INTEGRATED NATIONAL GUIDELINES FOR MANAGEMENT OF TUBERCULOSIS IN BHUTAN

National Tuberculosis Control Programme
Department of Public Health
Ministry of Health

March 2024 Update

FOREWORD

Bhutan has joined the global and regional community in taking forward the agenda of TB through the Sustainable Development Goals (2016-2030) and has adapted the End TB Strategy into the National Strategic Plan III (2024-2028) which is aligned to the 13th Five-Year Plan (2024-2028). As part of our commitment to ensuring the most up-to-date and effective guidelines for the management of TB, we have incorporated the recent changes in TB & DR TB management recommended by the WHO to achieve our National and End TB targets.

This 8th edition of our guideline builds upon the key elements outlined in the Integrated Guidelines, 7th edition, 2020 update. This guideline has incorporated the latest advancements and best practices in terms of diagnosis, treatment and management of DS-TB, DR-TB and TB Infection. With the introduction of newer evidence based shorter regimens, novel drugs for MDR-TB will be introduced in the country. The chapters on aDSM and treatment monitoring have been revised accordingly. Our primary focus will remain on ending TB through early diagnosis and initiating prompt and effective treatment with vigorous follow up and monitoring. The guideline also describes the roles and responsibilities of various actors at different levels including community and TB patients and emphasizes the support needed from all parties to achieve our goals and meet the targets.

This guideline will serve as a comprehensive resource for our healthcare professionals in patient management, care and prevention. The adoption of this guideline will also facilitate the implementation of other TB control interventions in the country. I trust that each and every one of you will utilize this guideline optimally, ensuring standardized and effective management of TB cases in Bhutan. The Ministry of Health anticipates and values your commitment in providing timely and comprehensive services to the TB patients and the population at large.

(Karma Jamtsho)
DIRECTOR
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The updates in this National Guidelines for Management of Tuberculosis, 2024 are the result of collaborative efforts of professionals from a range of specialties who have expertise in the clinical and technical management of TB. The recommendations herein have been discussed and adopted through several meetings of the TB Technical Advisory Group (TAG).

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ABBREVIATIONS

ADA	Adenosine Deaminase
AFB	Acid Fast Bacilli
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Aminotransferase
ART	Antiretroviral Therapy
AST	Aspartate Aminotransferase
ATT	Anti-tubercular Treatment
BCG	Bacillus Calmette-Guerin
CBC	Complete Blood Count
CD4	Cluster of Differentiation 4
CP	Continuation Phase
CPT	Cotrimoxazole Preventive Therapy
CSF	Cerebrospinal Fluid
CT	Computerized Tomography
DPHO	District Public Health Officer
DMP	Department of Medical Products
DoPH	Department of Public Health
DOT	Directly Observed Treatment
DOTS	Directly Observed Treatment Short Course Strategy
DRS	Drug Resistance Surveillance
DST	Drug Susceptibility Testing
ECG	Electrocardiogram
EPTB	Extrapulmonary Tuberculosis
EQA	External Quality Assessment
FDC	Fixed Dose Combination
FEFO	First Expiry First Out
FL-DST	First Line Drug Susceptibility Testing
FLD	First Line Drug
FNAC	Fine Needle Aspiration Cytology
GDF	Global Drug Facility
GF	Global Fund
HIV	Human Immunodeficiency Virus
HMIS	Health Management and Information System
IEQAS	International External Quality Assessment Scheme
IP	Intensive Phase
IRIS	Immune Reconstitution Inflammatory Syndrome
JDWNRH	Jigme Dorji Wangchuck National Referral Hospital
LDH	Lactate Dehydrogenase
LED	Light Emitting Diode
LFT	Liver Function Test
MGIT	Mycobacteria Growth Indicator Tube
MRI	Magnetic Resonance Imaging
MTB	Mycobacterium Tuberculosis

MTBC	Mycobacterium Tuberculosis Complex
NAAT	Nucleic Acid Amplification Test
NEQAS	National External Quality Assurance Scheme
PHC	Primary Health Centre
PMDT	Programmatic Management of Drug Resistant Tuberculosis
PPD	Purified Protein Derivative
PPE	Personal Protective Equipment
PTB	Pulmonary Tuberculosis
RR	Rifampicin Resistant
SCC	Short Course Chemotherapy
SNRL	Supra National Reference Laboratory
STAC	SAARC Tuberculosis and HIV AIDS Centre
TAG	Technical Advisory Group
TBI	TB Infection
TBM	Tuberculous meningitis
TbISS	Tuberculosis Information and Surveillance System
TPT	Tuberculosis Preventive Treatment
TBST	Mycobacterium tuberculosis Antigen-based Skin Test
VHW	Village Health Worker
WRD	WHO Recommended Rapid Diagnostics
XDR-TB	Extensively Drug Resistant Tuberculosis
ZN	Ziehl Neelsen

