of children with DR-TB are similar to those used to treat adults. A special exception is that for children, regimen construction should prioritize the WHO Group A and B drugs, as well as delamanid (Group C). (Refer to Paediatric section).

Drug-drug interaction

PLHIV

- The antiretroviral drug efavirenz induces metabolism of bedaquiline, so its co-administration with bedaquiline may result in reduced bedaquiline exposure and loss of activity; therefore, co-administration is to be avoided.
- Efavirenz also reduces pretomanid exposures significantly; therefore, an alternative antiretroviral agent (potentially dolutegravir, although there is currently insufficient evidence for this) should be used if pretomanid or the BPaLM/BPaL regimen is considered.
- Ritonavir may increase bedaquiline exposure, which could potentially increase the risk of bedaquiline-related adverse reactions. Individuals who are prescribed both bedaquiline and ritonavir should be monitored closely for adverse events, including QTc prolongation.
- Antiretroviral regimen including zidovudine should be avoided, if possible, because both zidovudine and linezolid may cause peripheral nerve toxicity and are known to have myelosuppression cross-toxicity.

10.4.3. Evaluation and monitoring of patients on MDR-TB treatment

Patients to be initiated on second-line anti-TB medicines should have a thorough pre-treatment evaluation and, after initiation of treatment, should have regular scheduled clinical evaluations.

10.4.3.1. Pre-treatment evaluation and screening

Pre-treatment assessment should be systematically conducted for all patients to identify those patients at greater risk of adverse effects, and poor outcomes, and to establish a baseline for monitoring.

- Before patients are started on MDR-TB treatment, healthcare workers should:
- Ensure that all details regarding the treatment are communicated to the patient
- Counsel and educate the patient and family members
- Confirm patient's physical and work address
- Perform baseline clinical assessment including lab investigations
- Enquire about close contacts at home or work
- Arrange for screening of and testing of all contacts

10.4.3.2. Treatment monitoring and follow-up

Each DR-TB patient should be monitored closely for signs of both treatment efficacy and adverse effects of the medications (aDSM). The success of the programme on treatment depends on the intensity and quality of monitoring and supervision activities.

- Patients should be assessed by trained DR-TB clinicians frequently during the period of treatment.
- The responsible clinician should assess clinical, microbiologic, and radiologic response to treatment and encourage the patient to continue treatment.
- Treatment cards should be updated after each follow-up visit.
- Frequent clinical and adherence assessments should be done for patients receiving treatment on ambulatory bases at least for the first few months until the patient's condition stabilises.

The monitoring should follow standard clinical assessment:

Clinical history

- Resolution or worsening of symptoms of TB (cough sputum production, haemoptysis, chest pain, respiratory distress, fever, weight loss)
- Adherence (missed oral pill doses, and reasons for the missed doses)
- Implementation of active drug safety monitoring and management (aDSM).
- Systematic assessment for co-morbid illness
- Pregnancy/family planning in reproductive-age women

Physical examination:

Vital signs, anthropometry (height, weight, BMI, mid upper arm circumference), focused systemic examination (HEENT, CVS, respiratory, abdomen, skin, musculoskeletal, neurologic)

Laboratory monitoring:

Scheduled laboratory monitoring tests should be done for all DR-TB patients enrolled to treatment, including total blood count, electrolyte analysis, biochemistry (creatinine, ALT/AST) pregnancy test, AFB microscopy, culture test and DST as appropriate.

The most important objective evidence of improvement is conversion of sputum smear and culture. Sputum smear is still very important because of shorter turnaround time and readily available in most healthy facilities. The recurrence of TB symptoms after sputum conversion may be the first sign of treatment failure.

		Individualized /standardized regimen
Parameter	**Baseline**	**During the period of treatment**
Clinical assessment	Yes	Monthly
Screening by DOT worker	Yes	At every DOT encounter
Sputum smear	Yes	Monthly
Sputum culture	Yes	Monthly
Phenotypic DST or LPA	Yes	Repeat if smear or culture is positive
Weight	Yes	Monthly
Liver function tests	Yes	If clinically indicated
Serum Creatinine	Yes	When clinically indicated especially for HIV-infected, diabetic and/or other high-risk group
Serum potassium	Yes	If clinically indicated
HIV testing	Yes	If clinically indicated
Pregnancy test (women aged 15-49 years)	Yes	If clinically indicated
CXR	Yes	At 6 months or when clinically indicated and at end of treatment
Total blood count and haemoglobin	Yes, for HIV+ or anaemia	If clinically indicated
Lactic acid	Yes	For patient receiving Linezolid or ART

** ECG is mandatory for patients on Bdq and or Dlm at baseline, week 2 and monthly while on either drug. ECG may be done more frequently in patients with low albumin (<3.4 g/dl), low electrolytes, hypothyroidism or heart conditions.*

Table 10.4-4 Schedule for clinical monitoring in drug-resistant TB treatment

THE SCHEDULE OF BASELINE, ROUTINE AND POST-TREATMENT MONITORING EXAMINATIONS FOR THE BPALM/BPAL REGIMEN

Examination	Baseline	2 weeks	Monthly	End of treatment	6- and 12-months post treatment
Clinical evaluation					
Clinical assessment	X	X	X	X	X
Psychosocial assessment	X	X	X	X	X
Weight/BMI	X	X	X	X	X
Peripheral neuropathy screening	X	X	X	X	
Visual acuity and colour discrimination screening	X	X	X	X	
Assessment and follow-up of adverse events	X	X	X	X	X
Outcome consultation				X	X
Bacteriological evaluations					
Sputum smear	X		X	X	X
Sputum culture	X		X	X	X
Sputum DST	X		If smear or culture positive		
Other samples (smear/ culture/DST	X		If no documented response to treatment		
Radiology, ECG and laboratory evaluations					
Chest X-ray	X			X	X
ECG	X	X	X	X	
Full blood count	X	X	X	X	
Liver function tests (AST, ALT and bilirubin)	X	X	X	X	
Serum electrolytes	X				
Urea, creatinine	X				
Pregnancy test	X				
HIV/HBV/HCV tests	X				
BSL/HbA1c	X				

ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; BSL: blood sugar level; DST: drug susceptibility testing; ECG: electrocardiography; HbA1c: glycosylated haemoglobin; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; TB: tuberculosis; WHO: World Health Organization.

Table 10.4-5 The schedule of baseline, routine and post-treatment monitoring examinations for the BPaLM/BPaL regimen

Clinical assessment

Vital signs, TB symptom screen, pain, nausea, appetite, and nutrition, diarrhea, and candidiasis. Clinical assessment should focus on monitoring the response to treatment and addressing common symptoms associated with TB treatment and long-term antibiotic use, with the goal of supporting adherence.

Psychosocial assessment

Food security, housing, mental state, and substance use. Psychosocial assessment should offer an opportunity to assess supportive factors for treatment adherence and should be directly linked to relevant interventions wherever possible, use the Psychosocial Assessment Form at the facility and during home visits.

Sputum DST

Ideally, the patient should at baseline have a WHO-recommended rapid molecular test (for rifampicin and fluoroquinolone resistance). Other investigations include culture-based second-line DST, next-generation sequencing, and DST for the BPaLM component drugs.

THE SCHEDULE OF BASELINE, ROUTINE, AND POST-TREATMENT MONITORING EXAMINATIONS FOR THE MODIFIED 9-MONTH MDR/RR-TB REGIMEN

*Prompt action on abnormal clinical or laboratory findings is essential **Circle each test completed												
Patient name:						**DR-TB registration number:**						
Age: **Sex:**						**Height:**						
Month/Year												
Examination	Baseline	1	2	3	4	5	6	7	8	9	10	11
Clinical exam	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X
Psychosocial, functional status	X	X	X	X	X	X	X	X	X	X	X	X
Weight/body mass index (wt/ht2)	X	X	X	X	X	X	X	X	X	X	X	X
Xpert MTB/RIF	X											
SL LPA or Xpert MTB/XDR	X	Repeat if smear or culture positive or suspect failure										
Smear	X	X	X	X	X	X	X	X	X	X	X	X
Culture	X	X	X	X	X	X	X	X	X	X	X	X
Phenotypic DST	X	Repeat if smear or culture positive or suspect failure										
X-ray	X						X					X
Full blood count1	X											
Creatinine, potassium2	X	X	X	X	X	X	X	X				
Liver function tests (ALT/AST)	X			X			X			X		
Fasting blood sugar	X											
Vision test charts3	X											
HIV test4	X			X								
Hepatitis B (HBsAg)	X											
Pregnancy test5	X											

CD4 count (HIV positive patients)	X						X					
Viral load (HIV positive patients)	X						X					

Table 10.4-6 The schedule of baseline, routine, and post-treatment monitoring examinations for the modified 9-month MDR/RR-TB regimen

- Repeat FBC as necessary if HIV-infected (a special care in patient with AZT) or if basal result is low.
- Repeat vision testing if any change/complaint in acuity or color vision.
- If HIV negative at baseline, HIV testing should be repeated at month 3 and then every 6 months.

Pregnancy test: at baseline, then offer the use of effective contraceptives (Depo-provera or Intra uterine device-IUD).

10.4.3.3. General considerations during DR-TB patient monitoring

- For children, height, and weight should be measured regularly to ensure that they are growing normally and adjust the dosage accordingly
- CXR may be unchanged or show only slight improvement (lesion regression may require 3 to 9 months), especially in patients with chronic pulmonary lesions, thus regular CXRs may not add value unless a surgical intervention is being considered, or the patient's clinical situation has worsened
- The most important objective evidence of improvement is the conversion of sputum smear or culture to negative
- Most patients who are adherent to an effective regimen are expected to convert to negative by month 3 of treatment
- The recurrence of TB symptoms after sputum conversion may be the first sign of treatment failure
- Persistently positive cultures beyond month 6 of treatment is a sign of likely treatment failure. Non-tuberculous mycobacterial infection could also be a possibility
- For patients who remain smear- and culture-positive during treatment or for whom treatment failure is suspected, second-line DST should be requested
- Recurrence of positive cultures after culture conversion is a sign of likely treatment failure, especially if it occurs after month 6 of treatment
- Paucibacillary culture results should not be automatically regarded as negative when treating drug-resistant-TB. Acquired drug resistance and treatment failure often begin with the growth of one or two colonies on a sputum culture
- Culture conversion is not equivalent to cure. (A proportion of patients may initially convert and later revert to positive sputum culture)
- Treatment outcomes should be assigned based on laboratory and clinical criteria during drug-resistant TB treatment

10.4.3.4. Post-treatment monitoring

Post-treatment monitoring is important to:

- Assess for relapse
- Monitor adverse events like neuropathy, and psychosis
- Assess and manage sequelae of drug-resistant TB like bronchiectasis, pneumothorax, and lung fibrosis
- Contact screening.

Once the patient has completed the course of treatment, the assessment must be performed at least every six months during the following one year. The assessment should include the following examinations:

- Clinical history and focused physical examination

- Body weight and anthropometry
- Sputum smear examination and culture
- CXR
- DST (if culture result is positive).

If during post-treatment examination the patient shows evidence of active TB, a full course of treatment with an individually constructed regimen based on history and DST must be restarted.

10.4.3.5. Adjuvant Therapies in drug-resistant TB Treatment

- The role of adjuvant therapies has not been well established. Nonetheless, some adjunctive modalities have proven beneficial in specific indications (i.e., use of corticosteroids in certain forms of TB such as central nervous system and pericardial involvement), while others show potential to improve outcomes.
- Corticosteroids can be beneficial in conditions like severe central nervous system or pericardial involvement. Prednisone is commonly used with a tapering of dosage over several weeks.
- Vitamin B6 (pyridoxine) should be given to all DR-TB patients receiving Cycloserine, and a high dosage of isoniazid or linezolid to prevent neurological side effects.
- Vitamin (especially vitamin A) and mineral supplements can be given in areas where a high proportion of the patients have these deficiencies.
- If multivitamins and minerals are given, they should be dosed three to four hours apart from the fluoroquinolone, as these can interfere with the absorption of these drugs.

10.4.3.6. Patient support

- Drug-resistant TB treatment and care should contain integrated nutritional assessment counselling and support for the duration of the illness.
- Drug-resistant TB can be exacerbated by poor nutritional status.
- Without nutritional support, patients, especially those already suffering from borderline hunger, can become enmeshed in a vicious cycle of malnutrition and disease.
- Second-line anti-TB medication can also further decrease appetite, making adequate nutrition a greater challenge.
- Providing free food probably improves weight gain during treatment, and may improve quality of life.

10.4.3.7. General consideration for patient support

- NTP procures nutritional supplements and distributes them to district hospitals quarterly.
- District hospitals distribute nutritional items monthly for patients on MDR-TB treatment and keep the necessary documentation.
- Hospitalised DR-TB patients should receive additional nutritional support
- Provision of nutritional support can be scheduled along with the patient's monthly follow-up visit at the registration site.
- The district hospital DR-TB officer-in-charge should keep records of patients who received support.

10.4.4. Treatment of drug-resistant TB and HIV

- Drug-resistant TB is often associated with higher mortality in PLHIV. Early diagnosis of drug-resistant TB and HIV, prompt initiation of appropriate second-line anti-TB drugs and antiretroviral treatment (ART), are all vital for optimal treatment outcomes.
- Perform provider-initiated HIV testing and counselling in all patients with presumed or diagnosed drug-resistant TB.

- Perform HIV test when sputum is sent for smear microscopy, culture or DST.
- Health care workers should use Xpert MTB/RIF as the initial diagnostic test for HIV-positive presumptive TB patients.
- Use mycobacterial cultures in HIV-positive TB suspects when Xpert MTB/RIF is negative but TB is still suspected (or if Xpert MTB/RIF is not available).
- In general, HIV patients have a higher rate of adverse drug reactions to both TB and non-TB medications, and the risk of adverse drug reaction increases with the degree of immunosuppression.
- Many of the medications used to treat drug-resistant TB and HIV have overlapping, or in some cases additive, toxicities.
- When possible, avoid the use of agents with shared side-effect profiles.
- If two drugs with overlapping toxicities are determined to be essential in a patient's regimen, it is recommended with increased monitoring of adverse effects rather than disallowing a certain combination.
- Second-line anti-TB drugs should be initiated first, followed by ART as soon as second-line anti-TB drugs are tolerated. ART is recommended for all patients with HIV and drug-resistant TB requiring second-line anti-TB drugs, as early as possible (within the first 8 weeks) following initiation of anti-TB treatment. Provide CPT for patients with active DR-TB and HIV as co-trimoxazole is not known to interact significantly with any of the second-line drugs but should be closely monitored. Implement sound patient follow-up and monitoring.

10.4.5. Treatment of drug-resistant TB in special conditions and situations

10.4.5.1. Pregnancy

- All female patients of childbearing age should be tested for pregnancy upon initial evaluation.
- Pregnancy is not a contraindication for treatment of active drug-resistant TB, but poses great risk to the lives of both the mother and foetus.
- Pregnant patients should be carefully evaluated, taking into consideration the gestational age and severity of drug-resistant TB.
- Since most teratogenic effects occur in the first trimester, treatment may be delayed until the second trimester when the patient is very stable with minimum disease (and HIV negative) but this should be agreed to by at least the patient and the doctor, after analysis of the risks and benefits.
- Treat with three or four oral second-line anti-TB drugs which are likely to be highly effective against the infecting strain.
- **In lactating mothers**, it is preferable to provide infant formula options as an alternative to breastfeeding. Clinicians and parents may agree to breastfeeding when formula is not a feasible option.

10.4.5.2. Contraception

Birth control is strongly recommended for all non-pregnant sexually active women receiving therapy for drug-resistant TB because of the potential consequences for both the mother and foetus resulting from drug-resistant TB treatment during pregnancy. There is no contraindication to the use of oral contraceptives with non-rifamycin containing regimens.

10.4.5.3. Renal insufficiency

Renal insufficiency caused by longstanding TB infection or previous use of aminoglycosides is not uncommon. Care should be taken in the administration of second-line drugs in patients with renal insufficiency, and the dose and/or the interval between dosing should be adjusted as per the patient's creatinine clearance, which is an estimate of the glomerular filtration rate or renal function.

10.4.5.4. Liver disorders

- All first-line drugs (isoniazid, rifampicin and pyrazinamide) are associated with hepatotoxicity. Although rifampicin is least likely to cause hepatocellular damage, it is associated with cholestatic jaundice.
- Pyrazinamide is the most hepatotoxic of the three first-line drugs. Among the second-line drugs, ethionamide,

prothionamide and PAS can also be hepatotoxic, although less so than any of the first-line drugs. Hepatitis occurs rarely with fluoroquinolone.

- In general, patients with chronic liver disease should not receive pyrazinamide. All other drugs can be used, but close monitoring of liver enzymes is advised. If significant aggravation of liver inflammation occurs, the drugs responsible may have to be discontinued.

10.4.5.5. Psychiatric disorders

It is advisable for psychiatric patients to be evaluated by a health care worker with psychiatric training before the start of treatment for drug-resistant TB. The initial evaluation documents and any existing psychiatric condition establish a baseline for comparison if new psychiatric symptoms develop while the patient is on treatment. Any psychiatric illness identified at the start of, or during, treatment should be fully addressed. Adverse effects from **cycloserine** may be more prevalent in psychiatric patients, but the benefits of using this drug may outweigh the potentially higher risk of adverse effects. Close monitoring is recommended if cycloserine is used in patients.

10.4.5.6. Seizure disorders

- Use the same regimen for patients with active seizure disorders.
- Adjust anti-seizure medication upwards to control seizures, especially where cycloserine is used.
- Seizures that present for the first time during anti-TB therapy are likely to be the result of an adverse effect of cycloserine.

10.5. Definition of terms and treatment outcomes

10.5.1. Culture conversion and reversion

For a patient to be considered bacteriologically positive at the start of second-line treatment, the following criteria must be met:

- At least one pre-treatment specimen was positive for smear, Xpert MTB/RIF or culture
- The collection date of the sample on which the laboratory examination was performed was <30 days before, or 7 days after, initiation of second-line treatment
- At least one sputum sample for smear and culture should always be taken at initiation of DR-TB treatment.
- Examinations are required at the start of treatment firstly to confirm the diagnosis of TB and determine the infectiousness.
- Sputum smear positive forms are the most infectious.
- Both sputum smear and sputum culture testing should be used to monitor patients throughout therapy.
- The monitoring of sputum culture is important for decisions on changes in treatment.

Bacteriological response: refers to bacteriological conversion with no reversion.

Bacteriological conversion: describes a situation in a patient with bacteriologically confirmed TB where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only), taken on different occasions at least 7 days apart, are negative.

Bacteriological reversion: describes a situation where at least two consecutive cultures (for DR-TB and DS-TB) or smears (for DS-TB only), taken on different occasions at least 7 days apart, are positive either after the bacteriological conversion or in patients without bacteriological confirmation of TB.Interim outcome indicators for MDR-TB

Negative culture at month six: Proportion of microbiologically confirmed pulmonary DR-TB cases registered and started on DR-TB treatment who have a negative culture at month 6.

Positive culture at month six: Proportion of microbiologically confirmed pulmonary DR-TB cases registered and started on drug-resistant treatment who have a positive culture at month 6.

Died at month six: Proportion of confirmed DR-TB cases registered and started on DR-TB treatment who died of any cause by the end of month 6.

LTFU at month six: Proportion of confirmed DR-TB cases started on DR-TB treatment who interrupted by the end of month 6.

10.5.2. Drug-resistant TB treatment outcomes

All drug-resistant TB patients who are registered to receive treatment with second-line drugs should be assigned one of the following treatment outcomes upon completion or interruption of treatment by NTP or the decision clinical team.

Treatment failed

A patient whose treatment regimen needed to be terminated or permanently changed to a new regimen or treatment strategy.

Cured

A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who completed treatment as recommended by the national policy, with evidence of bacteriological response and no evidence of failure.

Treatment completed

A patient who completed treatment as recommended by the national policy, whose outcome does not meet the definition of cure or treatment failure.

Died

A patient who died before starting treatment or during the course of treatment.

Lost to follow-up

A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.

10.5.3. Management of MDR-TB contacts

10.5.3.1. Clinical evaluation and investigation of contacts of DR-TB

Routine screening of all household contacts should include:

- Asking about cough, fever, weight loss, and other symptoms of TB.
- Detailed medical history for additional risk factors
- Physical examination
- Asking about HIV status of household contacts or performing HIV counselling and testing
- A household contact with any symptoms suggestive of active TB should receive all the following:
- Evaluation by a physician, including history and physical examination.
- CXR to look for signs of active TB (e.g., infiltrates cavities). The CXR should be kept to compare with subsequent CXRs.
- Bacteriological investigations of sputum or other samples:
  - Xpert MTB/RIF or Ultra is the recommended initial diagnostic test
  - Culture and DST must be done if Xpert MTB/RIF or Ultra is negative and suspicion of active TB or DR-TB remains high.

Remember that follow-up of DST results is necessary because delay in the diagnosis of DR-TB and start of appropriate treatment can lead to increased morbidity and mortality.

10.5.3.2. Management of symptomatic contacts

10.5.3.2.1. Household contacts of DR-TB patients with active PTB

Household contacts of DR-TB patients with active PTB should almost always be treated with DR-TB regimen. Such patients should be immediately referred to DR-TB treatment initiating centres for consideration of second-line treatment.

10.5.3.2.2. Household contacts of DR-TB patients with EPTB

EPTB is often culture-negative and DST will not be available. These contacts should be started on an DR-TB regimen based on the DST of the index patient. Every effort should be made to culture aspirates of pleural, peritoneal, or cerebrospinal fluid, depending on the site. Such patients should be referred to DR-TB treatment initiating centre for further evaluation and consideration of second-line treatment.

10.5.4. Management of drug-resistant TB interrupters

Length of treatment received prior to interrupting therapy	Result of last culture prior to interrupting treatment-OR-Result of smear and culture upon return to treatment	Actions
<3 months	Positive or negative	• Restart original regimen; patient will need full course of treatment. • Send sputum for culture and DST and adjust regimen to results.
3 months to end of Intensive phase	Negative	• Continue regimen patient was taking before interruption until two cultures return. • All patients should get a minimum of 20 months of therapy
	Positive	• Restart original regimen; patient will need full course of treatment for 20 months. • Send sputum for culture and DST and adjust regimen to results. • If treatment failure was suspected before interruption, consider designing a new regimen.
Continuation Phase	N/A	• If the patient has no evidence of clinical deterioration during interruption, restart the continuation phase. • Send sputum for culture and DST; • If negative, proceed with continuation phase • If positive, perform second-line DST and review with report and design new DR TB regimen • All patients should get a minimum of 20 months of therapy total.

Table 10.5-1 Management of drug-resistant TB interrupters

11. Pharmacovigilance

Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of Adverse Drug Reactions (ADRs) or any other drug related problems. All patients on TB treatment for Drug Sensitive and Drug Resistant TB should be monitored for ADRs. The following stepwise approach is helpful in assessing suspected ADRs in order to gather enough information necessary for causality assessment:

a. Take a detailed medical and full drug history to understand how the symptoms started.
b. Do a thorough physical examination with relevant laboratory tests to understand the nature of the symptoms.
c. Verify that the medicine prescribed was the medicine received and actually taken by the patient.
d. Verify that the onset of the suspected ADR was after the drug was taken and examine carefully the observations made by the patient.
e. Determine the time interval between the beginning of drug treatment and the onset of the event. Some reactions may occur immediately after administration of the medicine while other reactions will take time to develop.
f. Consider the effect of de-challenge and re-challenge. Resolution of suspected ADR when the drug is withdrawn is a strong, although not conclusive indication of drug- induced disease.
g. Analyse the alternative (non-drug) causes of the reaction. However, be mindful that the presence of alternative causes does not overrule the drug-related cause. It could be that the drug potentiates development of the ADR in presence of those alternative causes.
h. Once an ADR is suspected, Systematic and standardized recording and reporting should be done.

11.1. aDSM Definitions

Adverse drug reaction (ADR): is a response to a TB medicine which is noxious and unintended, and which occurs at doses normally used in humans. This term is used to qualify adverse events that are thought to be related to a drug. E.g: Peripheral neuropathy is an adverse reaction of linezolid.

Serious adverse event (SAE): is an AE that leads to: death or a life-threatening experience; hospitalization or prolongation of hospitalization; persistent or significant disability; or a congenital anomaly. SAEs that do not immediately result in one of these outcomes but that require an intervention to prevent it from happening are included. SAEs may require a drastic intervention, such as termination of the drug suspected of having caused the event. All SAEs require completion of the SAEs Reporting Form, and should be reported within 24 hours as part of the core package of aDSM.

Adverse event of clinical significance: is an AE which is either (i) serious, (ii) of special interest, (iii) leads to a discontinuation or change in the treatment, or (iv) judged as otherwise clinically significant by the clinician. Only provincial hospitals providing the advanced package of aDSM (e.g. a selected sentinel site) will include all AEs of clinical significance in their reporting.

Causality assessment: is the evaluation of the likelihood that a DR-TB drug was the causative agent of an observed adverse reaction. The formal causality assessment is performed by experts at the national Pharmacy and Medicines Regulatory Authority (PMRA).

11.2. Active TB Drug Safety Monitoring and Management (aDSM)

Active TB drug safety monitoring and management (aDSM) refers to the active and systematic clinical and laboratory assessment of patients while on DR-TB treatment and is a component of pharmacovigilance.

aDSM objectives

- To reduce risks from drug-related harms in patients on second-line treatment for drug-resistant TB and to generate standardized aDSM data to enable causality assessment for SAEs, determine their frequency (rates) and detect signals.
- This will contribute to future policy updates on the use of such medicines

11.2.1. To whom does aDSM apply

In general, all patients on DR-TB treatment in Malawi are eligible for aDSM. Specifically, aDSM applies to:

- TB patients treated with new medicines, such as Bedaquiline or Delamanid or Pretomanid;
- TB patients enrolled on treatment with novel regimens (medicines are not new but they have been combined in a new way to constitute a regimen), such as the shorter MDR-TB treatment regimen;
- All XDR-TB patients on second-line treatment (as these regimens often include multiple repurposed medicines and in some instances new medicines)

aDSM components

1. **Monitoring of AEs:** active and systematic clinical, laboratory, ECG, and Audiometry assessment during treatment to detect drug toxicity and AEs
2. **Management of AEs** in a timely manner
3. **Systematic and standardized recording and reporting of AEs**
   - Data collection to include safety data
   - SAEs and AEs of special interest should be reported to the PV and assessed for causality.