Acronyms for ATT Drugs

Am	Amikacin
Bdq	Bedaquiline
Cfz	Clofazimine
Cm	Capreomycin
Cs	Cycloserine
Dlm	Delamanid
E	Ethambutol
Eto	Ethionamide
FQ	Fluoroquinolone
Gfx	Gatifloxacin
H	Isoniazid
Imp/Cln	Imipenem/Cilastatin
Km	Kanamycin
Lfx	Levofloxacin
L or Lzd	Linezolid
M or Mfx	Moxifloxacin
Mpm	Meropenem
PAS	Para- aminosalicylic Acid
Pa	Pretomanid
Pto	Prothionamide
R	Rifampicin

RFB	Rifabutin
P or RPT	Rifapentine
S	Streptomycin
Trd	Terizidone
Z	Pyrazinamide

CONTENTS

CHAPTER 1
INTRODUCTION

1.1 Background

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis* and it is one of the top 10 infectious causes of death worldwide. The disease is spread via air when people who are sick with pulmonary TB expel bacteria while coughing and sneezing or any other act that result in the expulsion of respiratory secretions. TB usually affects the lungs (known as Pulmonary TB) but can affect other sites as well (known as Extra-pulmonary TB). When the tubercle bacilli enter the body and infect an individual but remain dormant without causing disease it is called TB Infection (TBI). Approximately 10% of people infected with TB bacillus will develop the active disease during their lifetime. A person is said to have TB disease when he/she starts manifesting symptoms and signs. However, the disease may also remain asymptomatic, necessitating active screening for those who are vulnerable. The probability of developing TB is much higher among people who are undernourished, infected with HIV or have other co-morbid conditions that compromise one's immunity.

1.2 TB Situation

As per the Global TB Report 2023, 10.6 million people fell ill with TB globally, and 1.3 million died due to TB. COVID-19 related disruptions are estimated to have resulted in almost half a million excess deaths from TB in the three years 2020–2022, compared with the number that would have occurred if pre-pandemic trends had been maintained.

Bhutan has successfully achieved the targets of Millennium Development Goals (MDGs) of halving the TB incidence and mortality compared to that of 1990. However, TB remains a major public health concern in the country. Bhutan relies on annual estimates of TB disease burden produced by the WHO. According to the WHO Global TB Report 2023, the estimated incidence of all forms of TB in Bhutan was 164 per 100,000 population and the total number of incident TB patients notified in 2023 was 864 cases against the estimated 1300 cases. Similarly, for multidrug resistant TB (MDR-TB), Bhutan reported 63 cases in 2023 against the estimated 170 cases.

Table 1.1 Estimates of TB Burden (WHO estimates) as per Global TB Report 2023

Estimates of TB Burden	**Number (thousands)**	**Rate per 100,000 population**
Incidence of all forms of TB	1.3 (980-1.6K)	164 (125-207)
Incidence of RR/MDR-TB	170 (120-220)	22 (16-29)
TB mortality	230 (150-320)	30 (20-42)
Estimated proportion of TB Patients with RR TB/MDR-TB		
New cases	13% (11-15)	
Previously treated cases	17% (11-23)	

In 2023, Bhutan notified 864 of all forms of TB of which 61 were RR/MDR-TB. Among these patients, more than 80% were notified from eight Dzongkhags of Thimphu, Chukha, Mongar, Samtse, Sarpang, Samdrup Jongkhar, Paro, and Wangduephodrang. The age breakdown of these patients shows that about 58.5% of them are within the age group of 15 - 34 years.

There is a three-tier laboratory network in the country to support the diagnosis of TB and drug resistant TB. The Primary Health Care are responsible for referring symptomatic patients to the Microscopy and Reporting Centers for TB diagnosis and treatment. The initiation of TB treatment is done at 32 TB Reporting Centers (hospitals). The National TB Reference Laboratory (NTRL) at Royal Center for Disease Control is equipped to perform Drug Susceptibility Testing (DST) for first line and second line drugs to ensure that the patients receive the right treatment. Currently, there are 46 microscopy centres and 14 GeneXpert Sites (with 17 machines) capable of detecting TB, MDR-TB and even extensively drug resistant TB (XDR-TB). The MDR-TB cases are currently managed at Gidakom Hospital and at two regional referral hospitals (ERRH, Mongar and CRRH, Gelephu).

A Drug Resistance Surveillance (DRS) was initiated in 2010 by RCDC and the results for last four years (Table 1.2) report that a high proportion of RR-/MDR-TB were among new cases. This indicates that MDR-TB is being transmitted as a primary infection in the general population.

Table 1.2 Findings of Drug Resistance Surveillance among TB patients

Year of Survey report	Proportion of RR/MDR in new patients (%)	Proportion of RR/MDR in Retreatment patients (%)
2019	14.7	9.4
2020	11.60	22.86
2021	11.11	8.82
2022	10.7	10.2

National TB Control Programme has been consistently introducing newer diagnostics and efforts are made to improve the diagnostic algorithm based on the current WHO recommendations, while optimally utilizing the various diagnostic platforms available for early diagnosis of TB and DR TB.