• Acute kidney injury (acute renal failure) • Psychiatric disorders and central nervous system toxicity • Optic nerve disorder (optic neuritis) or retinopathy • Phospholipidosis • Prolonged QT interval	• Ototoxicity • Myelosuppression • Peripheral neuropathy (paraesthesia) • Hypokalemia, • Pancreatitis • Lactic acidosis • Hepatitis • Mental health problems (psychosis, depression) • Hypothyroidism	Adverse event of clinical significance is those which are either (i) Serious, (ii) of special interest, (iii) Leads to a discontinuation or change in the treatment, or (iv) Judged as otherwise clinically significant by the clinician

**The combination of Pretomanid and Linezolid increases the risk of liver toxicity. More intense ALT monitoring is required amongst patients on regimens that contain both medicines.*
***For FQ-containing regimens, the combination of Bdq and Mfx increases the risk of QT prolongation. More intense ECG monitoring is required*

Table 11.2-1 Adverse events of special interest

Levels of monitoring in aDSM

In addition to drug safety monitoring, aDSM also incorporates a component that promotes the clinical management of all ADRs and AEs regardless of their seriousness. All AEs should be documented in the patient file as part of good clinical practice. In terms of reporting, the minimum requirement for aDSM is that all SAEs be registered and reported, regardless of their severity or whether they have been attributed to any of the medicines to which the patient is exposed. All detected adverse events (AEs) need to be managed clinically in a timely manner, and systematic clinical and laboratory assessments should be performed for early detection of drug toxicity and AEs.

aDSM packages according to the adverse event reported:

1. **Core package:** requiring monitoring for and reporting of all SAEs at each site initiating and managing patients on DR-TB treatment.
2. **Intermediate package:** includes SAEs as well as AEs of special interest.
3. **Advanced package:** includes all AEs of clinical significance.

The NTLEP will implement the advanced package of aDSM, that requires the reporting of all ADRs.

11.3. Management of adverse reaction for second-line TB drugs

Management of adverse effects: key considerations

- Patient education
- Minor side effects can be managed with ancillary drugs if needed while continuing the treatment regimen.
- Some side effects may disappear or diminish with time, and patients may be able to continue receiving the drugs as recommended. The side effects of many second-line drugs are highly dose dependent
- Reducing the dosage of the offending drug is another method of managing adverse effects but only in cases where the reduced dose will not compromise the regimen. With Cycloserine and ethionamide, for example, a patient may be completely intolerant at one dose and completely tolerant at a slightly lower dose

Given the narrow therapeutic margins of these drugs, lowering the dose may also affect efficacy, so every effort should be made to maintain an adequate dose of the drug based on body weight. Lowering the dose by more than one weight band should be avoided. Psychosocial support is through patient education about drug side effects and encouragement to continue treatment. *Table 11.2-2* below summarizes the common adverse effects to second line drugs, the likely responsible agents, and the suggested management strategies.

Grading and management of adverse events

Grade	Description
GRADE 1: Mild	Mild or transient discomfort without limitation of normal daily activities*. No medical intervention or corrective treatment is required.
GRADE 2: Moderate	Moderate limitation of normal daily activities*. Minimal medical intervention or corrective treatment required.
GRADE 3: Severe	Marked limitation of normal daily activities*. Medical intervention, therapy, stop or reduction of the offending drug is required. Possible hospitalization.
GRADE 4: Life-threatening or permanently disabling	Severe limitation of normal daily activities*. Medical intervention and corrective treatment required almost always in a hospital setting.

**The term 'activity' covers basic self-care functions such as bathing, dressing, toileting, transfer/movement, continence and feeding, as well as usual social and functional activities or adaptive tasks and desirable activities, such as going to work, shopping, cooking, use of transportation, or pursuing a hobby.*

Table 11.3-1 Severity grading scale of adverse events[6]

Appendix: common adverse effects to second-line drugs, the likely responsible agents and the suggested management strategies

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Prolonged QT interval **Possible DR-TB drug causes: Bdq, Dlm, Mxf, Cfz**				
Normal Values (msecs)	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Potentially Life-Threatening**
Male: ≤430 Female: ≤450	Borderline: Male: 430-450 Female: 450-470	Prolonged: Male: > 450- <500 Female: > 470 -< 500	Pathological: > 500 or ≥ 60 above baseline	Life-threatening consequences: QTcF ≥ 500 or >60 ms change from baseline and torsade de pointes or other associated serious ventricular dysrhythmia
Action	Monitor ECG frequently	Monitor more closely; at least weekly ECG until QTcF has returned to grade 1 or less. Check electrolytes and replete as necessary	Confirm with two additional 12-lead ECG (15-30 min apart). Stop the suspected causative drug. Hospitalize and replete electrolytes as necessary. Check TSH.	Stop the suspected causative drug. Hospitalize and replete electrolytes as necessary. Check TSH.

Suggestions and precautions:

- Close follow-up of patients at high risk who take several medicines that prolong the QT.
- Follow-up of potassium in high risk patients.
- Be careful in case of diarrhea, vomiting, use of diuretics, alcohol.
- Stop the medicine if QTc persists over 500ms even if the patient is asymptomatic.
- Think of arrhythmia when the patient suffers vertigo, syncope, palpitations.
- If QTcF is prolonged ≥ 500 ms (confirmed with two additional 12 Lead ECG 15-30 minutes apart):
- Stop all QT prolonging drugs immediately. ART is usually not stopped unless the patient is severely unstable.
- Hospitalize (if symptomatic or other risk factors). Frequent ECG monitoring.
- Check electrolytes and manage accordingly. (If low potassium: urgent management with replacement and frequent monitoring). Give Magnesium sulphate supplements (orally or IV) and calcium.
- Check a TSH and treat any hypothyroidism found.
- Check albumin if on Delamanid.
- Once stable (QTcF < 450 and normal electrolytes), critical prolonging QT drugs can be added back:
- If the patient was on Mfx consider using Lfx instead.
- If the patient was on Cfz consider suspending it permanently (if not critical to the regimen).
- If the patient is on Bdq (or Dlm), and is critical to the regimen, add it back while suspending all other QT prolonging drugs (with the exception of stopping ART, which should not normally be suspended in the management of QT prolongation).

	Hb (g/dL)	Platelets(/ mm3)	Neutrophils (/mm3)	AST (UI/L)	ALT (UI/L)	Creatinine (µmol/L)	K+ (mEq/L) / (mmol/L)
Normal values	>12	>150,000	>1,500	*	*	*	3.5-5.0
Grade 1	10-11.9	100,000-149,999	1,000-1,500	1.5-2.5 x ULN	1.5-2.5 x ULN	1.1-1.5 x ULN	3.2-3.4
Grade 2	8- 9.9	50,000-99,999	750-999	2.6-5.0 x ULN	2.6-5.0 x ULN	1.6-3 x ULN	2.8-3.1
Grade 3	6-8	20,000-49,999	500-749	5.1-10 x ULN	5.1-10 x ULN	3-6 x ULN	2.5-2.7
Grade 4	<6	<20,000	<500	>10 x ULN	>10 x ULN	> 6 x ULN	<2.5

Table 11.3-2 Severity grading scale of main laboratory parameters [13,14]

**Normal values vary from laboratory to laboratory and might be slightly different in men, women and children (check normal parameters for local laboratory).*

ULN= upper limit of normal

Hepatotoxicity **Possible DR-TB drug causes: Z, H, Pto, Lzd, Cfz, Bdq, Mfx, Pa**				
	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
ALT (SGPT)	1,25 – 2,5 x ULN	2,6 – 5,0 x ULN	5,1 – 10,0 x ULN	> 10,0 x ULN
AST (SGOT)	1,25 – 2,5 x ULN	2,6 – 5,0 x ULN	5,1 – 10,0 x ULN	> 10,0 x ULN
Action	Continue treatment Patients should be follow until resolution (return to baseline) or stabilization of AST/ ALT elevation.	Continue treatment Patients should be followed until resolution (return to baseline). If JAUNDICE: Stop all anti-TB drugs until resolution	Stop all drugs, including anti-TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved.	Stop all drugs, including anti-TB drugs; measure LFTs weekly. Treatment may be reintroduced after toxicity is resolved

- Consider other potential causes of hepatitis: viral (hepatitis B and C), HIV, alcohol).
- Avoid potentially hepatotoxic non-tuberculosis drugs.

Reintroduction of anti-TB drugs:

- Check ALT/AST once a week. Reintroduce anti-TB drugs once liver enzymes return to at least Grade 2.
- Anti-TB drugs should be reintroduced in serial fashion. The least hepatotoxic drugs should be added first: Km-E-Cfz-Mfx. Then introduce the more hepatotoxic one by one every three days: Pto-H-Z while monitoring liver function tests after each one to identify the responsible drug.
- If reintroduction leads to signs of hepatotoxicity, stop the suspected drug and replace it by another if it is essential for the treatment. If the drug stopped is H or Z there is no need to replace by another agent. Follow transaminases monthly.
- If patient is on ART and experienced Nevirapine (NVP) hepatotoxicity should not be re-challenged with NVP.

Peripheral neuropathy **Possible DR-TB drug causes: Lzd, Cs, FQ** **Possible other causes: Diabetes mellitus, alcohol, HIV infection, Vitamin B deficiency, hypothyroidism and other drugs**				
	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Neurosensory alteration (including paresthesia and painful neuropathy)	Asymptomatic with sensory alteration on exam or minimal paresthesia causing no or minimal interference with usual social and functional activities	Sensory alteration or paresthesia causing greater than minimal interference with usual social and functional activities	Sensory alteration or paresthesia causing inability to perform usual social and functional activities	Disabling sensory alteration or paresthesia causing inability to perform basic self-care functions
Action	Stop offending drugs (Lzd). If symptoms improve after 2 weeks consider restarting Lzd at a lower dose (300 mg)	Stop Lzd. Do not reintroduce Lzd.	Stop Lzd. Do not reintroduce Lzd.	Stop Lzd. Do not reintroduce Lzd.

Suggested management strategy

The neuropathy associated with Linezolid is common after prolonged use and often extremely painful and irreversible. For this reason, Linezolid should be immediately stopped and not reintroduced when symptomatic neuropathy develops (grade 2 and above).

Symptomatic relief:

- Increase pyridoxine (Vit B 6) to a maximum of 150 mg.
- Nonsteroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms.
- Tricyclic antidepressants have also been used successfully. Start amitriptyline 25 mg at bedtime. The dose may be increased to a maximum of 150 mg daily for refractory symptoms.
- Carbamazepine may also be effective in relieving pain and other symptoms of peripheral neuropathy. Carbamazepine is a strong inducer of CYP3A4 and should not be used with Bedaquiline or Delamanid.

Myelosuppression (anemia, thrombocytopenia, or neutropenia) **Possible anti-TB drug causes: Lzd[1]** **Possible other causes: AZT, cotrimoxazole, HIV Infection, chemotherapy**				
	Grade 1	Grade 2	Grade 3	Grade 4
Absolute neutrophil count	Mild	Moderate	Severe2	Life-threatening2
Haemoglobin	1000 – 1300/mm3	750 – 999/ mm3	500 – 749/mm3	< 500/ mm3
Platelets, decreased	8.5 – 10.0 g/dl	7.5 – 8.4 g/dl	6.5 – 7.4 g/dl	< 6.5 g/dl

WBC, decreased	100,000 – 124,999 /mm³	50,000 – 99,999 / mm³	25,000 – 49,999 / mm³	< 25,000 /mm³
Action	2000 – 2500 /mm3	1500 – 1999 /mm3	1000 – 1499 /mm3	< 1000 /mm3
	Monitor carefully, and consider reduction of dose of Lzd to 300mg daily	Monitor carefully, and consider reduction of dose of Lzd to 300mg daily; in case of Grade 2 neutropenia, stop Lzd immediately. Restart at reduced dose (300 mg) once toxicity has decreased to Grade 1.	Stop Lzd immediately. If Hb ≤ 7 g/dl, transfuse. Restart at reduced dose (300 mg) once toxicity has decreased to Grade 1.	Stop Lzd immediately. Give transfusion and erythropoietin if available. Restart at reduced dose (300 mg) once toxicity has decreased to Grade 1.

Suggested management strategy

- All patients taking linezolid should also be receiving at least 100 mg of Pyridoxine daily. This is largely to prevent myelosuppression, but may also prevent peripheral neuropathy.
- Stop the causative drug immediately.
- Monitor full blood counts regularly.
- Hospitalize the patient and consider transfusion if the myelosuppression is severe (e.g. Hb ≤ 7 g/dl).

Optic neuritis
Possible anti-TB drug causes: Lzd, E
Possible other causes: Multiple sclerosis, quinine, Herpes, Syphilis, Sarcoidosis, Cytomegalovirus (HIV)
The first sign of optic neuritis is usually the loss of red-green color distinction. This is best tested using the Ishihara test. Other symptoms include central scotoma (loss of central vision or blind spot)

	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Optic neuritis is inflammation of the optic nerve resulting in permanent vision loss.	Visual changes causing minimal or no interference with usual social and functional activities.	Visual changes causing greater than minimal interference with usual social and functional activities.	Visual or changes causing inability to perform usual social and functional activities.	Disabling visual loss.
Action	Stop Lzd (or E immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd or E immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd or E immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd or E immediately if there are any suspicions of optic neuritis. Do not restart it.

Suggested management strategy

- Do not restart the suspected causative drug (linezolid or ethambutol)
- Refer patient to an ophthalmologist for further evaluation and management.
- Optic neuritis generally improves following cessation of offending drug, if it can be stopped early enough.
- Patients with diabetes are at increased risk for optic neuritis. They should be managed with tight glucose control as a means of prevention. Patients with advanced kidney disease are also at increased risk for optic neuritis.

Lactic acidosis **Possible anti-TB drug causes: Lzd** **Possible other causes: AZT, 3TC**				
	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Lactate and pH	< 2.0 x ULN without acidosis	≥ 2.0 x ULN without acidosis	Increased lactate with pH < 7.3 without life threatening consequences	Increased lactate with pH < 7.3 with life threatening consequences
Action	Continue treatment regimen. Patients should be followed until resolution (return to baseline).	Stop Lzd immediately. Do not restart it.	Stop Lzd immediately. Do not restart it.	Stop Lzd immediately. Do not restart it.

- Early signs and symptoms include nausea, vomiting, abdominal pain, anxiety, and increased respiration rate and heart rate. Late symptoms include lethargy, hypotension and septic shock. Early detection of lactic acidosis is important because full-blown lactic acidosis is often fatal.
- Diagnosis: analysis of an arterial blood sample showing a low pH and high lactate: anion gap, metabolic acidosis, lactate > 5 mmol/L, increased lactate/pyruvate.
- If laboratory is not available, start treatment with clinical features

Suggested management strategy

- Stop linezolid and NRTIs if lactic acidosis occurs. It may take months for the lactic acidemia to resolve completely even after the causative drug is stopped.
- Hospitalize patient and monitor serum electrolytes, renal function, arterial blood gas, and lactate levels.
- Check vital signs frequently and provide supportive care. Sodium bicarbonate therapy to correct a low pH has not been shown to be of benefit in lactic acidosis.
- After lactic acidosis resolves, do not restart the suspected offending medication.

Pancreatitis **Possible DR-TB drug causes: Bdq, Lzd** **Other causes: gallstones, heavy and long-term alcohol use, high triglycerides**				
	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Pancreatitis	Not Applicable	Symptomatic and Hospitalization not indicated	Symptomatic and Hospitalization indicated	Life-threatening consequences (e.g., circulatory failure, haemorrhage, sepsis)
Lipase	1.1 – 1.5 x ULN	1.6 – 3.0 x ULN	3.1 – 5.0 x ULN	> 5.0 x ULN
Amylase	1.1 - 1.5 x ULN	1.6 - 2.0 x ULN	2.1 - 5.0 x ULN	> 5.1 x ULN

Action	Continue treatment regimen. Patients should be followed until resolution (return to baseline).	Stop Lzd immediately. Do not restart it.	Stop Lzd immediately. Do not restart it.	Stop Lzd immediately. Do not restart it.
The most common symptoms and signs include severe epigastric pain (upper abdominal pain) radiating to the back in 50% cases, nausea and vomiting. **Suggested management strategy** • Monitor liver function tests, amylase, lipase, and full blood count. • Provide supportive care. • Permanently discontinue linezolid (or bedaquiline if it is suspected to be the cause of the pancreatitis)				
Gastrointestinal (Nausea and Vomiting) Possible DR-TB drugs: Eto/Pto, PAS, Bdq (less common H, E, Z, Cfz, Dlm)				
Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening	
1 episode in 24 hours	2-5 episodes in 24 hours	>6 episodes in 24 hours or needing IV fluids	Physiologic consequences requiring hospitalization or requiring parenteral nutrition	

Management and comments

- Nausea and vomiting are universal in early weeks of therapy and usually abate with time on
- treatment and adjunctive therapy. Some nausea and even vomiting may need to be tolerated at
- least in the initial period.
- Assess for danger signs including dehydration, electrolyte disturbances and hepatitis.
- Initiate rehydration therapy if indicated and correct any electrolyte disturbances.
- Initiate a stepwise approach to manage nausea and vomiting.

Phase 1:

- Give a light snack (biscuits, bread, rice, tea) before the medications.
- Another strategy is to stop the responsible medicine for two or three days and then add it back gradually increasing the dose (advise the patient that the medicine will be increased back to a therapeutic dose in a manner that will be better tolerated).

Phase 2: Start antiemetic(s):

- Metoclopramide 10 mg, 30 minutes before anti-TB medications.
- Ondansetron 8 mg, 30 minutes before the anti-TB drugs and again eight hours after. Ondansetron can either be used on its own or with metoclopramide. Odansetron prolongs the QT interval; avoid with bedaquiline or delamanid.
- If ondansetron is not available, promethazine can be used.) Promethazine25 mgPO,30 minutes before the anti-TB drugs (may be increased to 50 mg 3 times daily).
- Omeprazole or Ranitidine can also provide relief (omeprazole decreases the acid production, is also useful in the treatment of nausea).

Phase 3: Decrease dose of the suspected drug by one weight class if this can be done without compromising the regimen. It is rarely necessary to suspend the drug completely.

Note: For patients who are particularly anxious about the nausea, (and with "anticipatory nausea and vomiting") a small dose of an anti-anxiety medicine (5 mg of diazepam) can help when given 30 minutes prior to the intake of anti-TB drugs. Do not give diazepam longer than 2 weeks.

Gastritis
Possible DR-TB drug causes: Eto, Pto, Cfz, FQs, H, E, and Z

If symptoms are associated consistent with gastritis (epigastric burning or discomfort, a sour taste in mouth associated with reflux) initiate medical therapy (prolonged duration):

- Omeprazole 20 mg once daily (proton-pump inhibitors). Give 2 hours before or 3 hours after the TB medication
- Ranitidine 150 mg twice daily or 300 mg once daily (H2-blockers)
- Avoid the use of antacids as they decrease absorption of fluoroquinolones.
- Stop any nonsteroidal anti-inflammatory drugs the patient may be taking.
- Diagnose and treat for Helicobacter pylori infections.

Abdominal pain
Possible DR-TB drugs: Eto, Pto, Cfz, Lzd

- Abdominal pain is most commonly gastritis. However, can also be associated with serious adverse effects, such as pancreatitis, lactic acidosis (Lzd) and hepatitis. If any of these are suspected, obtain appropriate laboratory tests to confirm and suspend the suspected agent.
- For severe abdominal pain stop suspected agent(s) for short periods of time (one to seven days).
- Lower the dose of the suspected agent, if this can be done without compromising the regimen.
- Discontinue the suspected agent if this can be done without compromising the regimen.
- Severe abdominal distress has been reported with the use of clofazimine (deposition of Cfz crystal). Although these reports are rare, if this occurs, clofazimine should be suspended.

Diarrhea
Possible DR-TB drugs: PAS, Eto/Pto

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Mild or transient; 3-4 loose stools/ day or mild diarrhoea last < 1 week	Moderate or persistent; 5-7 loose stools/day or diarrhoea lasting >1 week	>7 loose stools/day or bloody diarrhoea; or orthostatic hypotension or electrolyte imbalance or >2L IV fluids required	Hypotensive shock or physiologic consequences requiring hospitalization

Management

1. Encourage patients to tolerate some degree of loose stools and flatulence.
2. Encourage fluid intake.
3. Check other causes of Diarrhea. Fever and diarrhea and/or blood in the stools indicate that diarrhea may be secondary to bacterial enteritis or pseudomembranous colitis (C. difficile) related to FQ. If HIV positive assess CD4 and think other possible causes (CMV, isospora, microsporidium)
4. Check serum electrolytes (especially potassium) and dehydration status if diarrhea is severe.
5. Treat uncomplicated diarrhea (no blood in stool and no fever) with loperamide 4 mg by mouth initially followed by 2 mg after each loose stool to a maximum of 10 mg per day.

Rash, allergic reaction and anaphylaxis
Possible DR-TB drugs: any drug

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Erythema; moderate pruritus	Extended maculopapular eruption (with or without pruritus)	Extensive papulovesicular eruption, palpable purpura cut., mist desquamation or ulcerations	Exfoliative dermatitis, mucous membrane involvement or erythema multiforme or suspected Stevens-Johnson or cutaneus necrosis requiring surgery

Management

1. For serious allergic reactions (grade 3-4), stop all therapy pending resolution of reaction. In the case of anaphylaxis manage with standard emergency protocols (including adrenaline). If Steven Johnson Syndrome treat with IV corticosteroid, IV fluids and IV broad spectrum antibiotic.Suspend permanently any drug identified to be the cause of a serious reaction. Any drug that resulted in anaphylaxis or Stevens–Johnson syndrome should never be reintroduced
2. Eliminate other potential causes of allergic skin reactions (like scabies or other environmental agents).
3. For minor dermatologic reactions, various agents may be helpful and allow continuation of the medication. They include:
   - Antihistamines
   - Hydrocortisone cream for localized rash
   - Prednisone in a low dose of 10 to 20 mg per day for several weeks can be tried
   - Dry skin may cause itching (especially in diabetics), liberal use of moisturizing lotion is recommended. Dry skin is a common and significant problem with clofazimine.

Arthralgia/ Arthritis
Possible DR-TB drugs: Z (less frequent FQ, Bdq)

	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Arthralgia (joint pain)	Mild pain not interfering with function	Moderate pain, analgesics and/ or pain interfering with function but not with activities of daily life (ADL)	Severe pain; pain and/or analgesics interfering with ADL	Disabling pain
Arthritis (inflammation involving a joint)	Mild pain with inflammation, erythema or joint swelling, but not interfering with function	Moderate pain with inflammation, erythema or joint swelling; interfering with function, but not with activities of daily life (ADL)	Severe pain with inflammation, erythema or joint swelling and interfering with ADL	Permanent and/ or disabling joint destruction

Management

- Give NSAIDs: ibuprofen 400 mg 3 times a day
- Rest the joint
- Initiate therapy with nonsteroidal anti-inflammatory drugs:
- Ibuprofen 400 mg three times a day or Indomethacin 50 mg twice daily
- Lower the dose or discontinue the suspected agent (most commonly pyrazinamide) if this can be done without compromising the regimen.
- Uric acid levels may be elevated in patients on pyrazinamide. There is little evidence to support the addition of allopurinol for arthralgia, although if gout is present it should be used.
- If acute swelling, redness and warmth are present in a joint, consider aspiration for diagnosis of gout, infections, autoimmune diseases, etc.

Psychosis
Possible DR-TB drugs: Cs, FQ, Eto/Pto

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening

Mild psychotic symptoms	Moderate psychotic symptoms (e.g., disorganized speech; impaired reality testing)	Severe psychotic symptoms (e.g., paranoid; extreme disorganization); hospitalization not indicated	Acute Psychosis (suicidal ideation, maniac status, hallucinations). Life-threatening consequences, threats of harm to self or others; hospitalization indicated

Management

The most likely drug is cycloserine followed by high dose isoniazid.

1. Stop the suspected agent for a short period of time (1–4 weeks) while psychotic symptoms are brought under control.
2. Always check creatinine in patients with new onset psychosis. A decrease in renal function can result in high blood levels of cycloserine, which can cause psychosis.
3. If moderate to severe symptoms persist, initiate antipsychotic therapy (haloperidol). Atypical antipsychotics should be used for DR-TB patients on multiple QT prolonging DR-TB drugs since haloperidol significantly prolongs the QTc interval and has been associated with torsades de pointes.
4. Hospitalize in a ward with psychiatric expertise if patient is at risk to himself/herself or others.
5. Increase pyridoxine to the maximum daily dose (200 mg per day).
6. Lower the dose of the suspected agent (most commonly cycloserine to 500 mg a day)
7. Discontinue the suspected agent if this can be done without compromising the regimen.
8. Once all symptoms resolve and patient is off cycloserine, antipsychotic therapy can be tapered off. If cycloserine is continued at a lower dose, antipsychotic therapy may need to be continued and any attempts of tapering off should be done after referring to a psychiatrist.

Some patients will need to continue antipsychotic treatment throughout DR-TB treatment (and discontinued gradually upon completion of treatment)

Previous history of psychiatric disease is not a contraindication to cycloserine, but its use may increase the likelihood of psychotic symptoms developing during treatment. Avoid if there is an alternative.
Psychotic symptoms are generally reversible upon completion of DR-TB treatment or cessation of the offending agent.