1.3 Targets of NTCP (as per National Strategic Plan III, 2024-2028)

The goal and objectives of the NSP III are:
Goal: To reduce the incidence of TB cases by 5% every year from 2027 (year 4) onwards

Objective 1: to reduce the TB death rate by 50% between 2024 and 2028
Objective 2: to increase the proportion of children notified out of the total number above 5% from 2026 onwards (Year 3)
Objective 3: to reduce RR/MDR-TB incidence by 5% every year from 2027 (Year 4) onwards

Objective 4: to impact the TB epidemic in Bhutan by increasing the number of individuals with TB infection undergoing TPT by 50% every year between 2024 and 2028
Objective 5: to assess into details the existing gap between the estimated incidence and notified cases by 2026 (Year 3) and take necessary actions

CHAPTER 2

TYPES OF TB, CASE DEFINITIONS AND TREATMENT OUTCOMES

It is important to classify TB patients appropriately based on bacteriology, site involvement and history of previous treatment (retreatment category), drug resistance and HIV status.

2.1 Presumptive TB

All the patients identified at a health centre with symptoms or signs suggestive of TB should be screened thoroughly and referred for Chest X-Ray, sputum or other biological sample examination.

Presumptive TB is defined as patient

Cough ≥ 2 weeks duration on its own

OR

Cough of any duration with any of the following symptoms:

- Fever
- Night sweats
- Loss of weight
- Haemoptysis
- Chest pain

OR

Abnormalities in CXR suggestive of TB

2.2 Case of tuberculosis

A case of TB could be either a bacteriologically confirmed or a clinically diagnosed:

2.2.1. A bacteriologically confirmed TB case: is one in which biological specimen (such as sputum, CSF, lymph node aspirate etc.) is positive by molecular WHO Recommended Rapid Diagnostics (mWRD) - such as Xpert MTB/RIF smear microscopy, or culture. All such cases should be notified, regardless of initiation of TB treatment.

a) **Molecular WHO Recommended Rapid Diagnostic (mWRD) Positive*:*** a patient with or without sputum smear positive for AFB but sputum or any biological specimen testing positive on Xpert MTB/RIF for *M. tuberculosis*.

b) Smear-positive pulmonary TB:

- a patient with at least two sputum smears positive for acid fast bacilli (AFB) by direct smear microscopy or
- a patient with at least one sputum smear positive for AFB by microscopy and Chest X-ray findings suggestive of TB.

b) **Culture positive:** a patient with or without sputum smear positive for AFB but sputum or any biological specimen testing positive by culture for *M. tuberculosis.*

2.2.2. A clinically diagnosed TB case is one that does not fulfill the criteria for bacteriological confirmation but that has been diagnosed with active TB by a clinician who has decided to give the patient a full course of TB treatment. This definition includes cases diagnosed on the basis of clinical suspicion supported by X-ray abnormalities or suggestive histology and EPTB cases without laboratory confirmation. **Clinically diagnosed cases that are subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.**