Depression
Possible DR-TB drugs: Cs, FQ, Eto/Pto
Other causes: Psychological and socioeconomic circumstances, chronic disease

Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening

Mild depressive symptoms; and/or PHQ9 depression score 1-9.	Moderate depressive symptoms; limiting instrumental Activities of Daily Life (ADL); and/or PHQ9 depression score 10-14.	Severe depressive symptoms; limiting self-care ADL; hospitalization not indicated; and/or PHQ9 depression score 15-19.	Life-threatening consequences, threats of harm to self or others; PHQ9 depression score 20-27; and/or hospitalization indicated.
Management: Anti-TB Therapy may contribute to depression. Depressive symptoms may fluctuate during the therapy. • Asses and address underlying emotional and socioeconomic issues. • Provide psychological support (for the patient and family) • If depression is significant, initiate antidepressant therapy (amitriptyline, fluoxetine) • Avoid serotonin reuptake inhibitors and tricyclic antidepressant with linezolid (risk of serotonin syndrome) • Lower the dose of the suspected agent if this can be done without compromising the regimen. (Reducing the dose of cycloserine and ethionamide to 500 mg daily). • Discontinue the suspected agent if this can be done without compromising the regimen.			
Seizures **Possible DR-TB drugs: Cs, H, FQ, Imp/Cln**			
First address other causes of seizures: infection, epilepsy, meningitis, encephalitis, alcohol withdrawal, hypoglycemia, cerebrovascular accident, malignancy or toxoplasma in PLHIV). Then: 1. Hold cycloserine, fluoroquinolones and isoniazid pending resolution of seizures. 2. Initiate anticonvulsant therapy (carbamazepine, phenytoin or valproic acid are most commonly used). 3. Increase pyridoxine to the maximum daily dose (200 mg per day). 4. Check serum electrolytes including potassium, sodium, bicarbonate, calcium, magnesium and chloride (replace accordingly). 5. Check creatinine level. A decrease in renal function can result in high blood levels of cycloserine, which can cause seizures. Adjusting the dose of cycloserine in the presence of low creatinine may be all that is needed to control the seizures 6. When seizures have resolved, restart medications one at a time. Cycloserine should not be restarted unless itis absolutely essential to the regimen. If cycloserine is reinitiated, start a dose one weight band lower. **Notes:** • An anticonvulsant is generally continued until DR-TB treatment is completed or suspected agent is discontinued. • History of previous seizure disorder is not a contraindication to the use of agents listed here if a patient's seizures are well controlled and/ or the patient is receiving anticonvulsant therapy. (Do not include cycloserine if an alternative drug is available.) • Carbamazepine is a strong inducer of CYP3A4 and should not be used with Bedaquiline or Delamanid.			

Table 11.3-3 Management of adverse events associated with DR-TB treatment

Reporting adverse drug reactions

Healthcare professionals should bear in mind that they are required to report a suspected causal association between a drug and an adverse event; as such they should not wait until when they feel certain that a causal link can be considered proven or otherwise. Any healthcare professional can report suspected Adverse Drug Reactions

(ADR) by completing the standard reporting forms. The minimum information required for the submission of an ADR report are a named suspected medicine, a suspected reaction, an identifiable patient and an identifiable reporter. If the data submitted in the report lacks any of this essential information, the report cannot be assessed objectively and will not be entered into the ADR database

Use standard reporting forms

ADR reports should be submitted to the National Pharmacovigilance Center using standard reporting forms in appendix 1 for ADR reporting form.

Healthcare professionals' approach to ADR reporting

- The points outlined below will help healthcare professionals to collect accurate and high quality information about a suspected adverse drug reaction
- Suspected ADRs should be reported as soon as they occur/identified. It is easier to gather information for recent events than older ones. Secondly, an ADR report is likely to be accurate when the event is recent.
- The decision to report an ADR should be made while the patient is still with you so that you can easily ask about the event and fill in the details in the reporting form. Ask the patient and/or look for other comorbidities that the patient has that might contribute to the reaction or the observed sign, symptom, or laboratory abnormality. Include as much details to support your suspicion including laboratory investigations, x-ray images, and patient photos where necessary.
- Ask the patient particularly about other products taken which may have contributed towards the event, e.g. other concomitant drugs, herbal products, food supplements, chemicals, etc.
- A follow-up report should be submitted if any additional data becomes available later e.g. if the same patient develops the effect again or if something happens which increases your suspicions or seems to exclude the effect.
- In cases where a fetus or breastfed infant sustains an ADR, information on the mother and the child/fetus should be provided.
- Always write legibly to ensure the correct interpretation of the information on the ADR report at the PMRA.

Flow of information

At district level, the safety monitoring system will be coordinated by the District Pharmacovigilance Focal Person (DPC) who will be chosen by the District Health Office. All healthcare facilities in the district should send ADR reports to the DPC who will submit the reports to PMRA.

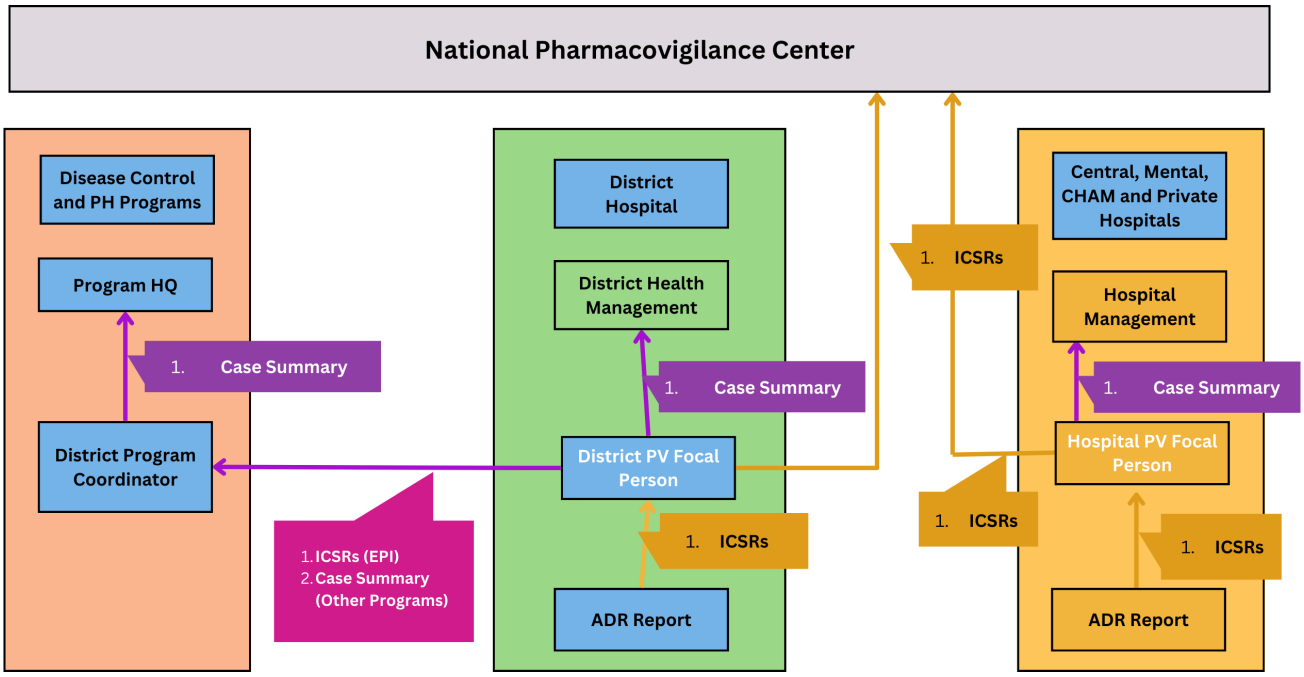


Figure 11.3-1 Flow of information

Roles of district pharmacovigilance coordinator

The District Pharmacovigilance Coordinator is responsible for the following:

- Ensure that facilities in the district have adequate reporting forms
- Ensure that reporting forms are easily accessible to health care workers
- Keep a record of ADR cases reported in the district
- Help with follow-up of safety cases and collection of additional information that may be required by the PMRA for causality assessment.
- Ensuring that safety reports are complete before sending to the PMRA.
- Provide feedback received from PMRA back to the reporter
- Reporting to facility Drug and Therapeutic Committees of ADR that occurred at their facilities

Reporting routes and timelines

Healthcare professionals should report all suspected ADRs to the District Pharmacovigilance Focal Person (DPFP) preferably within 24 hours who will then send the reports within two calendar days to PMRA for immediate action. ADR reports can be delivered by hand or sent to the following address:

Pharmacy and Medicines Regulatory Authority (PMRA)
P. O. Box 30241 Capital City,
Lilongwe 3
MALAWI

12. Post Tuberculosis Associated Disabilities (PTAD)

12.1. Definition of terms

TB associated disability

TB associated disability refers to the range of health conditions which, as a result of the illness, the disease and/or its treatment, in interaction with personal and environmental factors, limit the day to day physical, social and economic functioning (walking, self-care, family and community life, and ability to work) of people with TB and especially in this case, TB survivors.

Post TB lung disease (PTLD)

Post-TB Lung Disease refers to the residual pulmonary manifestations and structural changes that persist in individuals after the successful completion of treatment for tuberculosis (TB). Even after the eradication of active TB infection, the lungs may sustain damage due to the inflammatory response triggered by the Mycobacterium tuberculosis bacterium.

Signs and symptoms of PTLD

1. Shortness of breath
2. Chronic cough
3. Wheeze
4. Chest pain
5. Hemoptysis (coughing blood)
6. Fatigue
7. Expectorate copious sputum

Diagnostic criteria for post TB lung disease

1. Persistent respiratory symptoms
2. Abnormalities in lung function tests (spirometry)
3. Abnormalities on chest x-ray
4. Reduced exercise tolerance

Management of PTLD

1. Pulmonary rehabilitation

Lung Rehabilitation is a comprehensive, multidisciplinary program designed to improve the overall well-being and functional capacity of individuals with chronic respiratory conditions, such as chronic obstructive pulmonary disease (COPD), interstitial lung disease, and post-tuberculosis lung disease (Also refer to the post TB pulmonary rehabilitation pathway).

Self-motivated to participate in the Program	MRC (Medical Research Council) score of 4 (dyspnea)
Must have had TB and finished TB treatment and is diagnosed or presenting with one or more of the following conditions: 1. Lung problems 2. Shortness of breath 3. Reduced exercise tolerance 4. Limited functional capacity due to dyspnea or generalized body weakness linked to the TB illness	History of a serious cardiac event during the last 6 weeks
	Severe orthopedic or neurological disorders limiting their mobility.
	Active cancer
	Severe pulmonary arterial hypertension
	Exercise induced syncope
	Unstable diabetes
Children should be above 5 years	Severe induced hypoxemia
	Unstable angina or recent Myocardial infarction

Table 12.1-1 Inclusion and exclusion criteria into a pulmonary rehabilitation program

2. Medical management
   A. Bronchodilators: These medications help to open the airways and relieve symptoms like wheezing and shortness of breath, improving airflow and breathing capacity.
   B. Corticosteroids: In cases of inflammation and airway narrowing, corticosteroids may be prescribed to reduce inflammation and alleviate symptoms.
   C. Oxygen Therapy: Supplemental oxygen may be prescribed for individuals with severe lung impairment to enhance oxygen delivery to tissues and alleviate symptoms of hypoxemia.
   D. Symptom Management: Medications for cough suppression, mucus clearance, and pain relief can help manage common symptoms like cough, sputum production, and chest discomfort.

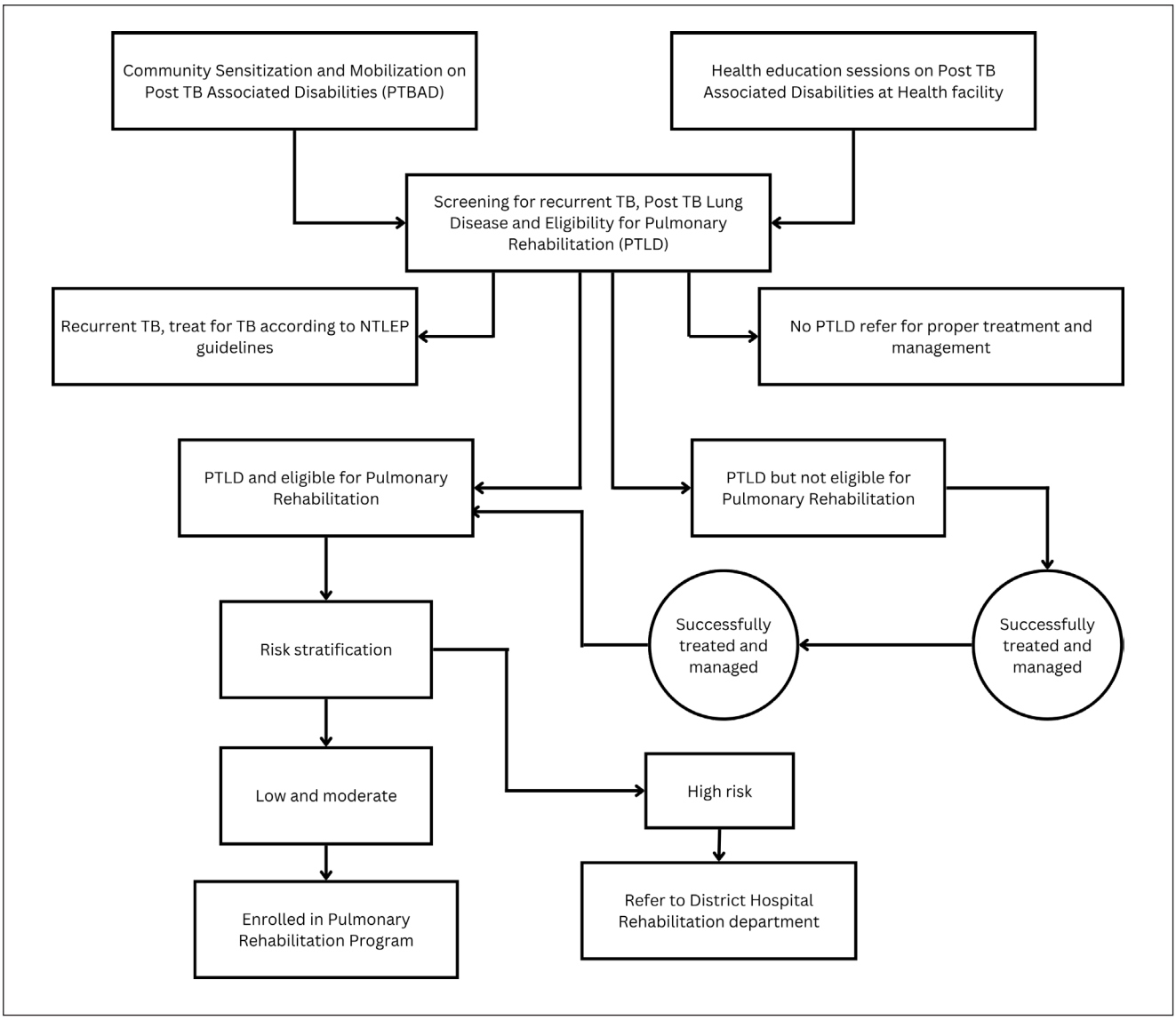


Figure 12.1-1 Post TB Pulmonary Rehabilitation Pathway

13. Monitoring and evaluation for TB

The national TB M&E system was designed to report on key data elements required by WHO and the program. All data recording and reporting tools were designed to report on the minimum requirements as defined by WHO. Through the system, the program is able to collect data on case notification as well as treatment outcomes for TB patients. Over the period, the program has made tremendous efforts to improve its surveillance system. Such efforts included capacity building of health care workers on documentation and reporting, periodic data quality assessments, customization of TB reporting modules on DHIS 2, E-health system (implemented in selected SATBHSSP supported project sites), Gx Alert system to support results transmission from GeneXpert sites.

Data Sources

The following data sources are currently being used by the program to collect TB data

1. Integrated TB/HIV supportive supervision
2. Routine TB reporting system (DHIS2)
3. Administrative reports (training, supervision, and mentoring)

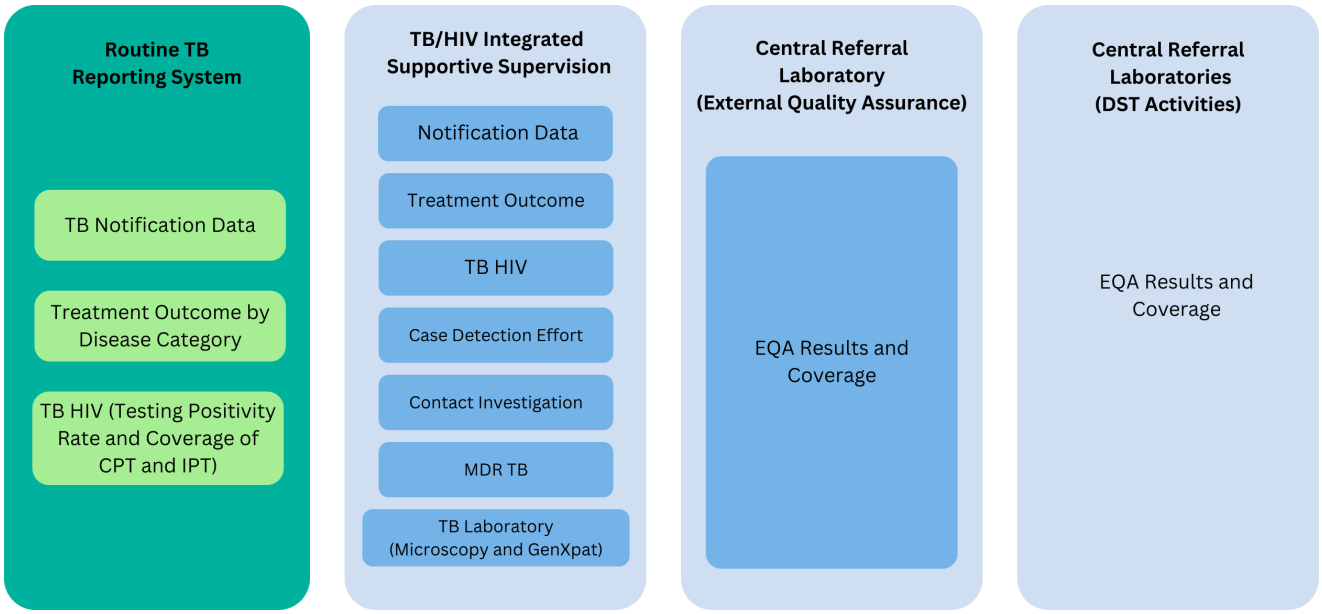


Figure 12.0-1 Sources of TB data

Data Collection and Reporting Mechanisms

Currently the program is using two data reporting mechanisms

1. Integrated TBHIV Supervision
2. Routine System (DHIS2).
3. One impact data recording tool.

Integrated TBHIV Supervision

This is done on a quarterly basis, and it covers more than 800 facilities that provide HIV services. All TB registration sites are also targeted during these supervisions. Thirty-two (32) teams composed of clinicians, program officers, technical personnel from programs, and partners participate in the supportive supervision. Prior to the supervision, a one-day meeting is organized for all supervisors to share program updates, discuss observations from the previous supervision, distribute materials, and organize logistics, transport, and accommodation.

Data sources: Data sources for TB/HIV supervision are the following: -

- **TB unit register:** source of data for notification, treatment outcome, and TB/HIV components
- **TB laboratory register:** data is available on presumptive TB cases examined, yield, GeneXpert performance and yield /outcome of these tests.
- **Presumptive TB register:** key source of data to monitor case detection effort in the facility. It is used to monitor the implementation of systematic TB screening health care settings.
- **Contact investigation register:** source of data to monitor the implementation of contact investigation.
- **Quarterly facility report:** Used to consolidate quarterly TB data. The same is used to check the quality of the data reported and verified during data quality assessment.
- **DR-TB register (second-line register):** DR TB detection and treatment outcomes are reported from this source.
- **Stock card (pharmacies, drug store and registration facility):** Stock status in the health facilities from both pharmacy stores and TB clinics are updated using the tool.
- **District Leprosy register:** Source of data on Leprosy for treatment initiation, outcome, disability, Reactions, and defaulters.
- **Components of supervision tool:** The supervision tool is composed of the following sections.
- **Basic facility information:** Basic facility information is provided in this part of the checklist.
- **Tuberculosis infection prevention:** help assess the implementation of all components of TB IC. (Administrative managerial, personal protective and others)
- **Case detection effort:** primary data source is the Presumptive TB register. Information on presumptive TB cases and outcome of investigation.
- **Case finding (notification data):** the notification data disaggregated by age, sex, and disease classification.
- **DST Coverage:** Assesses level of DST coverage in facilities
- **Data Quality:** Demonstrate the consistency on the figures reported by the facility and the recounted figures during supervision
- **TBHIV:** Assess ascertainment of HIV status among New and Relapse TB patients, TBHIV co-infection rate and ART uptake
- **Patient monitoring:** Assess smear follow up of TB patients and 2nd and 5th months
- **Treatment outcome:** Assesses treatment outcome for all categories of TB patients. Outcome for children and HIV patients are included in the tool.
- **TB Laboratory Services:** Demonstrate the performance of laboratories in terms of the number of tests conducted both Microscopy, LF-LAM, and GeneXpert.
- **Community TB Intervention:** Effectiveness of this intervention is assessed through the proportion of presumptive and cases contributed through community referral systems.
- **Other vulnerable and high-risk population:** The data source is the TB unit Register. The sections demonstrate the effectiveness of case detection effort among vulnerable and high-risk populations.
- **Contact investigation and IPT:** effectiveness of this intervention is assessed through proportion of household contacts screened, yield and proportion of eligible children on IPT.
- **DR TB (detection, treatment outcome):** this includes cascaded activities related to DR TB detection, diagnosis, and treatment.
- **Procurement and Supply Chain Management:** Records availability of TB drugs in the TB clinic and expiry date.

Routine TB Reporting System (DHIS2)

The routine reporting system uses the structure of the decentralized health system whereby data flows from health facility, district, and zone to national control program. Facility level data is available at national level. DHIS 2 system is at the center of routine reporting system. The routine reporting system captures the following data elements.

1. Notification data (disaggregated by age, sex, and disease category /classification)
2. Treatment outcome for new and retreatment cases with the following disease categories:
    a. Smear positive
    b. Pulmonary Clinically diagnosed TB cases.
    c. EPTB
    d. Relapse cases
    e. Treatment after failure, treatment after loss-to-follow-up and others
3. HIV status of TB cases
    a. Documentation of HIV test result among TB patients registered during the reporting period.
    b. Number of HIV positive TB patients
    c. ART and CPT coverage for newly registered TB/HIV co-infected patients during the reporting period
4. DR TB/ RR cases: Reported confirmed DR TB cases during the reporting period are included in the report. Case detection data relies on the national reference laboratory data.
5. Community TB data
6. Key population data

Data management: The national database was created in Epi Info 7. The database is inline with the TBHIV supervision tool. Data entry is done by two data clerks engaged for that purpose. Once the data entry is completed, data is exported to STATA for further reviews and analysis. Data quality is ensured through assessing consistency (within different data elements) and completeness (reporting rate). Data is summarized using tables and figures. Analysis is done as per predefined indicators to monitor performance of the program.

14. Supply Chain Management

Supply chain management refers to the entire network of entities and sub-units, directly or indirectly interlinked and interdependent to ensure the flow of required medicines and other supplies from the point of origin to the service delivery point. Logistics Management refers to the process and science of ensuring the right items are in the right place at the right time. The National TB Control Program (NTLEP) has overall responsibility of ensuring uninterrupted supply of essential TB commodities at all TB registration facilities. This includes first- and second-line anti-TB medicines, laboratory consumables/supplies and TB infection control items. Uninterrupted supply of commodities is essential for both service delivery and the Program's reputation. Stock-outs lead to an interruption of life-saving health services, predispose clients to drug-resistant TB and damage public confidence in the program.

Steps in Ordering TB Medicines & Key Supplies

TB commodities are ordered on a quarterly basis. Emergency orders can be initiated in-between scheduled deliveries when stocks are running low (less than one-month supply).

Step	Activity	Responsibility
1	Carry out a physical count in the Pharmacy & Clinic	Pharmacy personnel/ DTO
2	Obtain the number of cases notified in the previous quarter	DTO/Pharmacy Personnel
3	Complete the ordering form and submit to the district	Pharmacy personnel/Drug Store Clerk
4*	Aggregating facility data into Open LMIS , electronically approve the order and submit to NTP	District Pharmacy personnel/District Medical Officer
5	Final order approval and submission to CMST	NTP Pharmacist/Zonal TB Officer
6	Order processing, assembling and distribution	CMST
7	Order receiving and updating of stock cards	Facility Pharmacy personnel/DTC Member

**OpenLMIS is an MOH –wide electronic LMIS system (e-LMIS) used for reporting and ordering of TB commodities.*

Table 13.0-1 Steps in Ordering TB Medicines & Key Supplies

On a monthly basis, facility staff carries out a physical count and captures the information into the MOH wide -LMIS form. The forms are aggregated at the district level and transmitted to HTSS-pharmaceuticals for national-level data analysis.

Practical steps for ordering anti-TB medicines, laboratory supplies, and other essential Commodities

TB commodities (anti-TB medicines, laboratory supplies, infection control items, and other essential health products) are managed using a harmonized ordering and distribution system based on a pull ordering system. Under this arrangement, a health facility determines quantities to order and submit a request. Health centre orders must reach the district by the 5th of the last month of the quarter so that the district can submit them to CMST by the 10th to fit into the CMST Distribution/Delivery schedule. CMST deliveries start on the 10th of every month. It is important for the district to submit orders to CMST before the 10th. Anti-TB medicines order quantities are calculated based on case notifications. Cases enrolled from the previous quarter can be used for ordering. For the orders to reach the district by the 5th, of the last month of the quarter, the cut-off date for order submission for health centres is the last day of the month preceding the last month of the quarter. For the purposes of ordering, each Mobile Diagnostic Units (MDUs) is treated as a facility under a DHO. Supplies are

allocated to each district inclusive of MDU needs and distributed through CMST. MDU staff is responsible for determining order quantities and place an order to the District Pharmacy based on their consumption pattern. In the event of an outreach to a non-MDU district, there is a flexibility to order extra supplies from the outreach district to replenish stock that gets depleted during the outreach.

Illustration for ordering cycles and notification data used

Period of order placement (the order covers the needs of the coming quarter)	Deadline for order submission	Notification data used
Q1	February 28/29	Q4 of the previous year
Q2	May 31	Q1
Q3	August 31	Q2
Q4	November 30	Q3

Table 13.0-2 Illustration for ordering cycles and notification data used

TB commodity supply is pull based and forced ordering system, which means that CMST can only supply commodities based on an order generated by the facility. CMST has a set delivery schedule, late ordering results in delayed delivery. Emergency orders can be placed to the district in-between scheduled deliveries.

Facility inventory management tools

Document 4 (Anti-TB ordering book) is used by health centers for emergency orders from the district pharmacy or from other Facilities. Document 3 (Anti-TB balance book) is used whenever medicines are issued to patients at TB clinic. These inventory Books must always be kept up to date.

Assessing stock status and Min-Max stock levels

Calculate average monthly consumption (AMC) and months of stock for anti-TB medicines after conducting the monthly physical count. AMC = units used in the last 3 months /3. Months of stock on hand = stock on hand/ AMC. The minimum stock for anti-TB medicines is 3 months and the maximum stock is 6 months. When supplies cover less than 3 months, a facility is understocked and when supplies cover more than 6 months, the facility is overstocked.