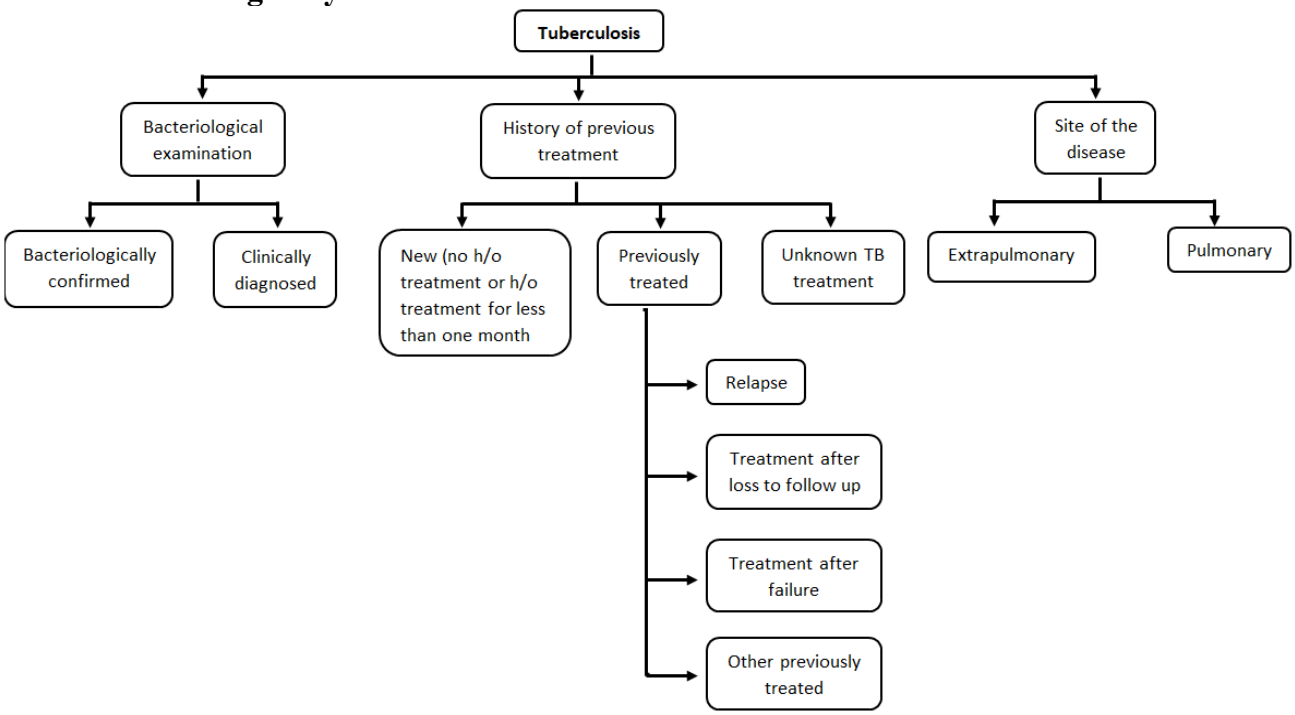


Figure 2.1 Classification of Tuberculosis

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

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

2.3 Classification based on anatomical site of the disease

2.3.1 Pulmonary tuberculosis (PTB)

Any bacteriologically confirmed or clinically diagnosed case of TB that involves the lung parenchyma or the tracheo-bronchial tree with or without the involvement of any other organs in the body.

Miliary TB is classified as PTB because there are lesions in the lungs (Box 1).

Extra-pulmonary tuberculosis (EPTB)

BOX 1: Miliary (disseminated) TB

Miliary TB results from wide spread blood dissemination of TB bacilli. In children it is often the consequences of a recent infection but in adults it may be due to either recent infection or reactivation of old disseminated foci. The clinical features are as follows (Figure 2.2);

- Present with constitutional features rather than respiratory symptoms
- They may have hepatosplenomegaly and choroidal tubercles on fundoscopy
- Often the presentation is associated with a fever of unknown origin and wasting may be marked
- A rare presentation seen in the elderly is cryptic miliary tuberculosis. It has a chronic course and remains undiagnosed unless there is a high degree of suspicion
- An acute septicaemic, non-reactive form of miliary tuberculosis occurs very rarely and is due to a massive haematogenous spread of tubercle bacilli
- Chest X-ray shows diffuse, uniformly distributed, small miliary (millet like seeds) shadows
- Blood investigations may show anaemia, leukopenia, neutrophilic leucocytosis, and leukemoid blood reactions
- Liver function tests may also be abnormal
- Bacteriological confirmation (smear or culture) is sometimes possible from sputum, cerebrospinal fluid, bone marrow, the liver, or blood
- Granulomas are evident in liver or bone marrow biopsy specimens from many patients. Broncho-alveolar lavage is more likely to permit bacteriological confirmation.

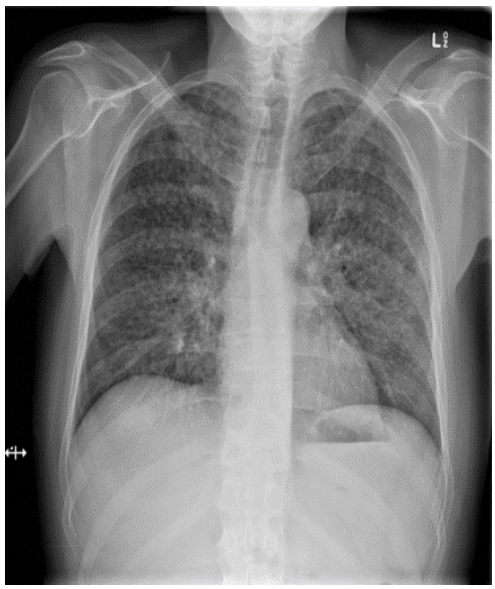


Figure 2.2 Chest X-ray showing miliary shadows.

EPTB is a case of 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, tuberculous intra-thoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion without radiographic abnormalities in the lung parenchyma, constitutes a case of EPTB. However, in EPTB, lung involvement should be ruled out. **As already stated, in case of lung involvement, even in the absence of symptoms, the case is classified as a pulmonary TB case (Figure 2.1).**

Currently, proportion of Extra- pulmonary TB (EPTB) cases are high, which accounts to 38% of the total TB cases notified in 2022 which suggest probable over diagnosis of EPTB cases due to misclassification especially lymph node TB.

It is mandatory for all EPTB cases to undergo Chest X-ray and Sputum bacteriological test to rule out pulmonary involvement and to avoid misclassification of cases.

TB lymphadenitis must have, asymmetry, matting and >1 node. Definitive diagnosis of tuberculous lymphadenitis is done preferably by bacteriological confirmation, and if not, by excisional biopsy and histopathologic examination if all other techniques fail.

a) Tuberculous pleural effusion

Pleural effusion is one of the common forms of EPTB. Clinical examination and Chest X-ray (CXR) will aid in diagnosis of pleural effusion in addition to GeneXpert as upfront tool for diagnosis. In addition, ultrasound can confirm the presence of fluid in the pleural space. Always perform diagnostic pleural aspiration if a patient has a pleural effusion. The pleural effusion is an exudate that has predominant lymphocytes.

b) Tuberculous pericardial effusion

Pericardial effusion refers to the accumulation of fluids in the pericardial sac. The patient often presents with chest pain and shortness of breath which improves while sitting upright and worsens while lying flat. In severe cases, it may lead to pericardial tamponade. Pericardiocentesis should be performed and the fluid is exudative in nature and tested for TB on GeneXpert as upfront tool for diagnosis.

c) Tuberculous ascites

Ascites results from peritoneal TB. Routes of spread of TB to the peritoneum include the following: i) from tuberculous mesenteric lymph nodes; ii) from intestinal TB (pulmonary TB patients may develop intestinal ulcers and fistulae as a result of swallowing infected sputum); and iii) blood-borne.