Equipment Maintenance

TB service delivery relies on the availability of functional equipment that is timely serviced and maintained. Maintenance and servicing of equipment is coordinated at Central level but facility staff is responsible for daily equipment care, fault reporting and facilitating the on-site maintenance works. The table below assigns the core responsibility for maintenance and servicing to NTP and HTSS-PAM. Core responsibility involves mobilization of funding, contract management, and identifying emerging priorities for servicing and equipment.

Equipment with core responsibility for maintenance and servicing through NTP	Cross cutting (health system) equipment with core responsibility for maintenance and servicing through HTSS-PAM
GeneXpert machines, Microscopes, MGIT machines, LPA machines, NTRL Air Handling Units, UVGI, Biosafety Cabinets	Chemistry machines, Chest X-ray machines,

Table 13.0-3 Equipment maintenance

15. Community Rights and Gender in TB Programming

15.1. Definition

Community, rights and gender (CRG) in TB response refers to meaningful engagement of TB affected community, and application of human rights and gender approaches in planning, implementation, monitoring and evaluation of TB programs.

Human rights-based approach to TB upholds the rights of people affected by TB, including the rights to life, health, non-discrimination, privacy, informed consent, housing, food, and water. The approach focuses on the social and economic determinants of the disease, addressing stigma, discrimination, and environmental conditions. It articulates the domestic and international legal obligations of governments and non-state actors to ensure that quality testing and treatment for TB.

Community Rights and Gender Objectives

The main objective of incorporating community rights and a gender perspective into a TB management manual is to ensure a more inclusive, equitable, and effective approach to TB prevention, treatment, and control by:

- **Promoting Community Engagement:** Foster active participation and involvement of communities in designing, implementing, and evaluating TB programs.
- **Respecting and Protecting Community Rights:** Uphold the rights of individuals and communities, including the right to health, non-discrimination, confidentiality, and informed consent.
- **Addressing Gender Disparities:** Integrate a gender-sensitive approach to understand and address the unique needs and challenges faced by men and women in relation to TB prevention, diagnosis, and treatment.
- **Reducing Stigma and Discrimination:** Combat social stigma and discrimination associated with TB through community-based education and awareness programs.
- **Enhancing Access to Services:** Improve access to TB services, particularly for marginalized and vulnerable populations, by addressing barriers related to gender, socioeconomic status, and geography.
- **Data Collection and Analysis with a Gender Lens:** Collect and analyse disaggregated data by gender to identify specific challenges faced by men and women in TB prevention and control.

Key Components of Community Rights in TB Program

Community is a group of people with diverse characteristics who are linked by social ties, share common perspectives, and engage in joint action in geographical locations or settings. Community rights refer to the recognition and protection of the rights of communities affected by tuberculosis. Key components include participation, access to information, non-discrimination and addressing social determinants.

- **Participation:** Involving affected communities in the planning, implementation, and monitoring of TB programs.
- **Access to Information:** Ensuring that communities have access to accurate and timely information about TB prevention, diagnosis, and treatment.
- **Non-Discrimination:** Preventing discrimination based on TB status and ensuring that affected individuals are treated with dignity and respect.
- **Addressing Social Determinants:** Recognizing and addressing gender-related social determinants that may affect TB outcomes, such as economic status, education, and access to healthcare.

Key Components of Gender in TB Program

Gender is a socially constructed set of norms, roles, behaviours, activities and attributes that a given society considers appropriate or valued for women and men. It is not just about biological differences but encompasses the ways in which these differences are perceived, valued, and experienced within a specific cultural and societal context. Understanding and integrating a gender perspective into TB programming in Malawi is crucial for designing effective and equitable interventions. Here are key components of gender in relation to TB programming:

Socio-cultural Factors: Recognizing and addressing gender norms, roles, and expectations within Malawian society is essential. Understanding how these factors influence health-seeking behaviour, access to healthcare, and adherence to TB treatment is crucial for designing targeted interventions.

Access to Healthcare: Gender often affects access to healthcare services, including TB diagnosis and treatment. Factors such as distance to health facilities, financial constraints, and cultural norms may disproportionately impact one gender, leading to disparities in health outcomes.

Stigma and Discrimination: Gender-related stigma and discrimination can affect TB patients differently. Women, for example, may face additional challenges due to societal expectations, while men may experience stigma related to vulnerability or seeking healthcare.

Economic Empowerment: Economic factors play a role in TB programming, as poverty and financial dependence can hinder individuals, particularly women, from seeking timely and appropriate healthcare. Integrating economic empowerment strategies can enhance TB prevention and treatment outcomes.

Education: Educational opportunities and literacy levels can influence awareness, prevention, and management of TB. Gender disparities in education may affect the understanding and adoption of health-promoting behaviours.

Healthcare Decision-Making: Understanding who makes healthcare decisions within households is crucial. In some contexts, traditional gender roles may impact decision-making, affecting individuals' ability to access TB services.

Caregiving Responsibilities: Women often bear the primary responsibility for caregiving within families. Considering caregiving responsibilities is important in TB programming to ensure that support systems are in place for both patients and their caregivers.

Community Engagement: Involving both men and women in community-based interventions is essential for the success of TB programs. Engaging with the community to challenge harmful gender norms and promote equitable access to healthcare is crucial.

Data Collection and Analysis: Collecting disaggregated gender data allows for a more nuanced understanding of how TB affects different genders. This information is essential for developing targeted interventions and monitoring the impact of programs.

LEPROSY

Guidelines

17. Leprosy

17.1. Background

Leprosy, also known as Hansen's disease, is defined as a chronic granulomatous disease that is caused by an acid-fast rod-shaped bacillus (as it retains the red colour after being stained with Ziehl Neelsen stain over a blue background) called *Mycobacterium leprae* (M.leprae). *Mycobacterium leprae* primarily affects the peripheral nervous system and the skin. It also affects other body parts such as the reticuloendothelial system (spleen, lymph nodes), musculoskeletal system, mucous membranes especially the nasal mucosa, eyes, testes, and sometimes the adrenals glands.

The incubation period is long and variable, it is assumed to be five years on the average but could be up to 20 years before occurrence of symptoms. If left untreated, it could lead to deformity and resultant disabilities. The disease is associated with stigma, especially when deformities are present.

In 1994, Malawi attained World Health Organization (WHO) leprosy elimination status, which is defined as achieving a point prevalence of below 1 case per 10,000 population. The country has over the years maintained this status. Cumulatively, in 2021 the country had a total of 671 leprosy cases out of 18 million people, representing 0.4 cases per 10,000 population. Despite attaining this status, Leprosy point prevalence is above 1 case per 10,000 population in Nkhotakota, Ntchisi, Mchinji, Nsanje, Balaka and Salima districts. Leprosy notifications data have revealed the presence of leprosy in children. The presence of leprosy among children is an indicator of on-going disease transmission in the community. Transmission of Mycobacterium leprae.

- It is considered that the only source of infection is an infected human being.
- Individuals with multibacillary leprosy have an infection capacity of between 4 -11 times higher compared with those that have Pauci-bacillary leprosy.
- The main exit route of *Mycobacterium leprae* from the human body is the nasal mucosa. It is estimated that the quantity of bacilli from nasal mucosal lesions in lepromatous leprosy ranges from 10,000 to 10,000,000 and this can be collected through blowing the nose.
- Upon being excreted through nasal secretions, *Mycobacterium Leprae* remains viable in the air for a longer period of time. This prolonged survival makes airborne transmission a reasonable possibility.
- The entry route of *Mycobacterium leprae* into the human body is also not definitively known. The upper respiratory tract is the most likely route.
- Prolonged exposure to close contact is a considered necessary factor for transmission to occur. However, in susceptible individuals even short duration of contact may occasionally cause the disease.

17.1.1. Leprosy case definitions and classifications

The Leprosy case definitions below are based on the WHO criteria for suspecting, diagnosing and classifying leprosy patients.

A case of leprosy is defined as a patient having one or more of the following:

1. Hypo-pigmented skin lesions with loss of sensation;
2. Impairment or involvement of the peripheral nerves as demonstrated by a) definite loss of sensation or b) weakness of hands/feet or face or c) autonomic function disorders such as anhidrosis (dry skin);
3. Signs of the disease with demonstrated presence of bacilli in skin smear or histopathological confirmation AND need of leprosy treatment as decided by a clinician.

17.1.2. Leprosy Case Classification

Leprosy case classification based on whether its a new or old case	
Leprosy class	**Definition**
New case	a patient diagnosed with leprosy who has never been treated for the disease.
Retreatment case	a patient diagnosed with leprosy who has already received treatment for the disease in the past. Retreatment can be further classified into 2
Retreatment after loss to follow up	A patient diagnosed with Leprosy who has abandoned treatment before its completion and returns to the health facility to complete treatment beyond 3 months for PB cases and beyond 6 months for MB cases.
Relapse case	A patient who has completed a full treatment course for leprosy in the past and who returns with signs and symptoms of the disease that are not deemed due to a reaction.
Transferred in case	A patient who has started treatment in one facility and reports to another facility to continue treatment.

Table 17.1-1 Leprosy case classification based on whether it is new or old case

Leprosy classification based on the number of skin lesions involved, presence of bacilli on slit skin smear and nerve involvement.

Both new and retreatment cases can be further classified into Paucibacillary (PB) cases and Multibacillary (MB) cases;

- **PB case;** a case of leprosy with 1 to 5 skin lesions, without a demonstrated presence of bacilli on a skin smear.
- **MB case;** a case of leprosy with > 5 skin lesions; or with nerve involvement (pure neuritis or any number of skin lesions and neuritis); or with demonstrated presence of bacilli in a slit skin smear (SSS) irrespective of the number of skin lesions.

Leprosy outcome definitions

- **Treatment completed within standard duration:** new patients who have been treated for leprosy with a full course of MDT (6 to 9 months for PB cases or 12 to 18 months for MB cases)
- **Treatment completed beyond standard duration (still on treatment beyond standard duration):** Patients who have been diagnosed and treated for leprosy with a full course of MDT, (6 months for PB and 12 months for MB) but the clinician has decided that the treatment needs to be extended beyond the standard duration.
- **Died:** Patients who have been diagnosed with leprosy and died due to any cause during the course of treatment.
- **Insufficient/ unsatisfactory clinical response to treatment:** Patients who despite adequate treatment do not respond clinically.
- **Lost to follow up:** Patients who have interrupted treatment for a total of 3 months or more, (if PB) or a total of 6 months or more (if MB).
- **Transferred out:** Patients diagnosed with leprosy who started treatment in one health facility that recorded them and then have been transferred to another facility. (as much as possible such patients shall be assigned a treatment outcome enquiring with the referral facility)

17.2. Case finding and clinical presentation of Leprosy patients

A suspect case of leprosy

When you suspect a patient with leprosy, make sure that you take a good history and do a thorough clinical examination.

History should include the following.

- General information (name, sex, age, address, occupation)
- Main complaints (onset, duration, description of symptoms)
- Previous treatment and present treatment
- Contact history with leprosy patient
- Any other known diseases (co-morbidities)
- An assessment of socio-economic status
- Identification of a Leprosy Suspect
- Leprosy should be considered in an individual who presents with
- Pale or reddish patches (skin patch with discoloration) on the skin;
- Painless swelling or lumps in the face and earlobes;
- Loss of or decreased sensation on the skin;
- Numbness or tingling of the hands and/or the feet;
- Weakness of eyelids, hands or feet;
- Painful and/or tender nerves.
- Burning sensation in the skin; or
- Painless wounds or burns on the hands or feet
- Painless swelling or lumps on the face & earlobes.
- Redness of the eyes
- Testicular pain
- Thickening of the skin especially on the face
- Foot drop or claw fingers
- Epistaxis

The health care workers should make a high clinical index of suspicion for leprosy if an individual presents with any of the above signs and symptoms.

Note: Pale or reddish discoloration of the skin is the most common & early symptom of Leprosy.

17.3. Patient evaluation to diagnose a Leprosy Case

Over 95% of leprosy cases can be diagnosed on clinical grounds. The diagnosis is usually made clinically based on the availability of one or more of the following cardinal signs; (1) definite loss of sensation in a pale (hypopigmented) or reddish skin patch; (2) thickened or enlarged peripheral nerve, with loss of sensation and/or weakness of the muscles supplied by that nerve; (3) microscopic detection of bacilli in a slit-skin smear. Laboratory investigation is indicated only in doubtful cases for confirmation and sometimes for patient classification. Evaluate the patient as follows:

17.3.1. Clinical History

The following information should be obtained from the individual suspected of leprosy:

- General information: socio-demographic information of the patient.
- Characterized the presentations: History of onset, duration of symptoms, painless wounds/burns; burning sensation; weakness in picking or holding objects or closing eyelids; unusual sensation in hands and feet (numbness, tingling); and presence of itching sensation.
- History of previous leprosy treatment.
- History of prolonged contact with a leprosy patient in the household or other confined spaces

17.3.2. Physical Examination

- A full general examination should be carried out in any patient.
- Leprosy specific examinations should be done in Leprosy suspected patients.
- Physical examination should be focused on skin, nerves and eyes:

17.3.3. Examination of the Skin

- Examination for skin lesions must always be carried out with adequate light (preferably natural light) and sufficient privacy for the patient to feel at ease.
- Inform client about purpose of the examination.
- Request the client to remove clothes if possible
- Examine systematically from head to toes, including the front and back sides.
- Check for presence of skin lesions (patches or nodules),
- Check for loss of sensation over the skin lesions (patches) using a “wisp of cotton wool”,
- Count the number of skin lesions if any

17.3.4. Skin sensation Testing

- Any skin lesions should be checked for sensory loss using a “wisp of cotton wool” as follows:

1. Explaining to the patient about the purpose of the test and what is expected from him.
2. Request the client to remove clothes if possible.
3. Examine systematically from head to toes, including the front and back sides.
4. Rolling the end of a wisp of cotton wool into a fine point. Touch the skin with the fine point of the cotton wool until it bends.
5. Touching the skin with the fine point of the cotton wool until it bends with the patient’s eyes opened and instructing the patient to point to the location where they feel the wisp of the cotton.
6. Continue until the patient has demonstrated understanding of the test. Repeating the step with the patient’s eyes closed, first on the normal skin and then on the skin patch, touching the normal skin now and then
7. Watching that the patient’s eyes are closed when the test is carried out

Note: Definite loss of sensation in the skin patch is indicative of leprosy

Note: If a patient points accurately to areas of normal skin, but sometimes points away from where the skin patch is, this is called mis-reference and it shows diminished sensation in the patch. If this is consistent during repeated testing of a patch, it is a cardinal sign justifying a diagnosis of leprosy. (see Figure 15.3-1)

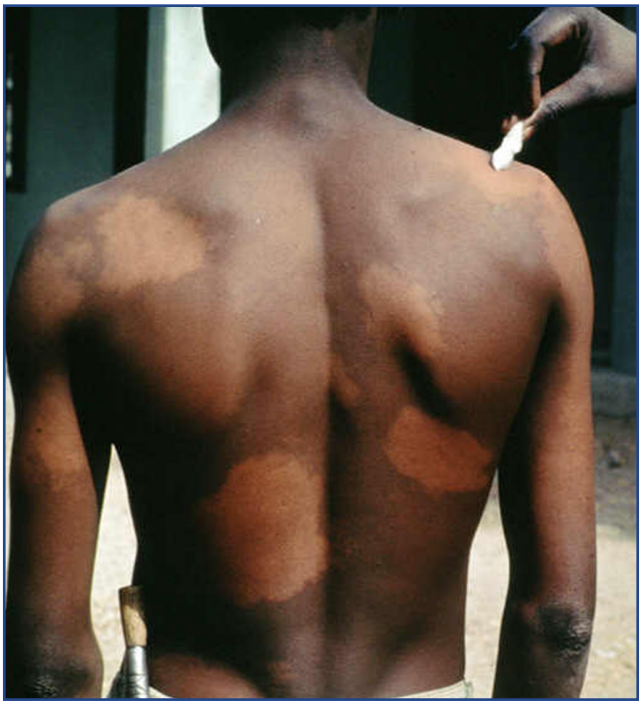


Figure 17.3-1 Checking the sensation in the skin patches:
It is important to draw the skin patches on a body chart for future reference.

Examining the nerves for enlargement

- Gentle palpation of the nerves at specific sites is done to assess for enlargement and tenderness.
- Palpate the nerves starting from the head and going down to the feet.
- Compare the right and left sides.
- When palpating a nerve, always use the pulp of two or three fingers to roll over the affected nerves.

Note: Leprosy may affect most peripheral nerves including greater auricular, ulnar, median, radial cutaneous, peroneal and posterior tibial nerve. The ulnar and peroneal nerves are the ones that are most commonly enlarged and can be felt quite easily.

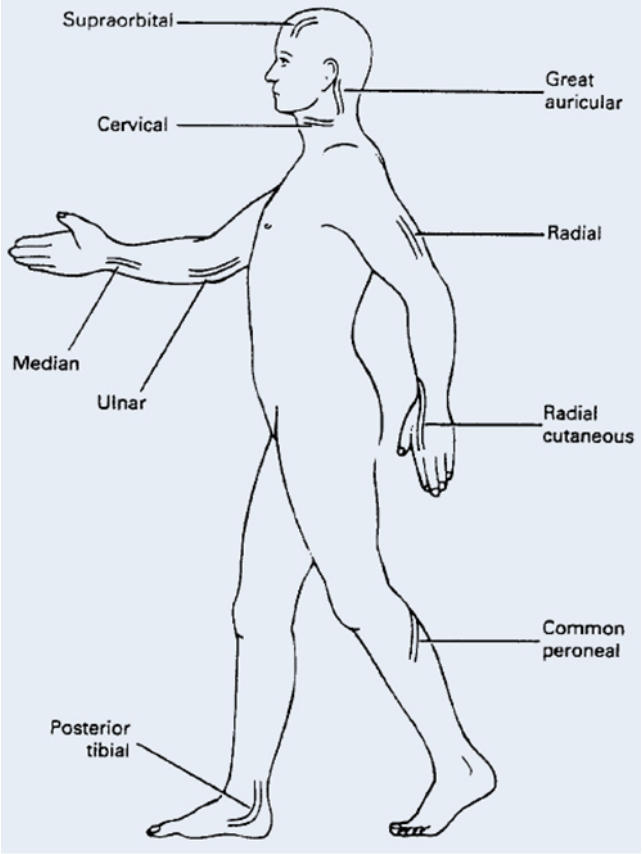


Figure 17.3-2 common sites of nerve enlargement

17.3.5. Examination of Skin Smears

- Bacteriological examination of a skin smear is recommended for doubtful cases to confirm the diagnosis and/ or classification of leprosy.
- Only one slide, with smears taken from two sites must be collected and examined.
- One positive-smear result is enough for diagnosis of leprosy.
- The finding of a negative-smear examination result doesn't rule out leprosy.

When encountering difficulty in reaching diagnosis of Leprosy, Do one of the following:

- Consider the possibility of another skin disease and treat appropriately.
- Refer the patient to an experienced for re-evaluation.
- If referral is not possible, Re-evaluate the patient.
- Examination of the peripheral nerves, eyes, hands, and feet

17.3.6. Nerve Function Testing

The assessment of nerve function is done by sensation Testing (ST) and Voluntary Muscle (function) Testing (VMT) in the face, hands and feet. The motor function of individual nerves is assessed by testing the power in the small muscles of the hands and feet that they innervate (Table 17.3-1).

Note: It is important to ensure that the muscle being tested is isolated by careful positioning. The effect of other muscles is thus removed so that they are unable to provide the movement being tested and give an erroneous result for a muscle that may be paralyzed. This may occur if the extrinsic extensor and flexor muscles are allowed to abduct the little finger when abductor digiti minimi is affected.

Nerve tested	Muscle	Movement tested
Facial nerve	• orbicularis oculi	Forced eye closure
Median nerve	• abductor pollicis brevis	Thumb abduction
Ulnar nerve	• abductor digiti minimi	Little finger abduction
Radial nerve	• extensor muscles	Wrist extension
Lateral popliteal nerve	• tibialis anterior, peroneus longus and brevis	Foot dorsiflexion
Posterior tibial nerve	• intrinsic muscles of foot	Great toe grip

Table 17.3-1 Commonly tested nerves and muscles in motor function assessment

Motor function is graded by using the 6 grades on the Medical Research Council (MRC) scale for muscle power (Table 17.3-2)(MRC 1981).

After diagnosis of leprosy is made, the health workers need to examine the peripheral nerves, eyes, hands and feet as these are the most commonly affected organs by leprosy.

The following nerve functions tests must be carried out:

1. Voluntary Muscle Testing (VMT)
2. Sensory Testing (ST)
3. Autonomic nerve function test for dryness of palms and sole

17.3.6.1. Voluntary Muscle Testing (VMT):

VMT is done to check Muscle strength of eye, hands and feet. The strength should be graded as Strong (S), Weak (W) or Paralyzed (P).

The muscle strength of eye, hands and feet can be done as follow:

1. Voluntary muscle testing (VMT) of the eyes: EYE closure
   - Ask the patient to close his eyes lightly as in sleep.
   - Observe whether or not the closure on both eyes is complete. Inability to fully close the eye is called lagophthalmos (paralysis “labelled as P” of the eyelid muscles).
   - If the patient is able to fully close his/her eyes, then ask the patient to close his eyes firmly, gently try to open the eyelids using the pulp of your thumbs to check for strength.
     - Grade the eye muscle strength as weak (W) if the eyelids open easily; or
     - Strong (S) if it is difficult to open the lids.

Voluntary Muscle testing (VMT) of the hands and feet

2. Check for range of movement on the FIFTH finger:
   - ASK the patient to abduct the 5th finger (move finger away from the rest).
   - If patient cannot move the finger, record as paralysis (P), an indication of ULNAR nerve damage
   - If movement is normal, test for resistance by PRESSING gently over the proximal phalanx of the 5th finger using your index finger, holding the other 3 fingers steady and ask the patient to maintain the position and RESIST the pressure of the examiner’s index finger as strongly as possible.
   - Press gradually more firmly and judge whether resistance is strong (S) or weak (W).

3. Check for range of movement of both THUMBS:
   - ASK the patient to first flex the thumb over the palm (touch the root of 5th finger) and later point the thumb to his/her nose while you hold the remaining 4 fingers.
   - If patient cannot move the thumb, record as paralysis (P), an indication of MEDIAN nerve damage.
   - If movement is normal, test for resistance by PRESSING gently over the proximal phalanx of the thumb using your (examiner') index finger as shown in the diagram below, holding the other 4 fingers steady and the ask the patient to maintain the position and RESIST the pressure of the examiner's index finger as strongly as possible
   - Gradually, press more firmly and judge whether resistance is strong (S) or weak(W).
4. Check the movement of the FEET
   - ASK a patient to dorsi-flex his foot (move up his foot at the ankle).
   - If a patient cannot dorsi-flex the foot, record as paralysis (P), an indication of PERONEAL nerve damage called FOOT DROP. If movement is normal, test for resistance by PRESSING gently over the dorsum of the foot as shown in the diagram below, whilst you (examiner) hold the leg with your other hand. And ask the patient to maintain the position and resist the pressure as strongly as possible.
   - Gradually, press more firmly and judge whether resistance is strong (S) or weak (W).
5. Check for the range of movement of the wrist joint:
   - Hold the forearm just before the wrist joint in a horizontal plane
   - Apply pressure at the back of the hand and ask the patient to resist the applied force by pushing the hand upwards
   - If there is no resistance and there is wrist drop, this is an indication of radial nerve paralysis.
6. Check the movement of the FEET
   - ASK a patient to dorsi-flex his foot (move up his foot at the ankle).
   - If a patient cannot dorsi-flex the foot, record as paralysis (P), an indication of PERONEAL nerve damage called FOOT DROP. If movement is normal, test for resistance by PRESSING gently over the dorsum of the foot as shown in the diagram below, whilst you (examiner) hold the leg with your other hand. Ask the patient to maintain the position and resist the pressure as strongly as possible.
   - Gradually, press more firmly and judge whether resistance is strong (S) or weak (W).

17.3.7. Sensory Testing (ST)

Sensory testing is done to check the presence of sensation in the eye's hands and feet. These can be done as follows:

Sensation of the eyes (cornea)

- ASK patient to blink his/her eyes.
- Observe the patient's spontaneous blinking while talking to him/her. If there is a blink, corneal sensation is normal. If there is no blink, the eye is at risk.

Sensation of palms and soles:

Sensory testing on palms and soles should be done with a ball point pen or Semmes-Weinstein monofilaments (SWM). The tests are done on ten standard points.