- Patients present with constitutional features and ascites
- There may be palpable abdominal masses (mesenteric lymph nodes)
- Aspirated fluid is exudative with high protein content and leucocytosis, predominantly lymphocytes
- Ultrasound of abdomen may show features consistent with TB, including enlarged mesenteric or retroperitoneal lymph nodes
- Definitive diagnosis rests on a peritoneal biopsy
- Laparoscopy enables direct visualization and biopsy of peritoneal TB lesions and
- Laparotomy will confirm the diagnosis in nearly every case but is too invasive for routine use

d) Gastro-intestinal TB

Any portion of the gastrointestinal tract may be affected by tuberculosis but terminal ileum and caecum are the sites most commonly involved.

- Abdominal pain (at times similar to that of appendicitis), chronic diarrhoea, subacute obstruction, haematochezia, and a right iliac fossa mass are common presentations
- Fever, weight loss, and night sweats are also frequent and
- A 'doughy abdomen' due to extensive intra-abdominal inflammation may also be detected. Diagnosis rests on a barium examination of the small and large intestine or on a colonoscopy or CT abdomen

e) Tuberculous meningitis (TBM)

A prodromal phase of low-grade fever, malaise, headache, dizziness, vomiting, and/or personality changes may persist for few weeks, after which patients can then develop more severe headache, altered mental status, stroke, hydrocephalus, and cranial neuropathies.

- Seizures due to TBM occur in about 50% of paediatric cases but are uncommon manifestations in adults
- Classic features of bacterial meningitis, such as stiff neck and fever, may be absent
- The diagnosis of TBM can be difficult and treatment initiation should be based on clinical and preliminary cerebrospinal fluid (CSF) findings without waiting for a definitive microbiologic confirmation.
- GeneXpert needs to be offered as upfront tool for diagnosis as direct microscopy for AFB on CSF has poor sensitivity. Mycobacterial culture can also be done and needs at least 1 ml of the specimen. About 0.5 ml of CSF should be sent for the Xpert MTB/RIF test
- Diagnosis of TBM can be supported by neuroimaging. Classic neuroradiologic features of TBM are basal meningeal enhancement and hydrocephalus. MRI is the imaging modality of choice.

f) Genito-urinary TB

Tuberculosis can involve any part of the genito-urinary tract and it is usually due to haematogenous seeding following primary infection. Local symptoms predominate. Urinary frequency, dysuria, haematuria, and loin pain are common presentations. However, patient may be asymptomatic with the disease only being discovered after severe destructive lesions of the kidneys have developed.

- GeneXpert needs to be offered as upfront tool for diagnosis on urine samples. Urinalysis gives abnormal result in 90% of cases, revealing pyuria and haematuria. Sterile pyuria first raises the suspicion of renal tuberculosis. An intravenous pyelography helps in the diagnosis. Calcification and ureteric stricture are also suggestive findings. AFB from a centrifuged urine specimen helps in the diagnosis. Culture of three morning urine specimens yields a definitive diagnosis in nearly

90% cases. In almost half of the cases of genitourinary tuberculosis, urinary tract disease is also present.

- Genital TB is more common in females and affects the fallopian tubes and endometrium causing infertility, pelvic pain, and menstrual irregularities. Diagnosis requires a biopsy and/or a culture of specimens obtained by dilatation and curettage.
- In male patients, genitourinary TB commonly affects the epididymis testes and prostate

g) Hepatic/Splenic TB

Disseminated TB may involve the liver or spleen and can cause diagnostic confusion. Solitary or multiple abscesses may develop. Ultrasound or CT scan and guided FNAC can give diagnosis in most of the cases.

h) Bone and joints TB

Tuberculous osteomyelitis and arthritis generally arise from reactivation of bacilli lodged in bone during the original mycobacteremia of primary infection.

- The sites most commonly involved are the lower thoracic vertebrae (with T-10 being the most common) and the upper lumbar spine and cervical spine is the least involved (Box 2).
- TB starts in an intervertebral disc and spreads along the anterior and longitudinal ligaments, before involving the adjacent vertebral bodies.
- With an advanced disease, a collapse of vertebral bodies results in kyphosis (Gibbus deformity, Figure 2.3). A para-vertebral cold abscess may also be formed. This may track to sites such as the lower thoracic cage or below the inguinal ligament (Psoas abscess, Figure 2.5).
- A plain X-ray of the spine is usually indicative of diagnosis. The typical appearance is erosion of the anterior edges of the superior and inferior borders of adjacent vertebral bodies. The disc space is narrowed. A CT scan or MRI can reveal the lesions more correctly.
- Aspiration of the abscess or bone biopsy confirms the tuberculosis etiology by histopathology and culture. GeneXpert needs to be offered as upfront tool for diagnosis on tissue samples for early diagnosis.

A patient with both Pulmonary and EPTB should be classified as a case of PTB.

BOX 2: TB spine (Pott's disease)

TB of spine involving two or more adjacent vertebral bodies leading to classic destruction of disc space and the adjacent vertebral bodies, destruction of other spinal elements, which is severe and subsequently leads to kyphosis is called **Pott's disease**. Paraplegia resulting from tuberculosis of the spine is called as Pott's paraplegia'.

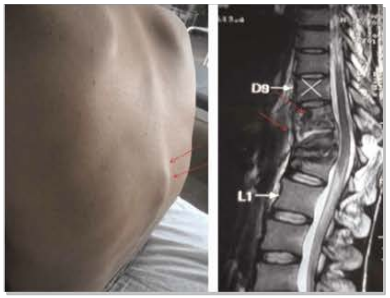


Figure 2.3 Gibbus deformity *(Picture courtesy: Dr Rinzin, Orthopedic Surgeon, CRRH, Gelephu).*

Complications

- *Neurological complications*
- *Spinal deformity*

Laboratory findings

Haematological and clinical data contribute little to the diagnosis, and leukocyte count is usually normal.

ESR and C-reactive protein concentration are often raised, but levels are lower than those seen in pyogenic vertebral infections.

TST is usually positive, although it is non-diagnostic in endemic regions and may be negative in immuno-deficient patients.

Diagnosis

Spinal TB can be suspected both clinically and radiologically.

Frequency of involvement of different spinal regions in spinal tuberculosis

Tuberculous vertebral osteomyelitis affects the thoracic or thoracolumbar segment in around half of the cases, followed by the lumbar segment, and to a much lesser extent, the cervical segment.

Plain X-ray

- Plain radiographs of the involved area are the most common initial study in patients with spinal infection.
- Plate irregularity or loss of the normal contour of the end plate, defects in the subchondral portion of the end plate, and hypertrophic (sclerotic) bone formation
- Occasionally, paravertebral soft tissue masses may be noted with involvement of nearby areas of the spine. Late radiographic findings may include vertebral collapse, segmental kyphosis, and bony ankyloses.

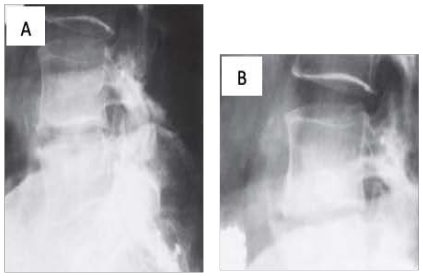


Figure 2.4 (A) Reduction of disc height associated with destruction of end plate and development of subchondral lytic defects. (B) After successful medical treatment.

MRI

A pattern of bone destruction showing a low signal on T1-weighted MRI and a bright signal on T2-weighted images in affected vertebral bodies with relative preservation of the disc and heterogeneous enhancement may differentiate spondylitic TB from pyogenic discitis, which usually shows peridiscal bone destruction and homogeneous enhancement

High-quality MRI is an accurate and rapid method for identifying spinal infection.

It identifies infected and normal tissues and probably best determines the full extent of the infection.

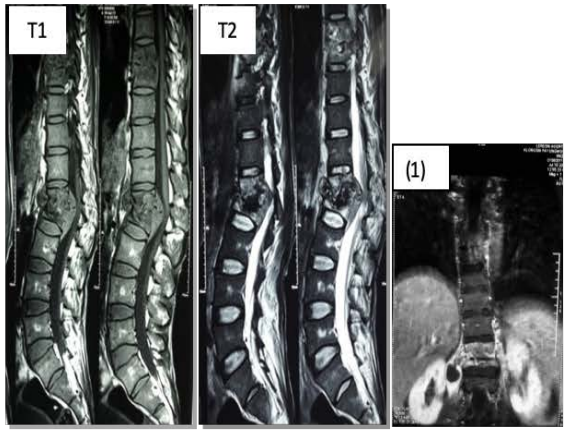


Figure 2.5 MRI (T1 & T2) showing paraspinal abscess and psoas abscess (1).

CT scan

CT adds another dimension to the plain radiographs. CT identifies paravertebral soft tissue swelling and abscesses much more readily and can monitor changes in the size of the spinal canal

Definitive Diagnosis

The definitive diagnosis of spinal TB is usually established by CT-guided needle aspiration cytology-biopsy and culture on Lowenstein Jensen medium (sensitivity of 50–75%), or by histological examination, which is highly suggestive of spinal TB when caseating granulomas are observed and diagnostic when acid-fast bacilli are found (sensitivity around 70%. Culture and histological study of a bone specimen obtained by surgery has a slightly higher diagnostic yield.