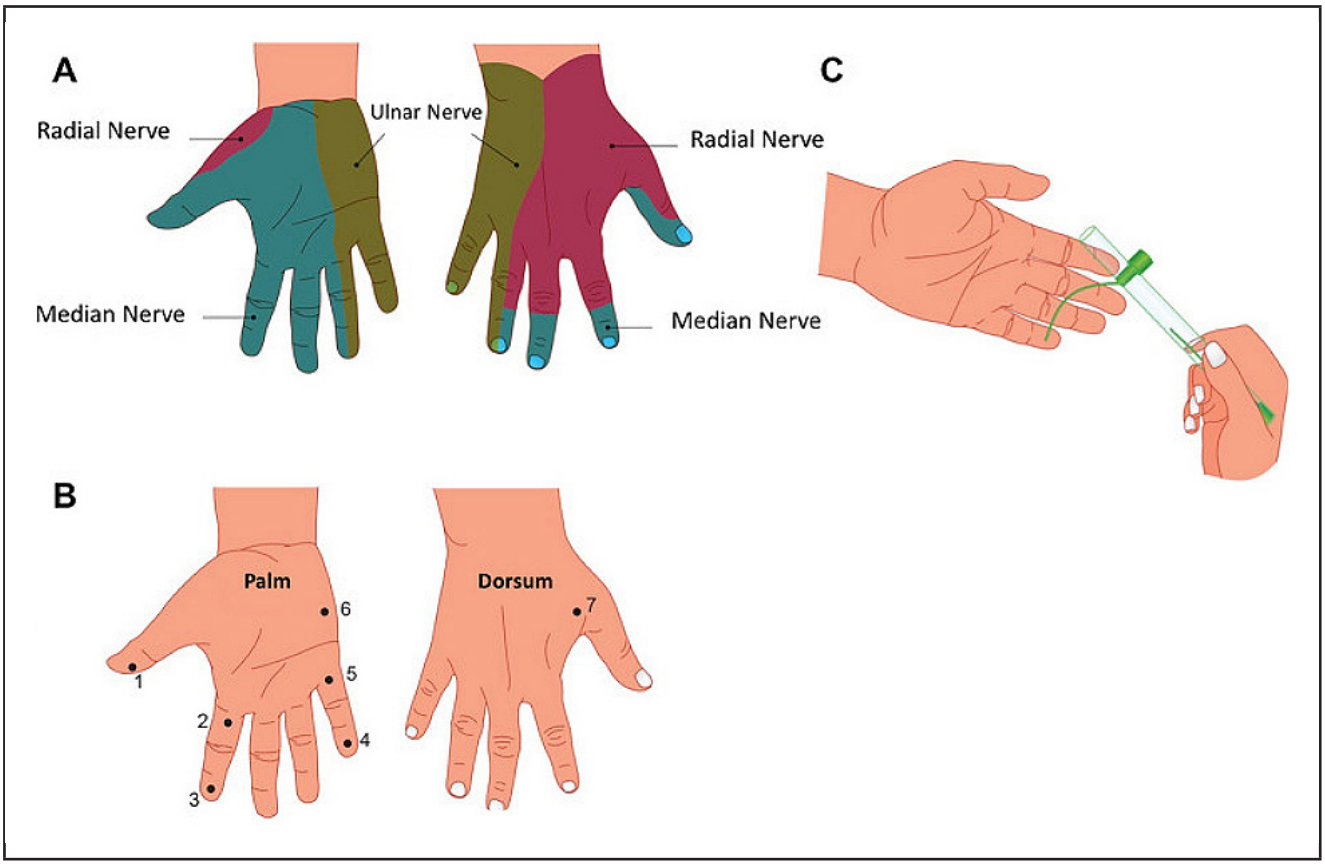


Figure 17.3-3 Hand Mapping, Including Sensation Test points to Diagnose Leprosy

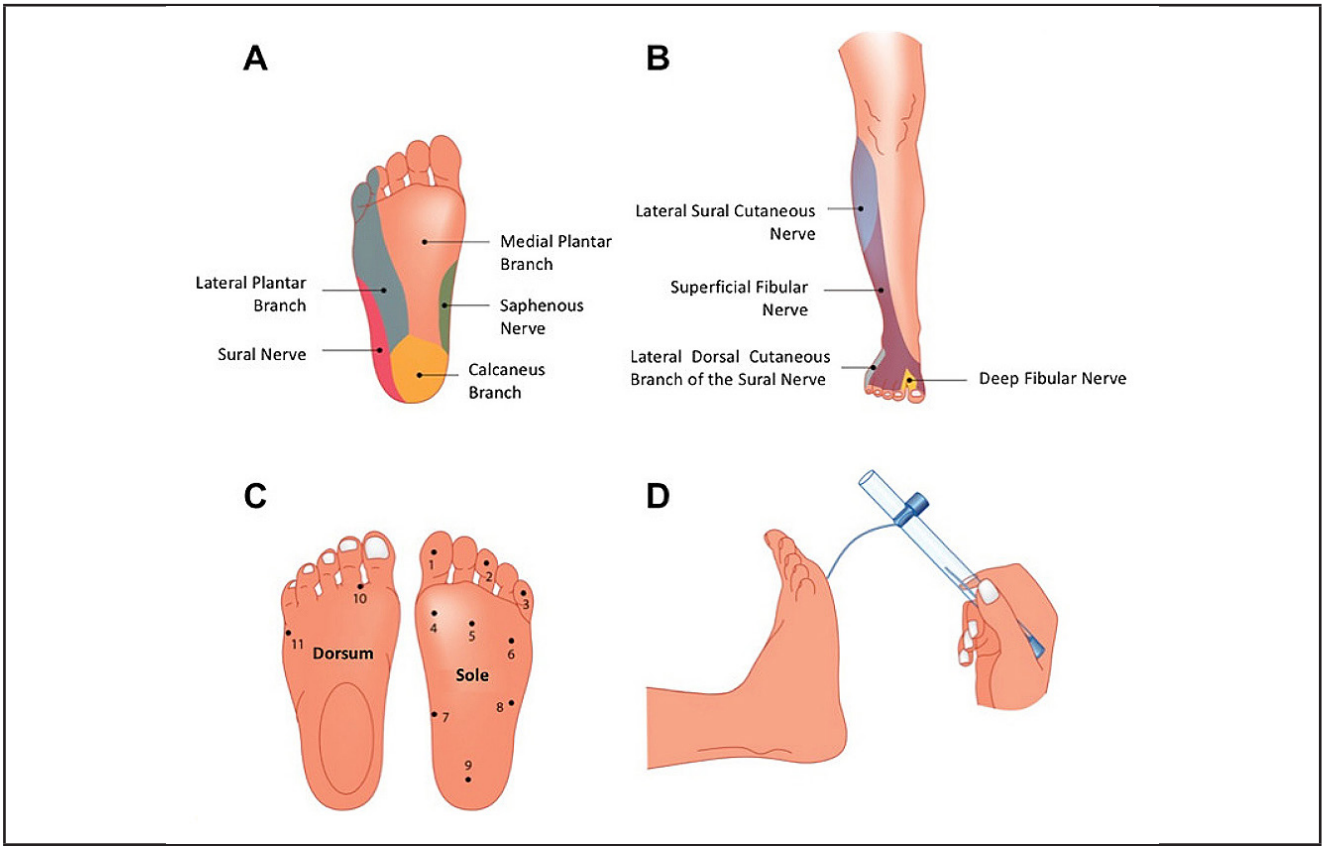


Figure 17.3-4 Foot mapping including sensation test points to diagnose leprosy

Further examination of the Eye

Check for Visual Acuity: Vision of both eyes of the patient should be tested according to the demonstration below and should be recorded on the Patient Record Card.

• Test vision with good light falling on the assessor. • Ask the patient to cover one eye, then count the number of fingers that the assessor holds up. Test at 6 meters. • If the patient cannot see at 6 meters, re-test at 3 meters. • Record the findings	

Further examination of Hands and Feet

Patients should also be examined for the following complications, which result from nerve damage:

- Skin cracks on palms and soles with sensation loss
- Wounds on palms and soles with sensation loss
- Clawed fingers and toes
- Foot drop Wrist drop
- Shortening and scarring in fingers and toes with sensation loss

MRC modified grading of muscle power	
Score	**Muscle response**
5	Full range of movement (FROM)
4	FROM but less than normal resistance
3	FROM but no resistance
2	Partial range of movement with no resistance
1	Perceptible contraction of the muscle not resulting in joint movement
0	Complete paralysis

Table 17.3-2 MRC scale for VMT

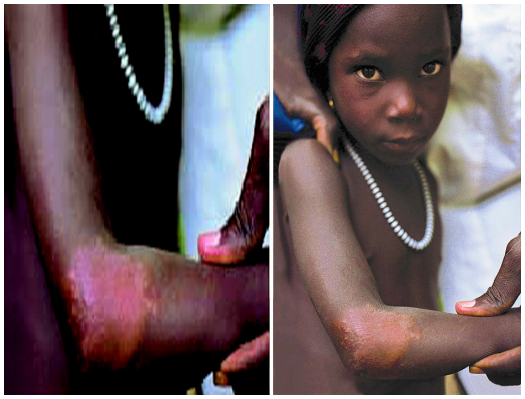


Figure 17.3-5 Pictorial presentation of reddish or pale patches on the skin

Figure 17.3-6 Pictorial presentation of the presence of nodules and thickened skin on the face and ears in leprosy

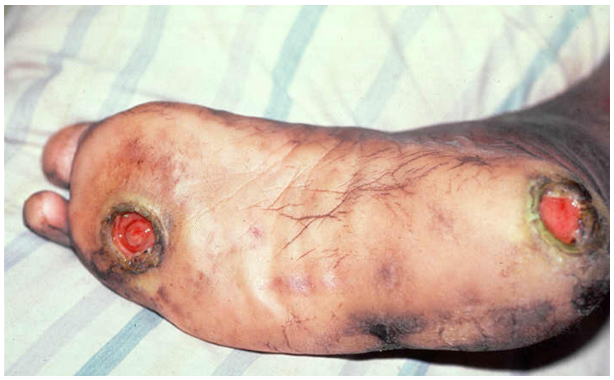


Figure 17.3-7 Pictorial presentation of painless ulcers

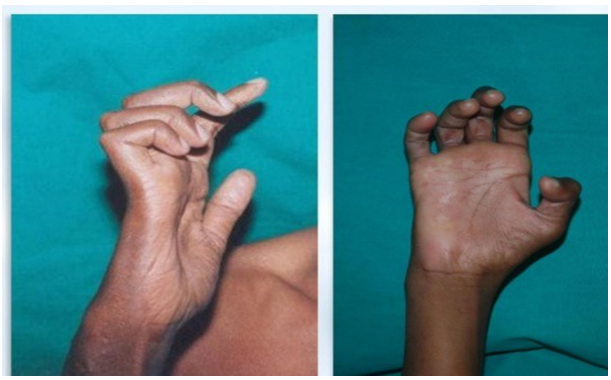


Figure 17.3-8 Pictorial presentation of claw finger

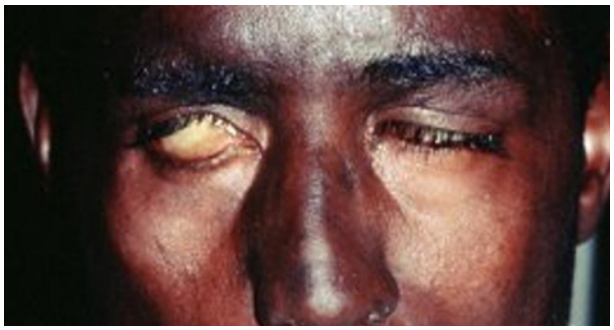


Figure 17.3-9 Pictorial presentation of weakness of the eyes

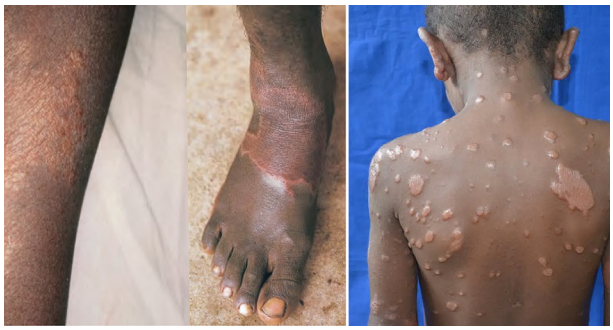


Figure 17.3-10 Some pictorial presentations of hypopigmented skin patches in leprosy

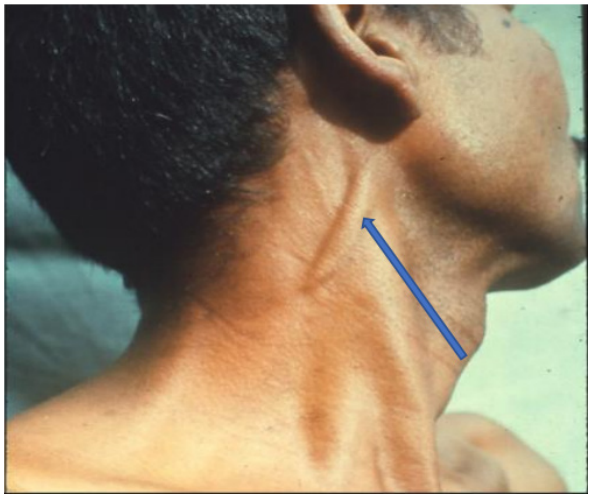


Figure 17.3-11 Pictorial presentation of auricular nerve enlargement as shown by the arrow which is an example of peripheral nerve enlargement in leprosy.

17.3.8. Differential diagnosis of Leprosy

- For a presumptive leprosy patient with hypopigmented patch/es the following are the differential diagnosis.
  - Pityriasis alba
  - Pityriasis versicolor
  - Vitiligo
  - Idiopathic hypomelanosis
  - Post inflammatory hypopigmentation
  - Birthmarks (nevus anemicus)
  - Nevus depigmentosus
  - Onchocerciasis and Discoid lupus erythematosus.
- For a presumptive leprosy case presenting with annular plaque lesions the following are the differential diagnoses;
  - Tinea corporis
  - Psoriasis, Pityriasis rosea
  - Secondary syphilis
  - Granuloma anulare
  - Annular sarcoidosis
  - necrobiosis lipoidica
  - eruptive syringoma
  - steatocystoma multiplex
  - Kaposi's sarcoma and drug reactions
- For a presumptive leprosy case presenting with Papular /nodular lesions, the following are the differential diagnosis;
  - Acne vulgaris
  - Diffuse cutaneous leishmaniasis
  - Lichen planus
  - Secondary syphilis

- Molluscum contagiosum
- Cryptococcal skin infection
- Neurofibromatosis

- For a presumptive leprosy case presenting with nerve thickening, the following are the differential diagnosis;
  - Amyloidosis
  - Neurofibromatosis
  - Familial neuropathy

17.4. The laboratory diagnosis of leprosy

17.4.1. Properties of mycobacterium leprae

The following are the properties of mycobacterium leprae;

- It is a non-cultivable, obligate intra-cellular bacillus.
- It is a slow-growing, acid-fast, Gram-positive bacillus,
- it is a straight or slightly curved, rod-shaped bacillus.
- It is about 1–8 µm long and has diameter of 0.3–0.6 µm,
- It can be found isolated or in clusters (cigar shaped or globi)
- It is a non-motile bacteria

17.4.2. Diagnostic methods of mycobacterium leprae

The following are the diagnostic methods for M.leprae;

- Microscopy, using ZN staining or Acid-fast staining technique: Slit-Skin Smear (SSS) test from skin patch, nodules, earlobes and Skin. A slit skin smear is also used to monitor if the patient is responding to the multi drug therapy (MDT) by looking at the morphological index.
- Serological tests
- Animal inoculation (mouse foot pad)
- Molecular technique: M. leprae specific DNA amplification (PCR)

LEPROSY - DIAGROSIS AND CLASSIFICATION

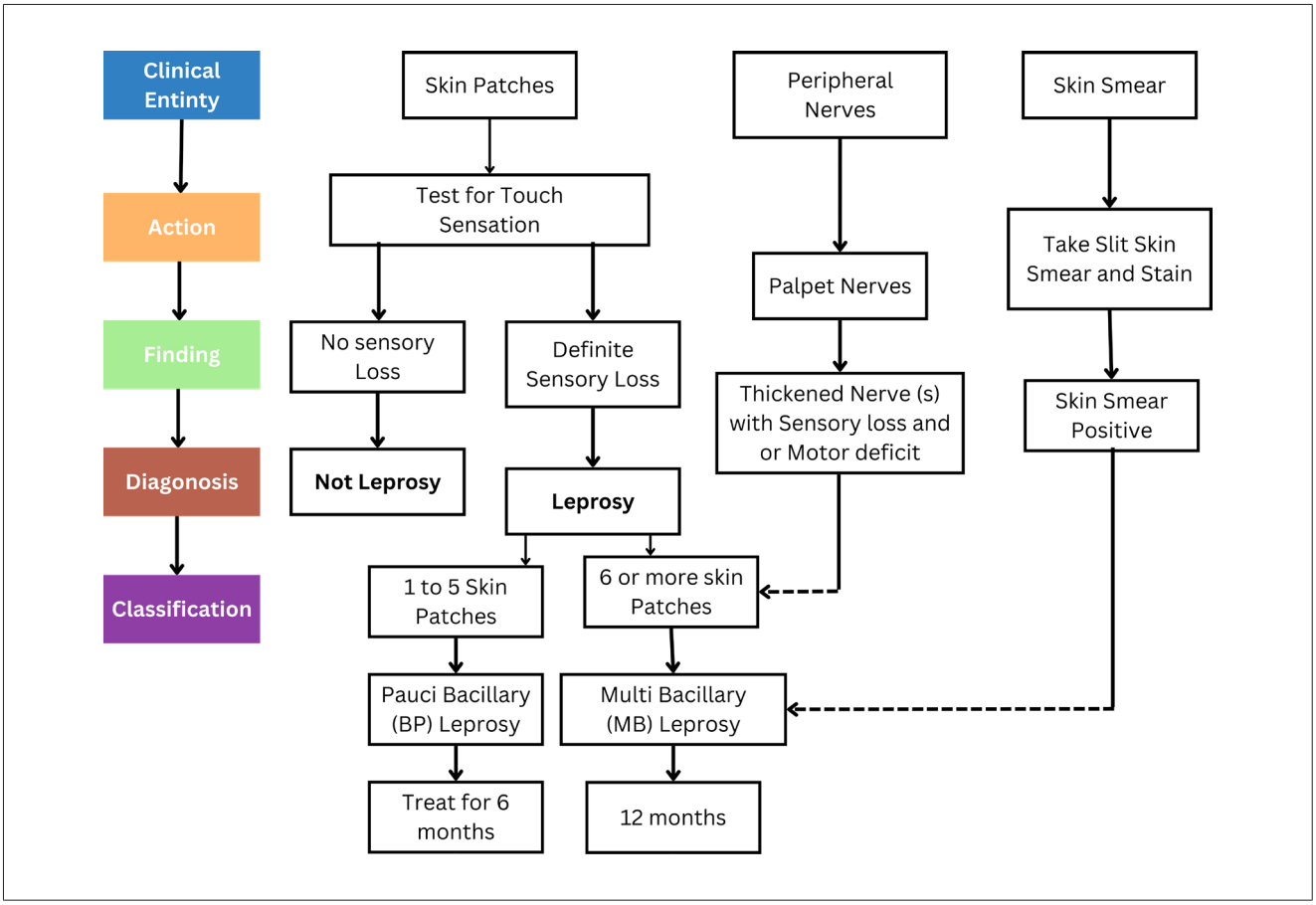


Figure 17.4-1 Leprosy diagnosis and classification

17.5. Leprosy treatment

17.5.1. Treatment

- Leprosy is treated using a combination of either two or three drugs commonly referred to as Multi Drug Therapy (MDT).
- The aims of treatment are to achieve the following; to cure the patients, to minimize the likelihood of disabilities, to render the patients non-infectious and thus control the spread of leprosy and to prevent the development of multi drug resistance leprosy.
- Drugs used in leprosy as recommended by WHO are a combination of rifampicin, clofazimine and dapsone (MDT).
- The duration of treatment for pauci-bacillary leprosy is 6 months and for multibacillary leprosy is 12 months.

17.5.2. Properties of Rifampicin

- It is the only bactericidal anti-leprosy drug, rendering the patient non-infectious within days of commencing therapy.
- A single 600mg monthly dose of Rifampicin has been shown to be effective.
- In this dosage it is almost nontoxic.
- The slow multiplication rate of M. leprae (about once in 12 days) justifies the use of rifampicin as monthly therapy.

- Patient must be warned that it will make the urine red for a few hours after its intake.

17.5.3. Properties of Clofazimine/ Lamprene

- It is a bactericidal and bacteriostatic drug. It is most effective when it is administered daily.
- It is well tolerated and virtually nontoxic in the dosage used for MDT.
- The drug causes brownish-black discoloration and dryness of the skin but this disappears within a few months after stopping treatment and this should be explained to patients starting the MDT regimen for MB leprosy.
- It also has anti-inflammatory activity and it is used to treat type 2 Lepra reaction.

17.5.4. Properties of Dapsone

- It is a bacteriostatic drug.
- It is very safe at the dosage that is used in MDT, which is usually at 1-2 mg per kg/day.
- Side effects are rare but the main one is allergic reaction, causing itchy skin rashes and exfoliative dermatitis. Therefore, patients known to be allergic to any of the sulpha drugs should not be given dapsone.
- In a few cases, there is a feeling of 'heat' or difficulty in sleeping and a mild hemolytic anemia is common.

17.5.5. Recommended Leprosy treatment regimens for adults

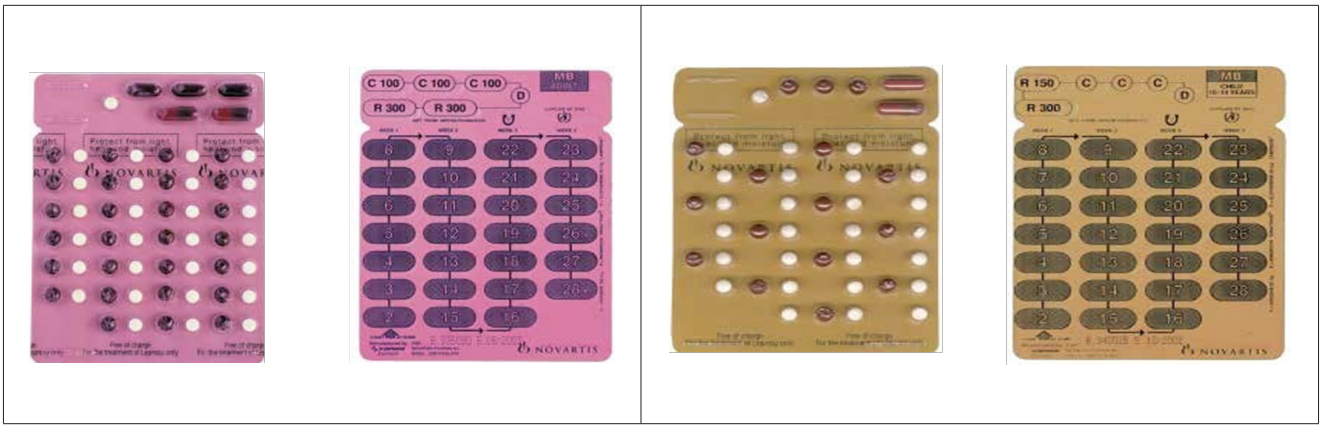


Figure 17.5-1 Above are pictures of the multi-therapy blister packs for adults and children.

Note: The maroon blister packs are the adult blister packs. The first blister pack to the left represents the front view whereby the second blister pack to the left represent the backview.

The gold blister packs represent the paediatric blister packs. The first blister pack to the left represents the front view and the second blister pack to the right represents the back view.

Age group	Drug	Dosage and frequency	Duration(months)	
			MB	PB
Adult	Rifampicin	600mg once a month	12	6
	Clofazimine	300mg once amonth and 50mg daily		
	Dapsone	100mg daily		
Children(10-14years)	Rifampicin	450mg once a month	12	6
	Clofazimine	150mg once a month and 50mg daily		
	Dapsone	50mg daily		
Children <10 years old or <40kg	Rifampicin	10mg/kg once a month	12	6
	Clofazimine	100mg once a month, 50mg twice a weekly		
	Dapsone	2mg/kg daily		

Guidelines for the diagnosis, treatment and prevention of leprosy - World Health Organisation 2018

Table 17.5-1 Recommended leprosy treatment regimens

Note: For children less than 10 years old or whose weight is less than 40Kgs, dosages should be calculated according to weight as shown in the table above.

17.5.6. Treatment for drug resistance leprosy

The World Health Organization Guidelines Development Group recommends for leprosy patients with rifampicin resistance to be treated using at least two of the following second-line drugs: clarithromycin, minocycline, or a quinolone (ofloxacin, levofloxacin or moxifloxacin), plus clofazimine daily for 6 months, followed by clofazimine plus one of the second-line drugs daily for an additional 18 months.

In case of rifampicin plus ofloxacin resistance, a quinolone should not be chosen; therefore, the recommended regimen is clarithromycin, minocycline and clofazimine for 6 months followed by clarithromycin or minocycline plus clofazimine for an additional 18 months.

Resistance type	Treatment	
	First 6 months (daily)	Next 18 months (daily)
Rifampicin resistance	Ofloxacin 400mg plus Minocycline 100mg plus Clofazimine 50mg.	Ofloxacin 400mg or Minocycline 100mg plus Clofazimine 50mg.
	Ofloxacin 400 mg plus Clarithromycin 500 mg plus Clofazimine 50 mg.	Ofloxacin 400 mg plus Clofazimine 50 mg.
Rifampicin and Ofloxacin resistance	Clarithromycin 500 mg plus Minocycline 100 mg plus Clofazimine 50 mg.	Clarithromycin 500 mg Or minocycline 100 mg plus clofazimine 50 mg.

Table 17.5-2 Recommended drug resistance leprosy regimens

Offending drug	Adverse drug reaction	How to manage the adverse drug reaction
Dapsone	Anaemia	Give iron supplements and continue treatment.
	Abdominal pain(s)	Symptomatic treatment of the pain.
	Exfoliative dermatitis	Stop dapsone and may need to refer to the next level.
	Jaundice	Stop dapsone and refer to the next level.
	Kidney damage	Stop dapsone and refer to the next level.
Rifampicin	Red discoloration of urine, saliva and sweat.	Reassure the patient and continue treatment.
	Jaundice	Stop rifampicin and refer to higher level.
	Flu-like illness	Symptomatic treatment but continue treatment
	Skin rash	Stop rifampicin
Clofazimine	Brown-red discoloration of skin and urine	Reassure the patient and continue treatment

Table 17.5-3 Management of adverse drug reactions during treatment

17.6. Leprosy reactions and their management

- A leprosy reaction is the sudden appearance of acute inflammation in the skin lesions, nerves, and other organs.
- This is due to increased activity of the body's immune system to fight the leprosy bacillus, and remains of dead bacilli and their by-products.
- These are some of the most common complications of leprosy and they are medical emergencies which can occur before, during and after MDT treatment.
- Reactions are often present at the time of diagnosis and around 22% of all new cases have some form of reaction. They often result in nerve damage.
- It has to be noted that leprosy reactions are different from adverse drug reactions or events.

Who can get leprosy reactions

- Any person with leprosy is at risk of developing reactions.
- 25-30% of leprosy patients will develop reactions at one time or another.

Precipitating factors of leprosy reactions

- Co-infections -malaria, viral infections
- Anaemia
- Mental and physical stress
- Puberty
- Pregnancy
- Surgical interventions
- Post partum

People at risk of developing leprosy reactions

- Patients within 6-8 months of starting MDT
- Pregnant and lactating mothers. Adolescents (10-25 years of age)
- Patients with other infections like TB.
- Patients with lesions around or near the eye and overlying peripheral nerve trunks
- Patients with neuropathy at the time of diagnosis

Types of leprosy reactions

The following are the two types of leprosy reactions:

1. Type 1 (reversal reactions)
2. Type 2 (erythema nodosum lepromatous.)

Note: It is much more urgent to recognize and treat lepra reactions, so as to prevent nerve damage, than to decide which type of reactions it is; the treatment of the nerve damage is usually much the same, regardless of the type.