In any suspected cases of EPTB, all samples should be sent for GeneExpert testing.

Tuberculous spondylitis should be differentiated from primary or metastatic neoplastic disease

Medical treatment

In Bhutan, combination of rifampicin, isoniazid, ethambutol, and pyrazinamide for two months followed by combination of rifampicin and isoniazid ATT duration for TB of bones and joints will be for 12 months and if there is no improvement, treatment may be extended up to 18 months.

Response to medical treatment

After 4-6 weeks of chemotherapy, tuberculosis symptoms and vertebral pain improves in almost all patients, and the ESR and C-reactive protein (CRP) also decreases. ESR and CRP are reliable parameters evaluating the response to treatment and prognosis of spinal tuberculosis.

Medical treatment alone even improves the neurological deficit. Thus, generally speaking, surgery is not the most appropriate first choice of treatment in many instances.

Outcome

With adequate anti-TB chemotherapy and surgery when required, relapses are uncommon (0–5%). Surgery, which is mainly indicated for neurological complications or spinal deformity-instability, is needed in more than 50% of cases. In patients with a delayed diagnosis, surgical requirements may be as high as 98%.

Surgical treatment

The indications for surgery in Pott's disease are cases with

- neurologic deficit paravertebral abscess, spine instability due to kyphotic deformity (especially in kyphotic angles of 50 to 60 degrees or more which is likely to progress)
- resistance to the current anti-tuberculosis drugs (which is more encountered nowadays in association with the presence of human immunodeficiency virus [HIV] infection) and to prevent/treat complications such as late-onset paraplegia.

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

In order to identify and prescribe appropriate treatment to those patients at increased risk of acquiring drug resistance, a case should be defined according to whether or not the patient has previously received TB treatment. The registration group focuses only on history of previous treatment irrespective of bacteriological confirmation or site of the disease.
Accordingly, all patients can be categorized as 'New' patients or 'Previously treated' patients. ***They are defined as follows:***

2.4.1 New: A patient who **has never taken treatment** for TB or a patient who has taken anti-tuberculosis drugs for **less than one month**. New patients may have positive or negative bacteriology and may have disease at any anatomical site.

2.4.2 Previously treated: Those who have **received one month or more of anti-TB drugs** in the past are classified as "previously treated" patients. They may have positive or negative bacteriology and may have the disease at any anatomical site. They are further classified by the outcome of their most recent course of treatment as 'relapse', 'treatment after failure' and 'treatment after loss to follow up'.

a) **Relapse:** Patients, who have been previously treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and is now diagnosed with a **recurrent episode of TB**.

b) **Treatment after failure:** Patients who have previously been treated or are currently on treatment for TB and whose outcome was recorded as **treatment failed**. Treatment failure could be after first or second-line treatment. It is important to note the previous treatment so as to use appropriate diagnostic algorithm and start with right treatment.

c) **Treatment after loss to follow up:** Patients 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***.**

d) **Other previously treated:** Patients who have **previously been treated for TB but whose outcome after their most recent course of treatment** is unknown or undocumented.

e) **Unknown previous TB treatment history:** Patients who were diagnosed with TB and started on treatment outside the NTCP but there are no treatment records, or a proper history cannot be elicited.

2.5 Classification based on HIV status

2.5.1 HIV-positive TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB who also has a positive result from an HIV confirmatory test at the time of TB diagnosis.

2.5.2 HIV-negative TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a negative result from an HIV testing conducted at the time of

diagnosis. Any HIV negative TB patient subsequently found to be HIV positive should be classified accordingly.

2.5.3 HIV status unknown TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB who has no result of HIV testing. **If the patient's HIV status is subsequently determined, he or she should be reclassified accordingly.**

2.6 Classification based on drug resistance

Cases are classified based on drug susceptibility testing (DST) pattern of *M. tuberculosis* clinical isolates*:*

2.6.1 Mono-resistance: When a TB patient's infecting isolates of *M. tuberculosis* are resistant in vitro to **one of first line anti-tuberculosis drug except rifampicin**. Rifampicin mono-resistance is categorized separately.

2.6.2 Poly-resistance: When a TB patient's infecting isolates of *M. tuberculosis* are resistant in vitro to **more than one first-line anti-tuberculosis drug, other than to both isoniazid and rifampicin.**

2.6.3 Multi-drug resistant TB (MDR-TB): When a TB patient's infecting isolates are **resistant in vitro to both isoniazid and rifampicin with or without resistance to other first-line drugs.**

2.6.4 Extensively drug-resistant TB (XDR-TB): TB disease caused by a strain of M. tuberculosis complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (levofloxacin or moxifloxacin) and to at least one other "Group A" drug (bedaquiline or linezolid)**.**

2.6.5 Pre-extensively drug-resistant TB (pre-XDR-TB): TB disease caused by a strain of M. tuberculosis complex that is resistant to rifampicin (and may also be resistant to isoniazid), and that is also resistant to at least one fluoroquinolone (either levofloxacin or moxifloxacin)

2.6.6 Rifampicin resistance TB (RR-TB): TB disease caused by a strain of M. tuberculosis complex that is resistant to rifampicin**.** RR-TB strains may be susceptible to isoniazid or resistant to it (i.e. multidrug-resistant TB), or resistant to other first-line or second-line TB medicines.