17.6.1. Type 1 (reversal reactions)

- Type 1 (reversal reaction) is a delayed cellular hypersensitivity reaction to M. leprae antigens (Gell and coombs type 4) that results in increased T cell activity (CD4+ Lymphocytes).
- It manifests as an inflammation that is usually limited to the skin overlying and peripheral nerves underlying an existing leprosy lesion.
- It causes severe nerve damage.

Clinical presentation of type 1 leprosy reaction

Type 1 leprosy reactions manifest in the following ways;

- Sudden inflammation of skin lesions and nerve function impairment, with no apparent systemic involvement.
- The typical features of inflammation are seen swelling, redness, heat, pain, and loss of function.
- Painful and tender nerves with or without loss of function.
- Crops of new lesions may suddenly appear in previously clinically uninvolved skin.

Grading of type 1 (reversal) leprosy reaction

Type 1 leprosy reaction is categorized into mild and severe forms, and this is how these forms present;

- Mild type 1 (reversal): Mild type 1 (reversal) reaction is characterized by inflammation of skin lesions without nerve involvement.
- Severe type 1 (reversal): Severe type 1 (reversal) reaction is characterized by reactional lesions overlying major nerves with nerve involvement which may or may not be associated with loss of function and edema of hands and feet. It has to be noted that mild reversal reaction persisting over four weeks is also considered as severe type 1 (reversal) reaction.

Treatment of mild type 1 (reversal) reactions

1. Type 1 reactions are mostly treated with steroids. The recommended medicine is Prednisolone at a dose of between 0.5 and 1.0 mg per kg of body weight per day for a duration of 20 weeks. Continue MDT

2. Give analgesics. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) such as Aspirin, Ibuprofen and Diclofenac are preferred. Analgesics without anti-inflammatory properties such as Paracetamol can be used in situations where NSAIDs are contraindicated or not available.
3. See the patient after 1-2 weeks and tell him/her to report back to the clinic if the symptoms become severe.

Treatment of severe reversal reactions

1. Continue MDT
2. Start prednisolone (It should be given in tapered doses as shown in table 14.61 below
3. Severe reactions are an emergency. The patient should be transferred to a specialized care center.
4. If a flare occurs, the dosage may be raised one step further for two weeks.
5. Test the nerve function every 2 weeks while the patient is on prednisolone

Dose	Week					
	1-2	3-4	5-8	9-12	13-16	17-29
40 mg						
30 mg						
25 mg						
20 mg						
10 mg						
5 mg						

Table 17.6-1 Prednisolone treatment schedule in Type-1 reaction treatment

Prednisolone (Steroids) is an immunosuppressive drug. Take care of the following areas:

- Give tablet Albendazole 400 mg twice daily for 3 days to reduce worm infection.
- Ask for expert advice if there are any signs of tuberculosis, corneal ulcer or osteomyelitis.
- Check and monitor urine for sugar - if positive or known diabetic, refer for expert advice.
- Check and monitor blood pressure.
- Steroids also affects the growth, so all the pregnant women and children should be referred for expert advice.

17.6.2. Type 2 leprosy reaction (Erythema Nodosum Lepromatous)

- The pathogenesis of ENL is unclear, but it is believed to result from antigen-antibody complex deposition in the skin with the subsequent activation of complement.
- It results in systemic inflammatory response affecting the skin, nerve, eye, spleen, kidney, liver, lymph nodes, testicles, muscle and bones.
- It also causes mild to moderate nerve damage.
- This type of reaction commonly occurs in MB patients and usually starts 6 months or more after the start of MDT. However, the reaction may occur earlier after the start of MDT.
- Type 2 Leprosy reaction is also sub divided into 2; mild ENL and severe ENL

Mild Erythema Nodosum Lepromatosum

This is characterized by the following signs and symptoms.

- Few crops of red and tender nodules.
- Mild fever and malaise.
- Few nodules may ulcerate.
- Eyes and testicles are not involved.

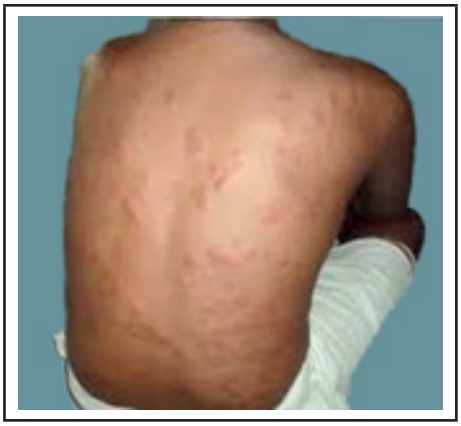


Figure 17.6-1 Mild Erythema Nodosum Lepromatosum

Severe Erythema Nodosum Lepromatosum (ENL)

Generally, a patient with type 2 reaction present with severe form of illness characterized by:

- Many crops of red and tender nodules are present at one time.
- Severe fever and malaise.
- Many nodules ulcerate.
- Swollen, painful and tender nerves with loss of function.
- Painful eyes with redness around the limbus.
- Reduced vision.
- Swollen, painful tender testicles.

General management of Erytherma Nodosum Lepromatosum (ENL)

The following constitute the general management principles of ENL management;

- Control acute pain.
- Halt eye damage.
- Bed rest.
- Treatment of specific symptoms appropriately.

Mild Erytherma Nodosum Lepromatosum (ENL) management

The management principles of mild erythema nodosum leprosum are;

- Continue MDT. If there is nerve tenderness, rest the affected limb
- Analgesia

Severe Erytherma Nodosum Lepromatosum (ENL) management

The management of severe ENL is made up of the following drugs;

- Predinisolone as per type 1 reaction
- Clofazimine 300 mg daily for 1 month
  - 200 mg daily for 3-6 months
  - 100 mg daily for as long as symptoms remain.

17.6.3. Management of relapse in Leprosy

Management of PB relapse

- PB relapse is diagnosed by the appearance of a definite new skin lesion and or negative skin smear. However, the diagnosis of a PB relapse can never be absolutely certain.
- A skin smear should be carried out, if at all possible, to ensure that an MB case is not being misclassified as PB.
- The evidence for either a relapse or a reaction must be weighed and a decision made.
- A PB relapse case is treated with a 6 month course of MDT.

Management of MB relapse

- MB relapse is diagnosed by the appearance of **definite new skin lesions and/or an increase in the bacterial index (BI) of 2 or more units** at any single site compared to BI taken from the same site at the previous examination.
- It is therefore important to perform a skin smear test at baseline and monitor changes in bacillary load over time.
- An MB relapse case is treated with MDT for 12 months.

In this case, the presence of solid staining bacilli in the smear provides support to the diagnosis of a relapse. If the diagnosis is uncertain after these investigations; a trial of steroids may be considered, and if it is a reaction, clinical signs would begin to settle in 10-14 days while they will remain constant if it is a relapse.

17.7. Leprosy prophylaxis

Prolonged contact with untreated leprosy patients is considered as a source of infection. Contacts at home, in the neighbourhood or in the community are considered at higher risk of being infected and developing leprosy. Screening of contacts and provision of chemoprophylaxis are crucial to break the chain of transmission.

Single dose of rifampicin (SDR) is recommended as a prophylaxis to contacts of all new leprosy patients to curb the further spread of the disease amongst adults and children above 2 years of age. Before initiating eligible contacts on SDR, it is important to exclude TB and leprosy and other contraindications. Recommended dosage schedules for SDR are given in table below.

Age/body weight	Rifampicin single dose
15 years and above	600mg
10-14 years	450mg
Children 6-9 years (weight ≥ 20 kg)	300mg
Children 6-19 years (weight at >20kg)	150mg
Children 2-5 years	10-15 mg/kg

Table 17.7-1 Dosage of rifampicin given as SDR for leprosy prophylaxis

BCG Vaccine

BCG vaccination at birth is effective at reducing the risk of leprosy, therefore its routine use as a preventive measure for TB should be maintained. This would particularly benefit children below two years since this age

group is ineligible for Rifampicin based Leprosy chemoprophylaxis.

17.8. Management of Leprosy in Special populations

The management of Leprosy requires special considerations in certain population subgroups, either from a treatment safety or a co-morbidity perspective. Special considerations should be directed towards pregnant women, infants and people presenting with the comorbid of Leprosy and HIV, TB and diabetes.

Sub-group/special condition	Important considerations /approach	Treatment regimen design
Pregnancy and breastfeeding	• Faster proliferation of M. Leprae • Leporatamatous leprosy and relapse after treatment are more common	• Leprosy MDT to continue unchanged during pregnancy and breastfeeding.
Leprosy-TB coinfection	• TB needs to be ruled out in cases of leprosy before treatment is initiated with rifampin (Rif)-based regimens • Higher risk of co-infection for Leprosy patients on concomitant steroid therapy • Higher risk of co-infections among individuals with pre-existing comorbid conditions like malnutrition, diabetes mellitus, chronic kidney • Risk of false positive TB on sputum amongst co-infected patients. Definitive TB diagnosis amongst Leprosy patients may require sputum culture • Clofazimine based DR-TB regimens can mask underlying Leprosy	• Leprosy MDT and TB regimens should be administered together • No modification in the co-administered regimens unless if there is clinical justification for the modification
Leprosy-HIV coinfection	• No increased HIV prevalence among leprosy cases • Similar clinical spectrum of leprosy among coinfected patients • Higher risk of reactions amongst HIV patients who presents with lepratomous forms of Leprosy • ART can mask underlying Leprosy	Leprosy MDT and ART regimens should be administered together • No modification in the co-administered regimens unless if there is clinical justification for the modification
Leprosy and DM	• Higher prevalence of DM amongst Leprosy patients • Both conditions cause neuropathy. Neuropathy associated with Leprosy typically unilateral while for DM it is bilateral • Routine Screening for steroid-induced DM • Interactions between Rifampicin and Sulfonylureas	Leprosy MDT and oral antidiabetics should be administered together • No modification in the co-administered regimens unless if there is clinical justification for the modification Close monitoring of glucose levels for patients on Sulfonylureas and Leprosy MDT

Leprosy in Kidney disease	• Renal nephropathy associated with high bacillary load • Leprosy induced nephropathy generally presents with mild form of disease • Clofazimine may accumulate in renal disease • Rifampicin may induce nephropathy	• No need for MDT modification • Consider dose adjustment in severe renal failure • Monitor for Leprosy and drug-induced nephropathy

Table 17.8-1 Management of Leprosy in special situations

17.9. Deformities and their management

- Deformity is defined as any deviation from the normal appearance of any part or parts of the body. Deformities arise due to tissue infiltration and nerve damage.
- The fear and the strong stigma associated with leprosy are mostly due to the gross deformities and mutilations generally regarded as essential features of the disease.
- As a single disease entity, leprosy is one of the foremost causes of deformities and crippling.
- It is estimated that approximately 25% of patients who are not treated at an early stage of the disease develop anesthesia and/or deformities of the hands and feet.

17.9.1. Factors associated with deformities in leprosy

The following factors have been associated with the likelihood of developing deformities.

Type of disease	Deformities or disabilities are commonly found in patients with multibacillary leprosy. Most of them follow reactions in such cases
Duration of disease	The incidence of deformities in a patient population and also the number of deformities per patient increase the longer the disease lasts. Deformities may develop earlier and during type 1 lepra reactions.
Nerve thickening	Nerve thickening is often associated with deformities however it is not uncommon to find patients with deformities but without any appreciable thickening or tenderness of the nerve concerned.
Age	Deformities due to leprosy are more frequent in the 20-50 year age group. however they may develop in any age group.
Sex	deformities are less common in women than in men.
Occupation	Deformities and disabilities are more commonly found among manual workers since they are more frequently exposed to injuries and infections.

Table 17.9-1 Factors associated with deformities.

Site	Nerve	Deformities	Associated Sensory Changes	Associated Motor Changes
Hand	Ulnar Nerve	Clawing and hyperextended metacarpophalangeal joints and flexion of interparietal joints of fourth (ring finger) and fifth finger (small finger) Uncoordinated grasp	Loss of sensation and sweat over little finger and over ulnar half of ring finger	• Wasting of hypothenar eminence and hollowing of interosseous spaces • Increased pressure on the fingertips and metacarpal heads • If neglected can lead to contractures
	Median Nerve	Clawing of index and middle fingers	Loss of sensation and sweating over the thumb, index and middle fingers and radial half of ring finger	• Wasting of the hand and of the radial side of the thenar eminence. • Inability to abduct and oppose thumb
	Ulnar and Median Nerves	Clawing of all fingers	Loss of sensation and sweating over whole palm	Wasting of the hand and of hypothenar and thinner eminence
	Radial Nerve	Wrist drop Functionless hand	Loss of sensation over dorsum of hand	• Paralysis of thumb, fingers and wrist extensors • If neglected can lead to contractures
Foot	Lateral popliteal nerve (Common Peroneal nerve)	Foot drop	Loss of sensation over dorsum of foot and lower leg	• Inability to lift the forefoot at the ankle, no heel strike, • Abnormal high stepping gait, high pressure on the sides of forefoot • If neglected can lead to contractures
	Posterior Tibial Nerve	Clawing of the toes and clawing of foot arches	Loss of sensation and sweating over sole of foot	Paralysis of almost of all intrinsic muscles of the foot
Face	Facial Nerve	Lagopthalmos and Inability to blink	Exposure keratitis and Impaired vision	Paralysis of obicularis oculi; paresis of orbicularis oris
	Trigeminal Nerve	Dryness of cornea, Corneal scaring, Corneal ulcer and Impaired vision.	Sensory loss leading to corneal anaesthesia and loss of stimulus to blink.	

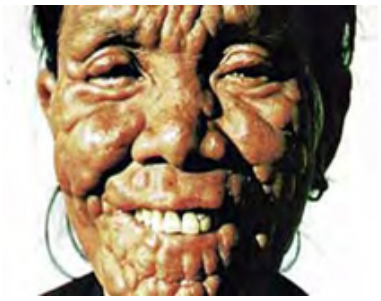
Table 17.9-2 Primary Deformities and Nerves involved in leprosy.

Note: *Type 2 lepra reaction can cause Iridocyclytis (Red eye), Glaucoma and Impaired vision.*

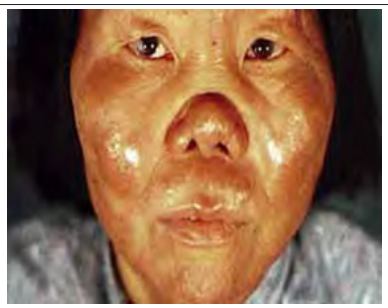
Other primary deformities

Other primary deformities are:

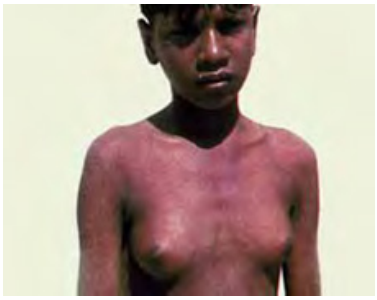
- Facies leonina
- Sagging face
- Loss of eyebrows (maradosis) is due to the lepromatous infiltrate destroying the hair follicles.
- Nasal deformities e.g. Depressed nose is mainly due to the destruction of the nasal septum and the septal perforation is caused by a non-specific infection destroying the cartilage.



Facies Leonina



Nasal Deformities



Gynaecomastia

Figure 17.9-1 Leprosy related deformities

Secondary Deformities

- Secondary impairments are due to neglect of primary impairments.
- These are consequences due to loss of sensation, loss of sweating and motor paralysis.
- Secondary deformities can occur on the hands, feet, eyes and other organs of the body.
- Examples of secondary deformities are plantar ulcers, loss of toes and fingers, corneal ulcers, Charcot joints, corneal ulcers, impaired vision, corneal scarring, gynaecomastia, neoropathic bone disintegration, contractures and joint stiffness.

Mechanisms of secondary impairments of hands and feet

They can occur due to:

- Increased pressure by prolonged standing or gripping objects forcefully

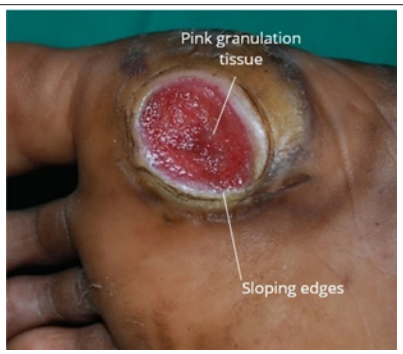
- Repetitive force on the pressure points in the palms and soles by walking, climbing, running and using tools or instruments or turning keys in locks.
- Use of inappropriate footwear or prosthetic appliances
- Shearing stress (repeated friction against handles of implements e.g. digging, cutting with sawing motion, filing, walking, running etc.)

Direct trauma (thorns, nails, sharp objects, burns)

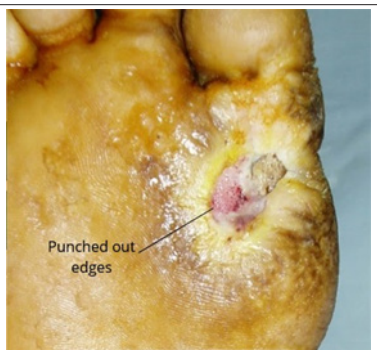
Simple ulcer	Any one of the conditions below will make it a complicated ulcer
Sloping edges	Punched out edges
Pink granulation tissue	Slough in the ulcer (presence of dead tissue)
No slough (no dead tissue)	Discharge, clear or purulent
No discharge	Presence of infection
No infection	Involvement of underlying structures (tendon or bone)
No involvement of underlying Structures	Evidence of malignant growth (sprouting granulation tissue or growth from the ulcer)
No evidence of Malignancy	

Table 17.9-3 Showing features of Simple and Complicated Ulcers of hands and feet in leprosy

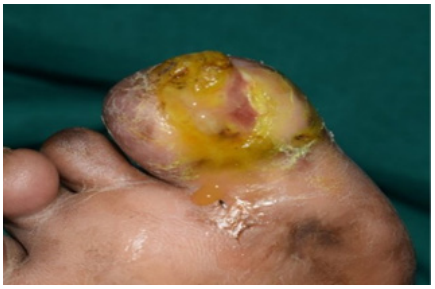
PICTURES SHOWING SIMPLE ULCERS AND COMPLICATED ULCER



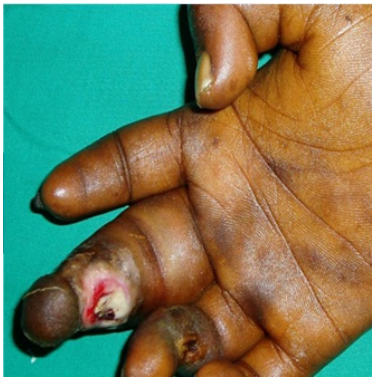
1. Simple Ulcer



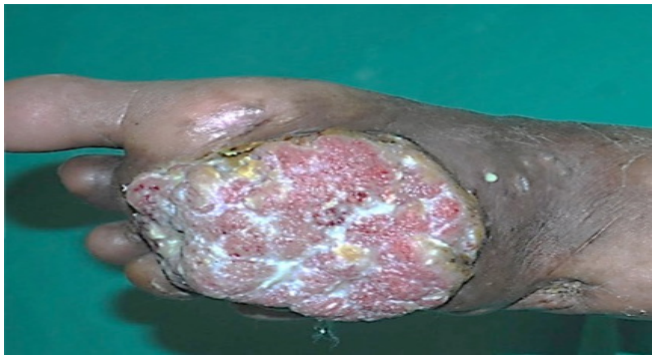
2. Complicated Ulcer



3. Complicated Ulcer with Purulent Discharge



4. Complicated ulcer with underlining tissue/bone Involvement



5. Complicated ulcer with Malignant Growth (Sprouting Granulation Tissue or Growth from Ulcer)

Grade	Hands and Feet	Eyes
Grade 0	No anaesthesia. No visible deformity or damage	No eye problems due to leprosy. No evidence of visual impairment
Grade 1	Anaesthesia present. No visible deformity or damage.	Eye problems due to leprosy are present. Vision 6/60 or better, the patient can count fingers at six metres
Grade 1	Visible deformity or damage present.	Severe visual impairment (vision less than 6/60, the patient is unable to count fingers at six metres), lagophthalmos, iridocyclitis and corneal opacities.

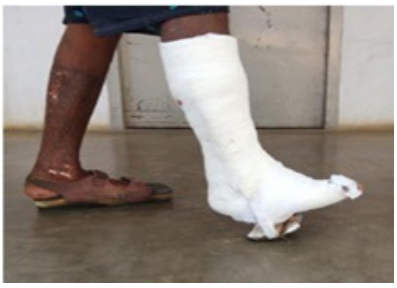
Table 17.9-4 The three-grade WHO classification of deformities/disabilities

Management of Simple Ulcers of the foot and hands

- Simple ulcers can be managed at home and do not require hospitalization.
- Dressings can be done at home after ascertaining that it is a simple ulcer.
- It is essential to give rest to the ulcer or rest to the limb (to prevent stresses on the ulcer). This can be achieved by;
  - Bed rest
  - Use of crutches or splinting
  - Use of off-loading devices like plaster casts or appliances

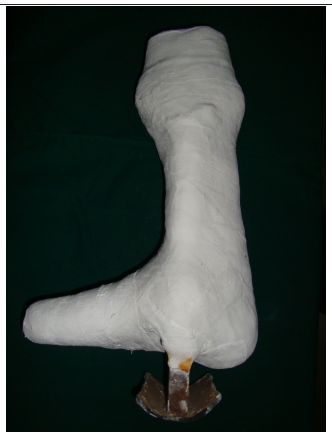
Bed rest

Use of crutches



Plaster Casts

Moulde Double Rocker Shoes (MDRS)



Below Knee (BK) Cast with Bholer Iron Plaster

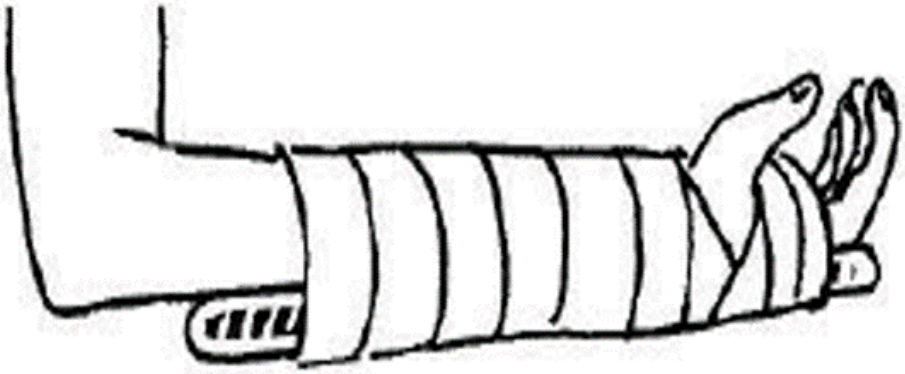


Figure 17.9-2 The hand resting in a sling

Note: If bulky dressings are used for the ulcer, it will not be necessary to splint the hand.

Management of complicated ulcers

- Complications can include infected tenosynovitis or osteomyelitis or infected arthritis
- Malignant change usually manifests as Squamous Cell Carcinoma
- Management of complicated ulcers require hospitalization where medical and surgical facilities are available. Refer the person with complicated ulcer to a specialized health centre.

Type of complication	Management
Infection or purulent discharge from the ulcer	Debridement and immobilization (rest), Elevation of the affected part (hand/foot), Daily dressing and Antibiotics.
Clear discharge from the ulcer	Immobilization (rest), Elevation of the affected part (hand/foot), and Daily dressings.
Slough (dead tissue in the ulcer)	Debridement, Immobilization (rest), Elevation of affected (hand/foot), Daily dressings, and Antibiotics.
Sprouting granulation tissue or growth of the ulcer	Biopsy to confirm whether the growth is malignant or benign, dressings, immobilization and debridement. If malignancy is confirmed, then ablation (local excision or amputation) surgery.

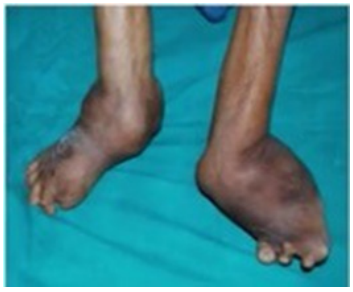
Table 17.9-5 Management of Complicated Ulcers

17.9.1.1. Neuropathic Bone Disintegration and its management

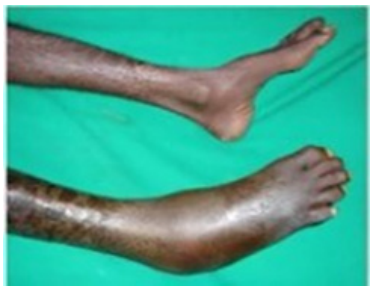
- This is the swelling of insensitive limb without ulceration which begins with destruction of the articular cartilage and later involves the bone which disintegrates.
- Divided into acute and chronic bone disintegration.

17.9.1.2. Acute disintegration of Neuropathic limb (Hot foot)

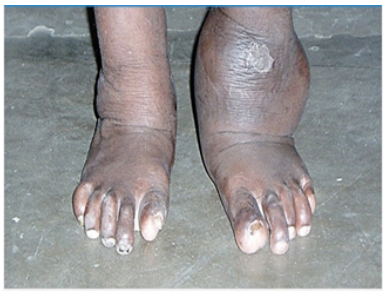
- The limb is warm to touch.
- This could be caused by fracture or dislocation of ligaments due to excessive or repeated force on the insensitive limb due to normal activities of daily living like walking



Fracture



Ligament Tear



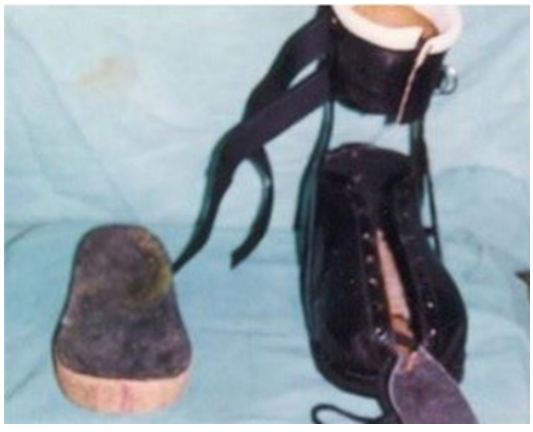
Acute Disintegration of Foot

Management of Acute disintegration of Neuropathic limb

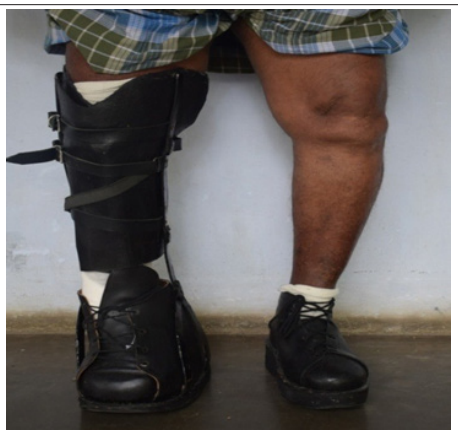
- Immobilization in a plaster cast and elevation for 1 month
- Once the swelling subsides (after one month) then change the plaster cast
- Plaster cast for 3 months for the hand and wrist. Plaster cast for 4 months for the foot and ankle
- Remove the cast and take a mold for a fixed ankle brace for the foot and reapply the cast for a month
- Remove cast and provide Fixed ankle brace for use for 1 year or 1½ years
- Re-evaluate after 1 year

Management of Chronic disintegration of Neuropathic limb

- This needs to be managed by special customized molded footwear or surgery or both



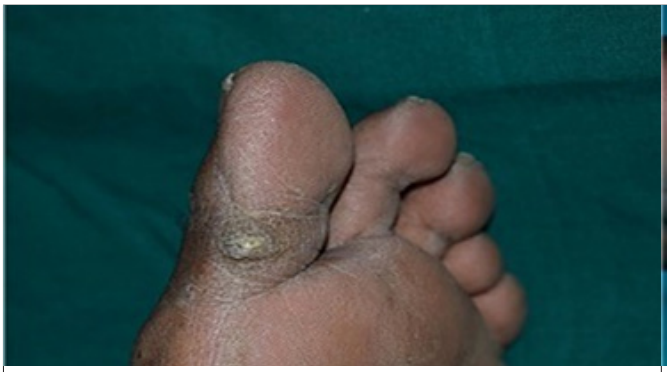
Fixed Ankle Brace (FAB)



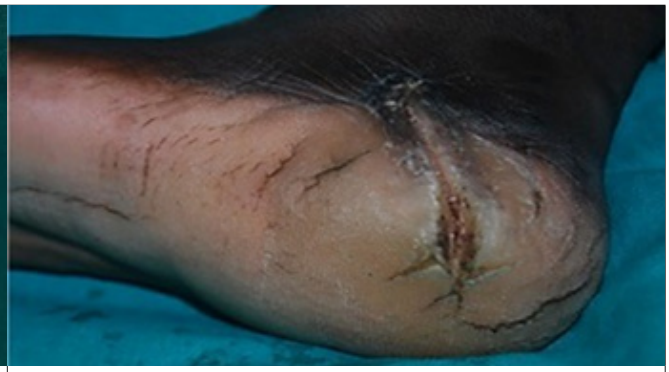
Patellar Tendon Bearing Brace (PTBB)

17.9.1.3. Consequences of loss of sweating in hands and feet and their management

1. Dry skin
2. Callus and Fissures/Cracks
   - These are caused by excessive dryness of the hands or feet
   - They are pre-ulcerative conditions which can lead to ulcers.
   - Cracks are most commonly found in the creases of the hand, around the heels of the foot and in the toe creases.
3. Infections and complicated ulcer.
   - If cracks are neglected, infections and complicated ulcers can occur
   - Infection can easily spread into the joints and bones causing loss of the infected finger or toe.
   - The Infection may track up tendons and spread to other parts of the hand or foot.
   - If infection tracks into the calcaneus (the heel bone), it can destroy the bone and the person may eventually lose the entire foot.
   - Even if cracks do not become infected they should be treated with care. If ignored they may eventually heal, but they will leave scar tissue which can cause the fingers or toes to become stiff, deformed and difficult to use.



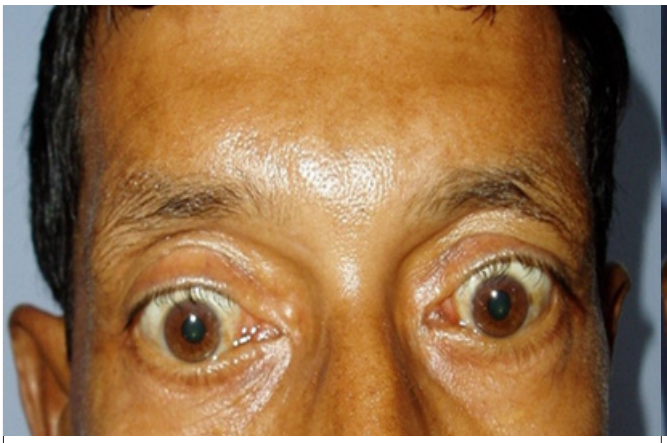
Callus



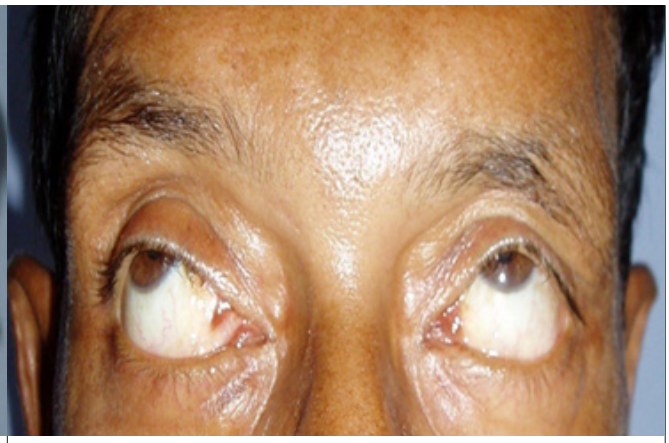
Fissures/Cracks

Management of Callus and Fissures

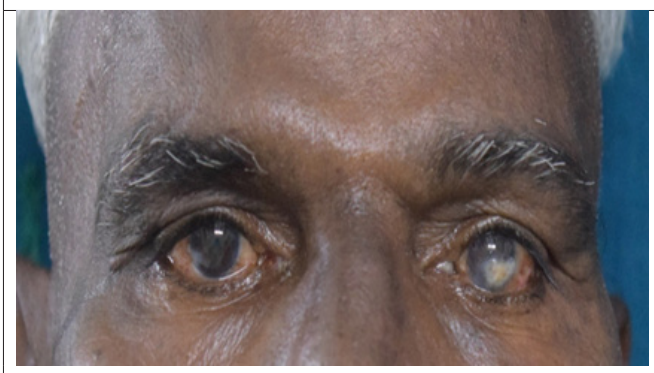
- Soak the feet or hands in warm water for 30 minutes
- scrape the dry skin off the foot
  - Use any abrasive object e.g. rough stones, coconut husks, coral, charred corn cobs, sand paper and files
  - Care should be taken not to use any object that might damage the person's hands.
- After soaking and scraping oil the hands or feet using Vaseline. Cooking oil may be used but can attract rats and insects.
- Do not to dry the skin before oiling, but if the person has fixed claw toes, or other deformed toes, it is wise to dry between the toes to reduce the chance of fungal infection.



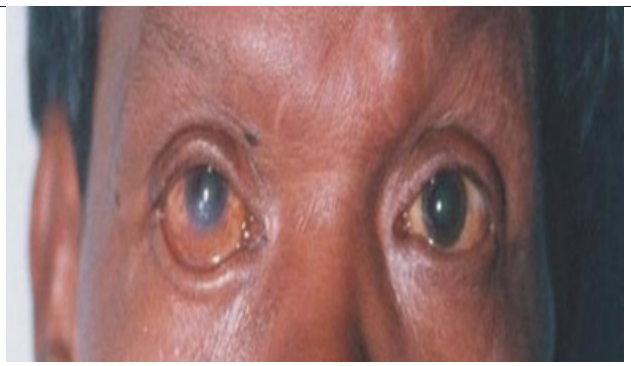
Lagopthalmos (Inability to Close the Eyes) due to Motor Loss (Damage to Facial Nerve)



Attempted Eye Closure



Corneal Scarring



Red Eye due to Type 2 Reaction

17.9.1.4. Management of Eye problems in leprosy

- Any eye complication due to leprosy is an emergency
- Eye complications can lead to blindness.
- Refer to a specialized health centre (Ophthalmologist)
- Passive and active Exercise for Facial Nerve – Orbicularis Oculi - Lagophthalmos

Note: It is imperative to explain to the patients that they can overcome this impairment by doing these passive and active exercises regularly.

Passive Exercise for Lagophthalmos:

- Ask the patient to place the index finger on the lateral side at the edge of the eye.
- The person is told to gently pull laterally.
- This will cause the eye to close

Active exercise for Facial Nerve – Orbicularis Oculi - Lagophthalmos

- The patient is asked to close the eye tight for 3 to 5 seconds.
- Then they must open the eye and after about 10 to 15 seconds, the exercise should be repeated again
- This exercise will strengthen the Orbicularis oculi muscle.

17.9.2. Rehabilitation

It is a set of measures that help individual who experience or are likely to experience disability achieve and maintain optimum functioning within their environment.

Rehabilitation is classified into four;

1. Physical therapy
2. Occupational therapy
3. Speech and language therapy
4. Prosthesis and Orthosis

17.9.2.1. Physical therapy

Is a health care profession that promotes mobility, function and quality of life through examination, diagnosis, prognosis and physical intervention.

17.9.2.2. Occupation therapy

- This is to make it possible for handicapped people to earn higher incomes
- Occupational rehabilitation activities include: crafts, cooperative ventures and Industrial ventures.

17.9.2.3. Speech and language therapy

- The assessment and treatment of people with speech, language and swallowing disorders.

17.9.2.4. Prosthesis and Orthosis

- A health profession that design, measure, fabricate and fit orthosis and prosthesis.

17.9.3. Disability prevention in leprosy

Individual self-care and self-care groups to prevent deformities and disability.

- Self-care is an act of caring for oneself to protect one's eyes, hands or feet from injuries and developing ulcers and to prevent further damage. The actions to be taken are to changes in lifestyle and a set of tasks to be done daily.
- Self-care Group is a group of people affected by leprosy (also can include family members) who share a common purpose of "self-care". The group meets regularly and helps one another by interacting, communicating and reacting.
- Objectives of a "self-care" Group are to create a cohesive group; learn from each other; support each other; bring positive change in the attitudes towards disabilities.

Psychosocial support for leprosy patients

- Psychosocial support is continuous care and support that is offered by a specialized or non- specialized psychological and social service provider to improve the individual psychosocial well- being.
- This includes emotional/ psychological, social, material support and spiritual support.
- All patients need psychosocial support.
- Psychosocial problems in people with leprosy include: lack of knowledge about the disease, stigma against sufferers, physical disability, socio economic disadvantage, long distance to get treatment, medicine side effects and many more that cause sufferers to feel challenged to get along with others in the community and comply with treatment.

Conceptual Framework/Key areas of psychosocial support services

- Psychosocial assessment, education and counseling at treatment initiation and throughout treatment.
  - Education about the disease, transmission, treatment duration, drug side effects, prevention of disabilities and self- care
- Providing the needs of the patient (material needs like food, transport support to and from the clinic, housing, self- care and rehabilitation needs and support.) where resources are adeqaute.
- Services to mitigate the impact of psychosocial challenges like helping the patients and families on income generating activities (IGAs), social cash transfers, gardening, small scale businesses, bank mkhonde and many more.
- Linking/ networking/ referral: Supporting patients to be linked for support either from partners, CSOs stakeholders or church organization. Referring to psychiatric care and support.
- Community support for the patients and their families and support for the care of carers (DOT supporters, community support groups)

Stigma and discrimination in leprosy

- To stigmatize someone: means labeling or seeing someone as inferior or below others because of leprosy.
  - People stigmatize others because they do not have the right information or knowledge.
  - People also stigmatize others because they are afraid.
- Discrimination: means treating someone unfairly or worse than others because s/he has leprosy.
- Different forms of stigma
  - Stigma towards others: Having a negative attitude towards others because they have leprosy. For instance, a person being stigmatized because s/he has got leprosy.
  - Self- stigma. Taking on or feeling affected by the cruel and hurtful views of others. This often leads to self -isolation from either the family or from the community. This can also be as a result of fears from infecting others as such resorts to be alone.

Effects of stigma and discrimination

- Keep the affected members from accessing good health care services ie leprosy / TB treatment, counseling, and community support because they want to hide their status from others.
- Cause a great deal of anxiety, stress and depression which contributes to breakdown to disease
- Make it hard for people to tell their partners about their status.
- Result in poor treatment adherence.
- Preventing others from caring for those affected in the family, community and in health care settings Reduces health seeking behavior.
- Undermines full recovery and sense of self, affect contact tracing
- Obstructs accurate recording and reporting - impact disease and mortality estimates

How to deal with stigma and discrimination against leprosy patients

Individual strategies to deal with stigma and discrimination

- Stand up for yourself
- Educate others
- Be strong and prove to yourself
- Talk to people whom you feel comfortable

- Join the support groups
- Ignore people who stigmatizes you
- Avoid people who you know will stigmatize you
- Be adherent to treatment and medications. Those who are open to the disease and taking the medications help reduce the stigma around the disease.

Means of dealing with stigma and Discrimination

- Individual Approach (i.e. consultation room- assessment counseling and education (use of checklist at every clinic- assess, plan and intervene).
- Group Approach (i.e. group discussions, role playing). Participating in support groups, self-groups.
- Home visit. Assess patient living condition that include stigma assessment and intervention).
- Mass Approach (i.e. Television, TB /leprosy day). Using Audio visual tools and equipments- IEC materials-posters.
- Community Awareness. Through community gatherings, funerals, church gatherings.

17.10. Community Engagement and Mobilization

Community engagement is critical to improve the reach and sustainability of Leprosy interventions. Community approaches would involve CHW and volunteers' training, improved collaboration between community and facility, between community volunteers and traditional healers, for strengthening referral services. In order to reach unserved populations and detect more Leprosy patients early in the course of their illness, a wider range of stakeholders needs to be engaged in community-based activities by increasing community awareness.

The engagement with these structures should be on a continuous basis for better outcomes. This should be done at three (3) levels namely:

1. National,
2. District/facility
3. Community.

Name of stakeholders	Roles played in Leprosy prevention and control
Roles played in Leprosy prevention and control	• Ensure government policy and action allows for the direct and meaningful participation in the communities on issues regarding Leprosy prevention • Support the NTLEP program plan to operationalise the national plan at community level • Support community mobilisation on Leprosy messages dissemination by increase community awareness • Lobby and mobilise financial and material resources to support the implementation of leprosy activities
Media professionals	• Support the NTLEP in prevention, treatment, stigma, and discrimination through messages dissemination` • Lobby and mobilise financial and material resources to support the implementation of Leprosy activities

Community health workers	• Provision of TB/Leprosy integrated services with multiple cadres • Provide supervision and mentorship to volunteers • Facilitating community engagement through established community structures • Investigate and report rumours and misconceptions on leprosy • Provision of Psychosocial support to leprosy patients as needed • Conduct contact investigation and default tracing • Conduct community-based surveillance on leprosy • Conduct health education sessions on leprosy prevention to improve on health seeking behaviour • Identify and refer leprosy suspects to facility for diagnosis
Chiefs, Village headmen and cultural castodia	• Conduct community awareness on Leprosy based on the messages shared by the Ministry of Health • Supporting compliance of guidance on Leprosy prevention • Identify and refer suspects to health facility • Establish/set bylaws to address stigmatisation of those affected • Support community mobilisation on leprosy prevention • Bringing together multiple actors and stakeholders working on Leprosy prevention in the catchment area to share information and avoid duplication of efforts
CSOs, FBOs, CBOs	• Raise awareness and risk communication on Leprosy in church gatherings or platforms • Disseminate Leprosy information as per Ministry of Health guidelines • Support preparedness and plan for leprosy prevention at all levels • Support contact investigation and default tracing • Conduct orientation of volunteers, chiefs and community groups with guidance from Ministry of Health • Ensure equality and non-discrimination of the leprosy affect population • Work with Government institutions to ensure health rights of the key affected Leprosy population are safeguarded • Support data management including compiling community level reports • Support mobilisation of resources for Leprosy prevention and treatment at all levels
General Population	• Ensure adherence to leprosy messages from Ministry of Health and Authorities • Ensure seeking medical care as advised by Leprosy medical professionals • Every community member has responsibility to ensure or maintain his/her health and that of the society by refraining from behaviour that might spread Leprosy at individual and community level
Traditional healers	• Support coordination of practices of traditional medicines or complementary alternative medicines in conjunction with Ministry of Health
Leprosy survivor	• Act as a role model. Gives testimony of prevention control and treatment of Leprosy

Table 17.10-1 Roles and Responsibilities of key stakeholders in Leprosy

18. Monitoring, Evaluation and Surveillance

Epidemiological definitions used in Leprosy.

- The incidence is the total number of new cases of leprosy that appear in a population during a given period.
- The incidence rate is the total number of new cases of leprosy that appear during a given period per 10,000 population.
- Detection is the identification, diagnosis and registration of all new cases in a population during a given time period.
- Detection rate is the identification, diagnosis and registration of all new cases in a population during a given time period per 10,000 population.
- Prevalence is the number of all active cases on treatment in a population at a certain point in time.
- Prevalence rate is the number of all cases on treatment in a population at a certain point in time per 10,000 population.

M&E System for the program

- The national Leprosy M&E system was designed to report on key Leprosy data elements as required by WHO and the program.
- All data recording and reporting tools were designed to capture and report on the minimum requirements as defined by WHO.
- Through the system, the program can collect data on Leprosy case notification as well as treatment outcomes.

Recording and reporting tools

Three additional registers will be used to record Information in relation to disabilities, contact screening and drug resistance testing.

- Disability register
- Contact register
- Register of the cases tested for drug resistance
- Leprosy register (district and health Centre)
- Patient treatment Chart
- Drug Dispensing Register
- Patient Treatment Card

Key impact indicators for Leprosy

1. Number of children diagnosed with leprosy and visible deformities (G2D)
2. Rate of newly diagnosed leprosy patients with visible deformities (G2D)
3. Legislation allowing discrimination on basis leprosy

Leprosy Pillars

The following are Leprosy Pillar and their indicators as provided in the Leprosy M&E guide:-

Pillar I: Strengthen Government Ownership Coordination and Partnership

- Availability of costed National plan
- Number of subnational jurisdictions with a formal alliance between government programme and other stakeholders
- Availability of web-based reporting system allowing disaggregation by age, sex, place of residence and other relevant criteria

Pillar II: Stop Leprosy and its complications

Case Finding

- New case-detection (number and rate)
- Prevalence (number and rate)
- Proportion of G2D cases among total cases detected
- Proportion of child cases among total new cases detected (or child new case rate)
- Proportion of female cases among total new cases detected
- Proportion of foreign-born cases among total new cases detected
- Proportion of MB cases among total new cases detected
- Proportion of Contacts screened

Case Holding

- Number and proportion of retreatment cases over the total leprosy notified cases
- MDT completion for PB
- MDT completion for MB
- Proportion of patients assessed for disability status at least both at beginning and at end of treatment
- Proportion of patients who have developed new disabilities during the course of treatment
- Number of cases with leprosy reactions during treatment
- Proportion of new patients with disability (G1D and G2D) that have received self-care training
- Proportion of leprosy drug-resistant cases among new and retreatment cases

Pillar III: Stop Discrimination and Promote Inclusion

- Number of formal alliances between association of persons affected by leprosy and the government leprosy programme
- Existence of norms and/or regulations facilitating inclusion of persons affected by leprosy and their communities
- Number subnational jurisdictions where persons affected by leprosy are involved in leprosy services
- Availability of information on prevalence of social stigma and discrimination
- Use by the programme of participation scale to assess the social participation of persons affected by leprosy

Data Sources

The following data sources are currently being used to record and report on Leprosy data

1. Leprosy Register (District and Facility Level)
2. Quarterly leprosy Reporting Form
3. Leprosy Treatment Card

Data Reporting Mechanisms

The following data reporting mechanism are currently being used by the program to collect Leprosy data

1. Routine Leprosy reporting system
2. Administrative reports (training, supervision, and mentoring)

Routine Leprosy Reporting System

The routine reporting system uses the structure of the decentralised health system whereby data flows from health facility, district, and zone to national control program. DHIS2 will be used as a centre for a routine reporting system. Facility level data is available at national level. The routine reporting system captures the following data elements.

1. Notification data (disaggregated by age, sex, and disease category /classification)
2. Grade 1 and Grade 2 disability disaggregated by age and sex
3. Treatment Reactions disaggregated by age and sex
4. Treatment outcome for new and retreatment cases

Administrative reports (training, supervision, and mentoring)

These are administrative data gathered through reports. At national level, there is a mechanism that tracks data from training, supervision and mentorship visits conducted. Normally, the data is used to develop an action plan to respond to gaps identified during supportive or mentorship visits.

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19. Annex (Leprosy)

19.1. Introduction to the slit skin smear

- The detection of Mycobacterium leprae in slit skin smear (SSS) is a gold standard technique for leprosy diagnosis.
- It is a valuable, cost-effective method in the routine management of the patient with leprosy disease.
- The smear is a means of estimating the number of acid-fast bacteria present, which is reported as the Bacterial Index (BI), and it is important in determining the type and severity of disease as well as assessing the response to treatment.

What is a slit skin smear?

- A slit skin smear is a test in which a sample of material is collected from a tiny cut in the skin and then stained for M. leprae, an acid-fast bacillus.

Why do we take a Slit Skin Smear?

The following are the reasons for taking a skin smear:

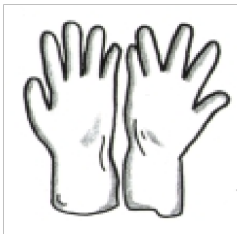
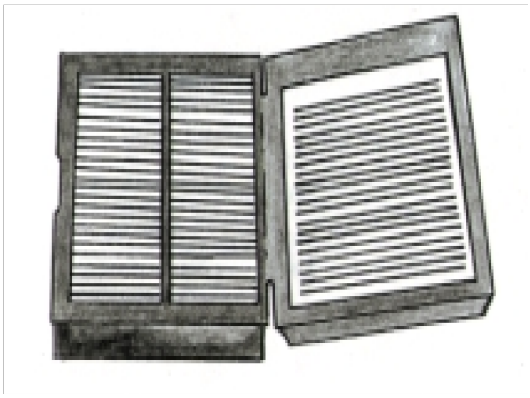
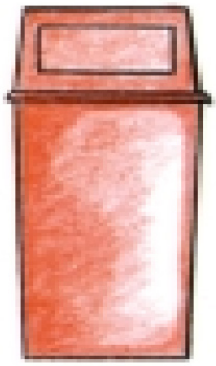
- To confirm a diagnosis of skin smear-positive multibacillary leprosy in a suspect.
- To help diagnose multibacillary relapse in a patient who has previously been treated.
- To help with the classification of new patients.

Preparations before taking a Slit Skin Sample for smear

It is necessary that all the materials that are needed should be within reach before sample collection. Below are some of the materials required.

- Alcohol 96-99% (methanol, ethanol)
- Clean or new microscopy glass slide.
- Gauze roll
- Dry cotton, adhesive or band-aid
- Container with cotton balls soaked in 70% alcohol.
- Charcoal or diamond pencil
- Lighter or matches.
- Scalpel handle Nr 3 and blade Nr15
- Slide box
- Spirit lamp or Bunsen burner
- Sharp or puncture proof container for disposable material used
- PPE: Gloves, surgical mask/N95 or FPP2, gown/apron , goggles, shoes
- One should not forget a carbon pencil or pen, matches and a laboratory request form.

AN ILLUSTRATION OF SOME OF THE MATERIALS REQUIRED

 Scalpelhandle and new blade	 Gloves	 Dressing strips	 Spirit lamp
 Slide box and new slides	 swabs and spits	 safe disposal for used blades	

Selecting a slit skin sample collecting sites

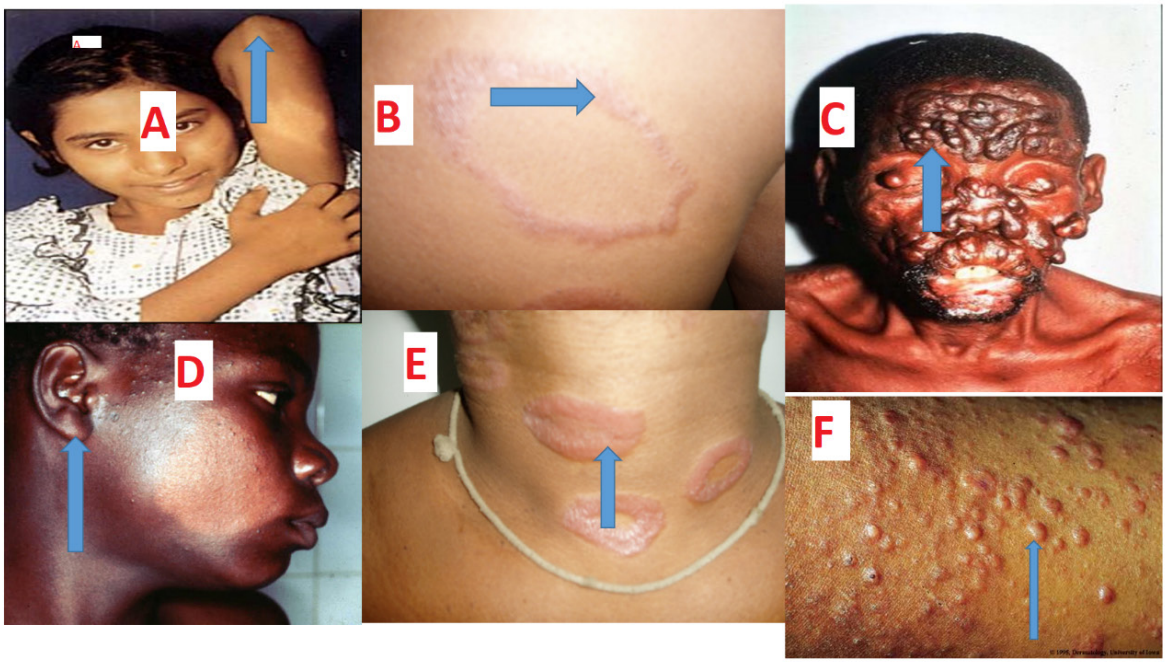
In general, clinically more active lesions are preferred to less active lesions. Skin smears should be taken from a minimum of three sites, including right ear lobe, left ear lobe and one representative active skin lesions respectively.

Routine slit skin smear collection sites

- Right and Left ear lobe
- Elbow(back of the hand)
- Knee
- Over the eyebrow
- Patch(lesion)
- Nodules

From skin lesion

- Well defined lesion (take the smear from the edge)
- Not well defined lesion (take the smear from the center)
- A raised lesion (nodules)-(take the sample from the center)



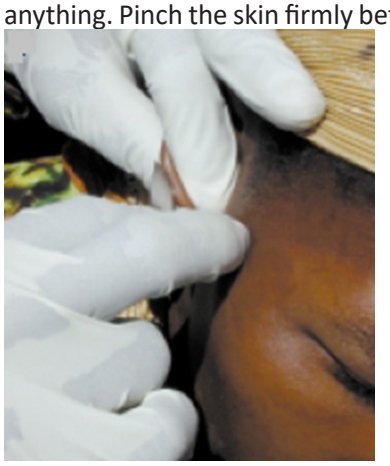
The picture above is showing slit skin smear collection sites; (A) Elbow, (B) Well defined lesion, (C) Over eyebrow, (D) Ear lobe, (E) Not well-defined lesion and (F) Nodules

19.1.1. Obtaining an informed consent

Ask the patient to sit down and relax. Explain what you want to do and why it is necessary. Answer any questions. Obtain the patient's permission to proceed and enter the details on the request form.

19.1.2. Slit skin sample collection and smear preparation

- Wash your hands and put on gloves.
- Take a new, clean, unscratched microscope slide. Using a permanent slide marker or lead/diamond/charcoal pencil, write the patient identification (ID) number at the frosted bottom of the slide. This same number must be on the laboratory request form.
- Clean the skin at the smear sites with a cotton wad drenched in 70% alcohol. Let it dry.
- Light the spirit burner.
- Put a new blade on the scalpel handle. If you put the scalpel down, make sure the blade does not touch anything. Pinch the skin firmly between your thumb and forefinger; maintain pressure to press out the blood.



- Make an incision in the skin about 5 mm long and 2 mm deep. Keep on pinching to make sure the cut remains bloodless. If bleeding occurs, wipe the blood away with cotton wad.
- Turn the scalpel 90° and hold it at a right angle to the cut. Scrape inside the cut once or twice with the side of the scalpel, to collect tissue fluid and pulp. There should be no blood in the specimen, as this may interfere with staining and reading.
- Stop pinching the skin and absorb any bleeding with a wad of cotton.
- Spread the material scraped from the incision onto the slide, on the same side as the ID number. Spread it evenly with the flat of the scalpel, making a circle 8 mm in diameter.
- Rub the scalpel with a cotton wad drenched in alcohol. Pass the blade through the flame of the spirit burner for 3 to 4 seconds. Let it cool without touching anything.
- Repeat the steps above for the second and third sites. Spread this smear next to, but not touching the other.
- Discard the scalpel blade safely in the safety box or sharp/puncture proof container .
- Dress the wounds and thank the patient.
- Let the slide dry for 15 minutes at room temperature, but not in direct sunlight.
- Fix the smears by passing the slide, with the smears upwards, slowly through the flame of a spirit burner, 3 times. Do not overheat. The slide should not be too hot to touch.

- Put the slide in a slide box and send it to the laboratory with the skin smear request form.

19.1.3. Nasal mucous membrane smears

- Patients should sit in good light with the head backwards as this will help to reach the nasal septum easily.
- Blunt, narrow scalpel or dry cotton swab is introduced into the nose.
- Piece of mucous membrane(Nasal mucosa) is taken by rubbing the upper part of the septum. The best time for this sample collection is early morning.
- Air dry the slide on the slide drying rack for at least five minutes after sample collection.
- Heat fix the slide by passing the slide through the flame three times.
- Fixed slides can be stored or sent to the laboratory to be stained.

19.1.4. Staining of a slit skin smear

On reagent preparation and staining of SSS, please refer to laboratory SOPs

Sample storage and transportation

All the prepared smears must be put in the slide box to avoid breakage, dust, etc. The slide box must be carried to the laboratory or the technical area of the laboratory. It is necessary to complete laboratory request forms with all the pertinent patient's details.

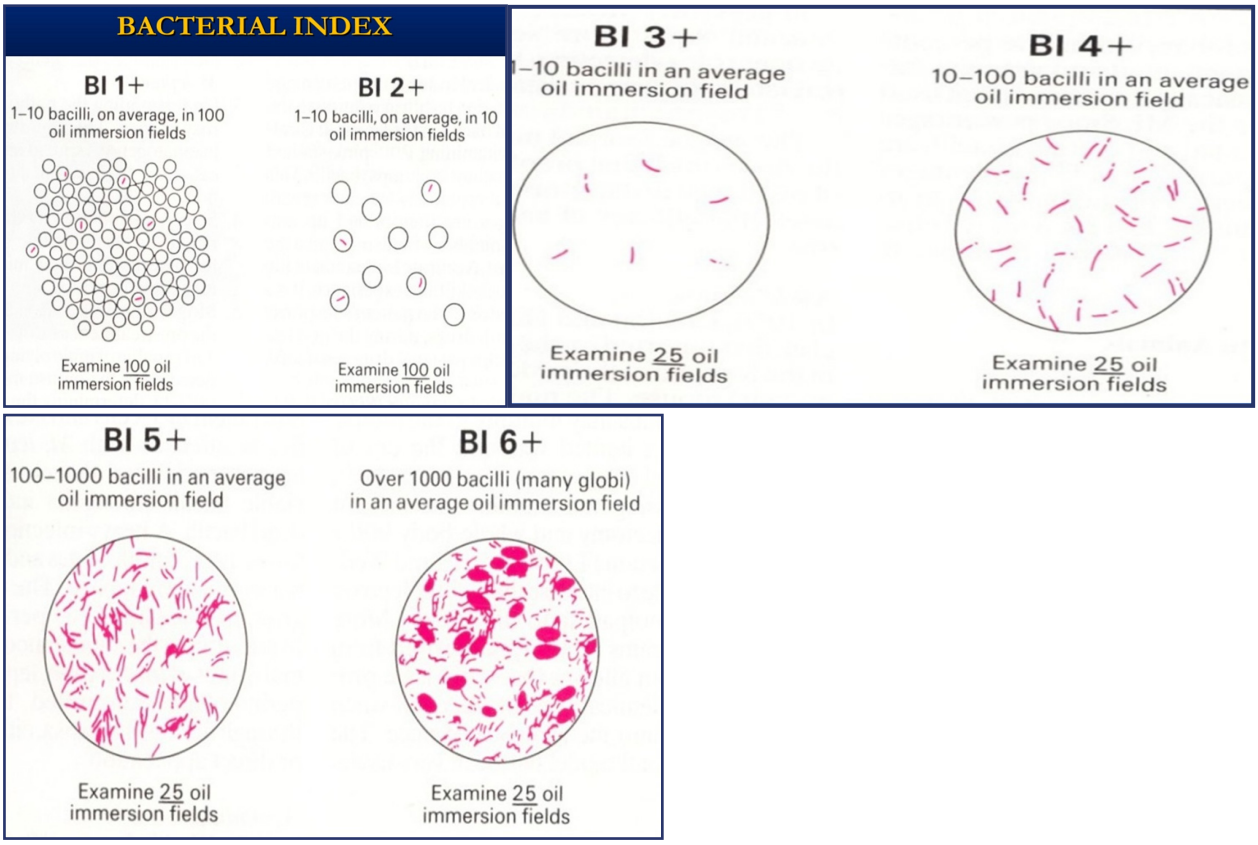
Staining of slit skin smear

Ziehl Neelsen is the technique currently in use for staining of slit skin smear. This method is based on the acid fastness principle. The bacteria are treated with carbolfuchsin which is a primary stain. Then there is a heating stage on a steam bath just to make the cell wall more porous to the stains. Then acid alcohol is applied as a decolorizer to wash off the primary stain. Finally, methylene blue is applied as a counterstain to provide a staining background

19.1.5. How to interpret a slit skin smear

Bacterial index interpretation

Bacteriological index denotes the density of mycobacterium leprae bacilli both living (solid staining) and dead (fragmented or granular) in the smear. According to Ridley's logarithmic scale, it ranged from 0 to 6+ and it is based on the number of bacilli seen in an average microscopic field of the smear using an oil-immersion objective.

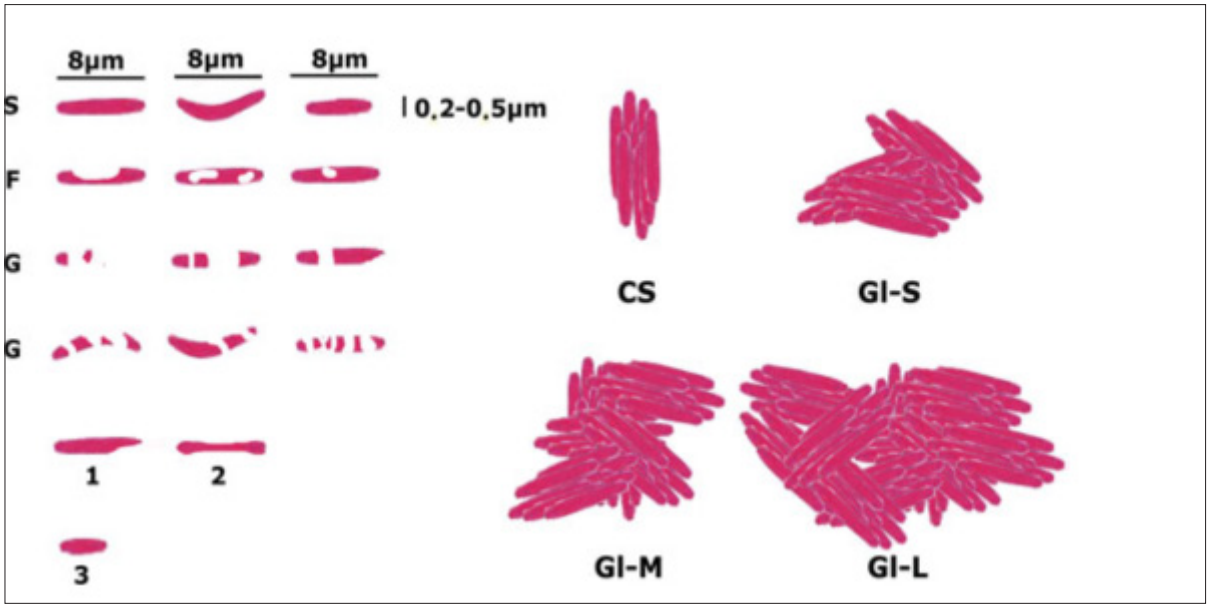


Morphological index interpretations

- The morphological index refers to the percentage of living bacilli(solid stain bacilli) to the total number of bacilli counted.
- It is important for assessing the progress of patients on chemotherapy response.
- Mycobacterium leprae might be present in different morphologies. During microscopic examination, M. Leprea usually appears in three different forms;

1. Solid form – rod shaped, straight or slightly curved and solidly stained form
2. Fragmented form- less stained or staining is interrupted at one or more points
3. Granular form – consist of small granules
4. }M. Leprea bacilli is sometimes found in globi (clumps form) of different sizes:

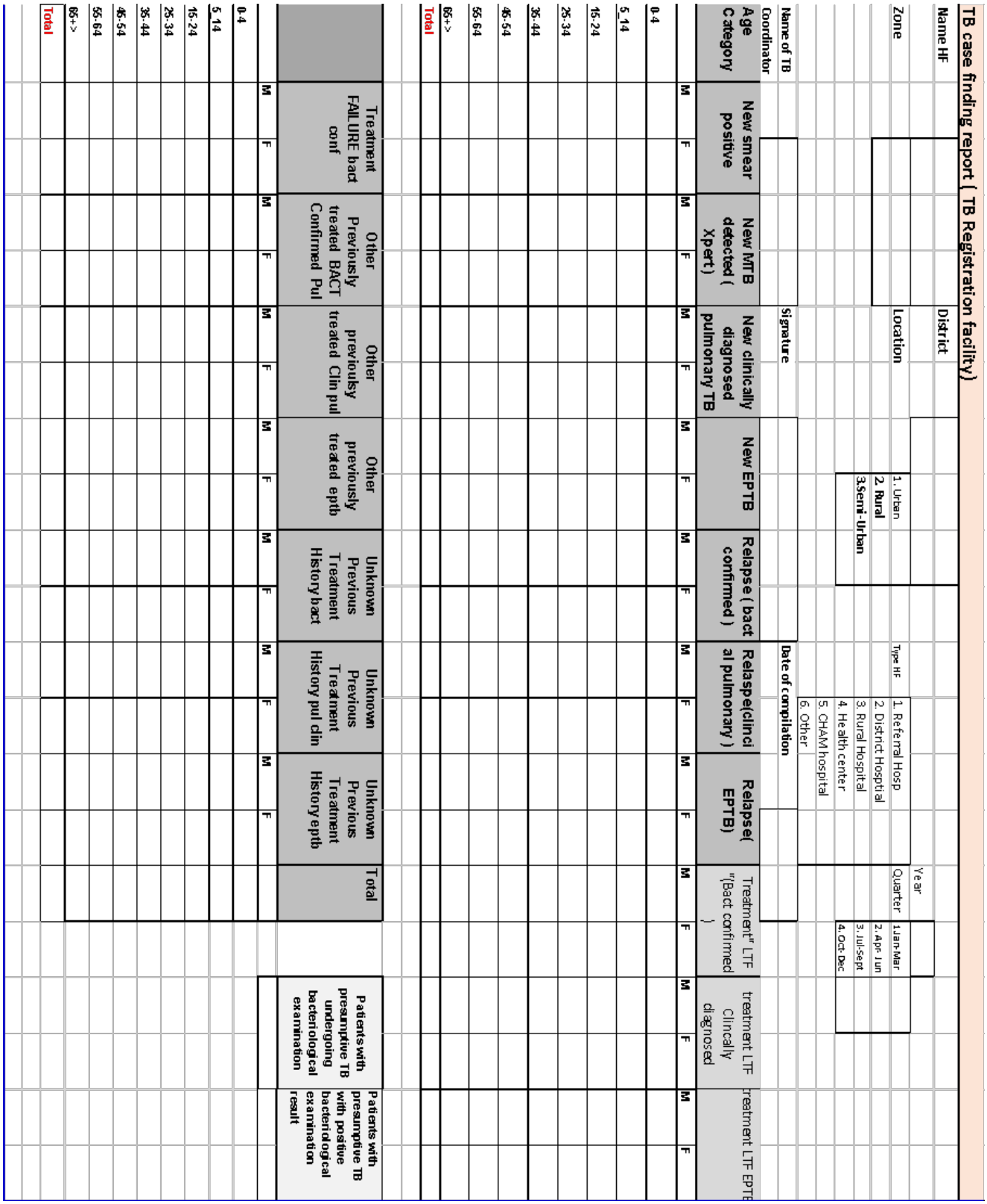
i. A large globus contains an app. 100 bacilli
ii. A medium globus contains an app. 60 bacilli
iii. A small globus contains an app. 30 bacilli



Solid (S), Fragment (F), and Granular (G). 1 and 2 are likely to be artifacts and should not be counted, clusters in Cigar shape (CS) and Globi small (GI-S), Globi medium (GI-M), and large Globi (GI-L) Gradular form (G)

20. Annex (Tuberculosis)

20.1. Reporting forms



TB case finding report (TB Registration facility)

Name HF | District | Year

Zone | Location | 1. Urban / 2. Rural / 3.Semi-Urban | Type HF | 1. Referral Hosp / 2. District Hospital / 3. Rural Hospital / 4. Health center / 5. CHAM hospital / 6. Other | Quarter | 1.Jan-Mar / 2. Apr- Jun / 3. Jul-Sept / 4. Oct-Dec

Name of TB Coordinator | Signature | Date of compilation

Age Category	New smear positive		New MTB detected (Xpert)		New clinically diagnosed pulmonary TB		New EPTB		Relapse (bacteriological confirmed)		Relapse(clinical pulmonary)		Relapse(EPTB)		Treatment" LTF "(Bact confirmed)		treatment LTF Clincally diagnosed		treatment LTF EPTB	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
0-4																				
5_14																				
15-24																				
25-34																				
35-44																				
45-54																				
55-64																				
65+>																				
Total																				

	Treatment FAILURE bact conf		Other Previously treated BACT Confirmed Pul		Other previoulsy treated Clin pul		Other previously treated epth		Unknown Previous Treatment History bact		Unknown Previous Treatment History pul clin		Unknown Previous Treatment History epth		Total		Patients with presumptive TB undergoing bacteriological examination		Patients with presumptive TB with positive bacteriological examination result	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F						
0-4																				
5_14																				
15-24																				
25-34																				
35-44																				
45-54																				
55-64																				
65+>																				
Total																				

20.1.1. Group A Drugs

Levofloxacin 100mg scored, dispersible tablets Recommended dosing: 15-20mg/kg/day Weight-based dosing			
Weight Band (kg)	**Dose**	**Number of 100mg tablets**	**Number of 250 mg tablets**
1kg	20mg	Mix 100mg tablet in 10ml of water and administer 2ml of mixture immediately	
2kg	40mg	Mix 100mg tablet in 10ml of water and administer 4ml of mixture immediately	
3kg	50mg	0.5	
4-6kg	100mg	1	0.5
7-9kg	150mg	1.5	0.5
10-12kg	200-250mg	2.0 to 2.5	1
13-15kg	300mg	3	1-1.5
16-18kg	300-350mg	3-3.5	1.5
19-20kg	400mg	4	1.5
21-23kg	400-450mg	4-4.5	2
24-25kg	500mg		2
26-35kg	750mg		3

Table 20.1-1 Levofloxacin

Moxifloxacin Recommended dosing: 10-15mg/kg/day Weight-based dosing			
Weight Band (kg)	**Dose**	**Number of 100mg tablets (dissolve in 10mL of water)**	**Number of 400mg tablets (dissolve in 10ml water)**
1kg	10mg	1kg= 1mL	
2kg	20mg	2kg= 2mL	
3kg	30mg	3kg= 3mL	
4-6kg	50-80mg	4-6kg=6mL	2ml
7-9kg	150mg	7-9 kg=1.5 tablet	3ml
10-15 kg	200mg	10-15kg=2 tablet	4ml
16-19 kg	300mg	16-19 kg= 3 tablet	0.5-.75 of a 400mg tablet
20-25kg	400mg	20-25kg= 4 tablet	1
26-35kg	400mg	26-35kg= 4 tablet	1

Table 20.1-2 Moxifloxacin

Linezolid Recommended dosing: 15mg/kg once daily in children < 16 kg and 10-12 mg/kg/day in children > 16 kg Weight-based dosing				
Weight Band (kg)	**Dose**	**50mg tablets (not yet available)**	**600mg tablet**	20mg/ml suspension
1kg	15mg once daily	Mix 150mg tablet in 15ml of water and administer 1.5ml of mixture immediately		1 ml once daily
2kg	30mg once daily	Mix 150mg tablet in 15ml of water and administer 3 ml of mixture immediately		1.5mL once daily
3kg	45mg once daily	Mix 150mg tablet in 15ml of water and administer 4.5ml of mixture immediately		2.5 mL once daily
4kg	60mg once daily	Mix 150mg tablet in 15ml of water and administer 6ml of mixture immediately		3 mL once daily
5kg	75mg once daily	0.5 of 150mg tablet		4ml
6kg	90mg once daily	Mix 150mg tablet in 15ml of water and administer 9 ml of mixture immediately	0.25	4ml
7-9kg	75-150mg once daily	0.5-1.0 tablet	0.25	6ml
10-15kg	150-225mg once daily	1-1.5 tablet	0.25	8ml
16-20kg	225-250mg once daily	1.5-2 tablet	0.5	11ml
21-25kg	300mg once daily if < 12 years of age	2	0.5	14ml
36-35kg	300mg once daily if < 12 years of age		0.5	

Table 20.1-3 Linezolid

Bedaquiline Weight-based dosing for children age 6 months or older			
Weight Band (kg)	**Dose**	**20mg tablet**	**100mg tablet**
3-4.99kg	60mg daily for 14 days followed by 20mg three times a week (i.e. M/W/F)	3 tablets daily for the first 14 days then one tablet three times a week (i.e. M/W/F)	
5-6.99kg	60mg daily for 14 days followed by 20mg three times a week (i.e. M/W/F)	3 tablets daily for the first 14 days then one tablet three times a week (i.e. M/W/F)	
7-9.99kg	80mg daily for 14 days followed by 40mg three times a week (i.e. M/W/F)	4 tablets daily for the first 14 days then 2 tablets three times a week (i.e. M/W/F)	
10-15.99kg	120mg daily for 14 days followed by 60mg three times a week (i.e. M/W/F)	Use the 100mg tablet plus a 20mg tablet daily for the first 14 days then transition to 3 of the 20mg tablets three times a week (i.e. M/W/F)	1 tablet daily for the first 14 days given with one 20mg tablets then transition to the 20mg dispersible tablets which will be give as 3 tablets three times a week (i.e. M/W/F)
16-23.99kg	200mg daily for 14 days followed by 100mg three times a week (i.e. M/W/F)		2 tablets daily for the first 14 days then 1 tablet three times a week (i.e. M/W/F)
24-29.99kg	200mg daily for 14 days followed by 100mg three times a week (i.e. M/W/F)		2 tablets daily for the first 14 days then 1 tablet three times a week (i.e. M/W/F)
>30kg	400mg daily for 14 days followed by 200mg three times a week (i.e. M/W/F)		4 tablets daily for the first 14 days then 2 tablets three times a week (i.e. M/W/F)

Table 20.1-4 Bedaquiline

20.1.2. Group B Drugs

Clofazimine Recommended dosing: 2-5mg/kg/day Weight-based dosing				
Weight Band (kg)	**Dose**	**50mg tablets**	**50mg gelcaps**	**100mg gelcaps**
<5kg	15mg	Mix 50mg tablet in 10 ml of water to make a 5mg/mL suspension. Administer 3ml of this 5mg/mL extemporaneous preparation immediately.	Give 1 gelcap M/F	Consult a specialist
5-6kg	10-30mg	1/2 tablet	Give 1 gelcap on alternative days	1 gelcap M/W/F
7-9kg	15-30mg	1/2 tablet	Give 1 gelcap on alternative days	1 gelcap M/ W/F
10-15kg	20-75 mg	1 tablet	Give 1 gelcap daily	1 gelcap M/W/F
16-23kg	32-115mg	1 tablet	Give 1 gelcap per day	1 gel cap on alternative days
24-35kg	100 mg	2 tablet	Give 2 gelcap daily	1 gelcap daily

Table 20.1-5 Clofazimine

Cycloserine Recommended dosing: 15-20mg/kg/day Weight-based dosing			
Weight Band (kg)	**Dose**	**125mg minicapsule**	**250mg capsule**
1kg	20mg	Mix 125mg capsule in 12ml of water and administer 2ml of mixture immediately	
2kg	40mg	Mix 125mg capsule in 12ml of water and administer 4ml of mixture immediately	
3-4kg	62.5mg	Mix 125mg capsule in 12ml of water and administer 6ml of mixture immediately	
5-9kg	125 mg	1	
10-15 kg	250mg	2	1
16-23kg	375mg	3	2
24-35kg	500mg	4	2

Table 20.1-6 Cycloserine

20.1.3. Group C Drugs (in order of how they should be used)

Delamanid Weight-based dosing for children age 3 months and older			
Weight Band (kg)	**Dose**	**25mg tablet**	**50mg tablet**
3-4.99kg	25mg once daily	1 tablet daily	Half a tablet (0.5 tablet) daily
5-6.99kg	25mg twice daily	1 tablet twice daily	Half a tablet (0.5 tablet) twice daily
7-9.99kg	25mg twice daily	1 tablet twice daily	Half a tablet (0.5 tablet) twice daily
10-15.99kg	25mg twice daily	1 tablet twice daily	Half a tablet (0.5 tablet) twice daily
16-23.99kg	50mg morning, 25mg evening	2 tablets morning, one tablet evening	One tablet morning, half a tablet (0.5 tablet) evening
24-29.99kg	50mg morning, 25mg evening	2 tablets morning, one tablet evening	One tablet morning, half a tablet (0.5 tablet) evening
30-49.99kg	50mg twice daily	2 tablets twice daily	One tablet twice daily
> 50 kg	100mg twice daily	4 tablets twice daily	Two tablets twice daily
Note that the 50mg tablet of delamanid when it is crushed, manipulated, or mixed does not result in the same blood levels as the 25mg pediatric formulation. Until the 25mg pediatric formulation is available, the 50mg tablet should be used with caution. Split tablets should not be saved for later administration for time periods longer than 12 hours.			

Table 20.1-7 Delamanid

Ethambutol 100mg Recommended dosing: 15-25mg/kg/day Weight-based dosing			
Weight Band (kg)	**Dose**	**100mg tablets**	**400mg tablets**
1kg	20mg	Mix 100mg tablet in 10ml of water and administer 2ml of mixture immediately	
2kg	40mg	Mix 100mg tablet in 10ml of water and administer 4ml of mixture immediately	
3kg	70mg	Mix 100mg tablet in 10ml of water and administer 7ml of mixture immediately	
4-6kg	100mg	1	
7-9kg	200mg	2	
10-12kg	250mg	2.5	
13-15kg	300mg	3	
16-18kg	350 mg	3.5	
19-20kg	400mg	4	1
21-23kg	450mg	4.5	1
24-31kg	500mg	5	1.5
31-35kg	800mg		2

Table 20.1-8 Ethambutol

Pyrazinamide Recommended dosing: 30-35mg/kg/day Weight-based dosing			
Weight Band (kg)	**Dose**	**150mg dispersible tablets**	**500mg tablet**
1kg	30mg	Mix 150mg tablet in 10ml of water and administer 2ml of mixture immediately	
2kg	60mg	Mix 150mg tablet in 10ml of water and administer 4ml of mixture immediately	
3kg	90mg	Mix 150mg tablet in 10ml of water and administer 6ml of mixture immediately	
4-6kg	150mg	1	
7-9kg	225mg	2	
10-12kg	375mg	2.5	
13-15kg	450mg	3	
16-18kg	525mg	3.5	1
19-20kg	600mg	4	1.25
21-23kg	675mg	4.5	1.5
24-30kg	750mg	5	1.5-2
31-35kg	1250mg		2.5

Table 20.1-9 Pyrazinamide

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