2.6.7 Rifampicin-susceptible, isoniazid-resistant TB (Hr-TB): TB disease caused by a strain of M. tuberculosis complex that is resistant to isoniazid but susceptible to rifampicin

2.7 Treatment outcomes

2.7.1. TB treatment outcomes for DS-TB

a) **Treatment failed**: A patient whose treatment regimen needed to be terminated or permanently changed to a new regimen or treatment strategy

b) **Cured:** Pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment and becomes smear- or culture-negative in the last month of treatment and on at least one previous occasion.

c) **Treatment completed:** A patient who completed treatment as recommended by the national policy but whose outcome does not meet the definition for cure or treatment failure.

d) **Died:** A patient who died before starting treatment or during the course of treatment.

e) **Lost to follow-up:** A patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.

f) **Not evaluated:** A patient for whom no treatment outcome was assigned

2.7.2 TB treatment outcomes for DR-TB

a) **Cured**: Treatment completed without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase for conventional regimen and three or more culture negative done monthly for shorter regimen.

b) **Treatment completed**: Treatment completed as recommended by the national guideline without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.

c) **Treatment failed**: Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of:

- Lack of conversion[a] by the end of the intensive phase; or
- Bacteriological reversion[b] in the continuation phase after conversion to negative; or
- Evidence of additional acquired resistance to Fluoroquinolones or second-line injectable drugs; or
- Adverse drug reactions.

[a] For *treatment failed*, lack of conversion by the end of the intensive phase implies that the patient does not convert within 6 months (shorter regimen) treatment.

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

- **Conversion (to negative):** culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.
- **Reversion (to positive):** culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. **For the purpose of defining *Treatment failure*, reversion is considered only when it occurs in the continuation phase.**

d) **Died**: A patient who dies for any reason during the course of treatment.

e) **Lost to follow-up**: A patient whose treatment was interrupted for two consecutive months or more.

f) **Not Known**: A patient whose treatment outcome is not known. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown).

CHAPTER 3
CASE FINDING

Passive Case Finding had been the mainstay of TB case finding so far in Bhutan. In addition to all the cases reporting to health facilities with signs and symptoms of TB who were already being referred for appropriate laboratory tests, NTCP will focus on intensifying active case finding.

Systematic screening for TB disease is defined as the systematic identification of people at risk for TB disease, in a predetermined target group, by assessing symptoms and using tests, examinations or other procedures that can be applied rapidly. For those who screen positive, the diagnosis needs to be established by one or several diagnostic tests and additional clinical assessments. This term is sometimes used interchangeably with "active tuberculosis case-finding.

Systematic screening for TB disease may be conducted among subpopulations with structural risk factors for TB. These include urban poor communities, homeless communities, monasteries & nunneries, prisons, communities in remote or isolated areas, indigenous populations, migrants, refugees, internally displaced persons and other vulnerable or marginalized groups with limited access to health care.

3.1 Signs and symptoms of PTB

The highest priority for TB control is early detection and successful treatment of all patients with TB. The disease should be screened in all at-risk groups and those considered vulnerable to TB.

Cough ≥ 2 weeks duration on its own

OR

Cough of any duration with any of the following symptoms:

- Fever
- Night sweats
- Loss of weight
- Haemoptysis
- Chest pain

OR

Abnormalities in CXR suggestive of TB

Bacteriological confirmation through mWRD/GeneXpert should always be first offered to all who are presumed to have TB including all having cough for two weeks or longer, or CXR abnormality even if in the absence of any other symptom. In certain cases, the patient may present with constitutional symptoms other than cough.

3.2. Signs and symptoms of EPTB

It depends on the anatomical site involved. Most common examples are:

- TB lymphadenitis: swelling of lymph nodes
- TB arthritis: pain and swelling of joints
- TB of the spine: radiological findings with or without loss of function
- Meningitis: headache, fever, stiffness of neck and subsequent mental confusion, seizures in some patients
- Pleural effusion: fever, chest pain, shortness of breath

The diagnosis of EPTB should always be made by a physician or specialist and often requires special examinations such as X-ray, bacteriological testing of specimen, biopsies and FNAC. All efforts need to be undertaken to establish microbiological confirmation in case of presumptive EPTB. **Appropriate specimens from the presumed sites of involvement needs to be obtained for GeneXpert and Culture & DST or Histopathological examination**. **GeneXpert needs to be offered upfront for EP TB samples along with, Chest X-ray and VCT should be done in all cases during the initial diagnosis.** Wherever possible, the biological specimen should also be sent for bacteriological confirmation using culture examination as per the diagnostic algorithm. Ultrasonography, Computerised Tomography (CT) Scan, Magnetic Resonance Imaging (MRI) are other Screening tools which can also help in diagnosing difficult cases.

Algorithm for TB screening among high-risk groups

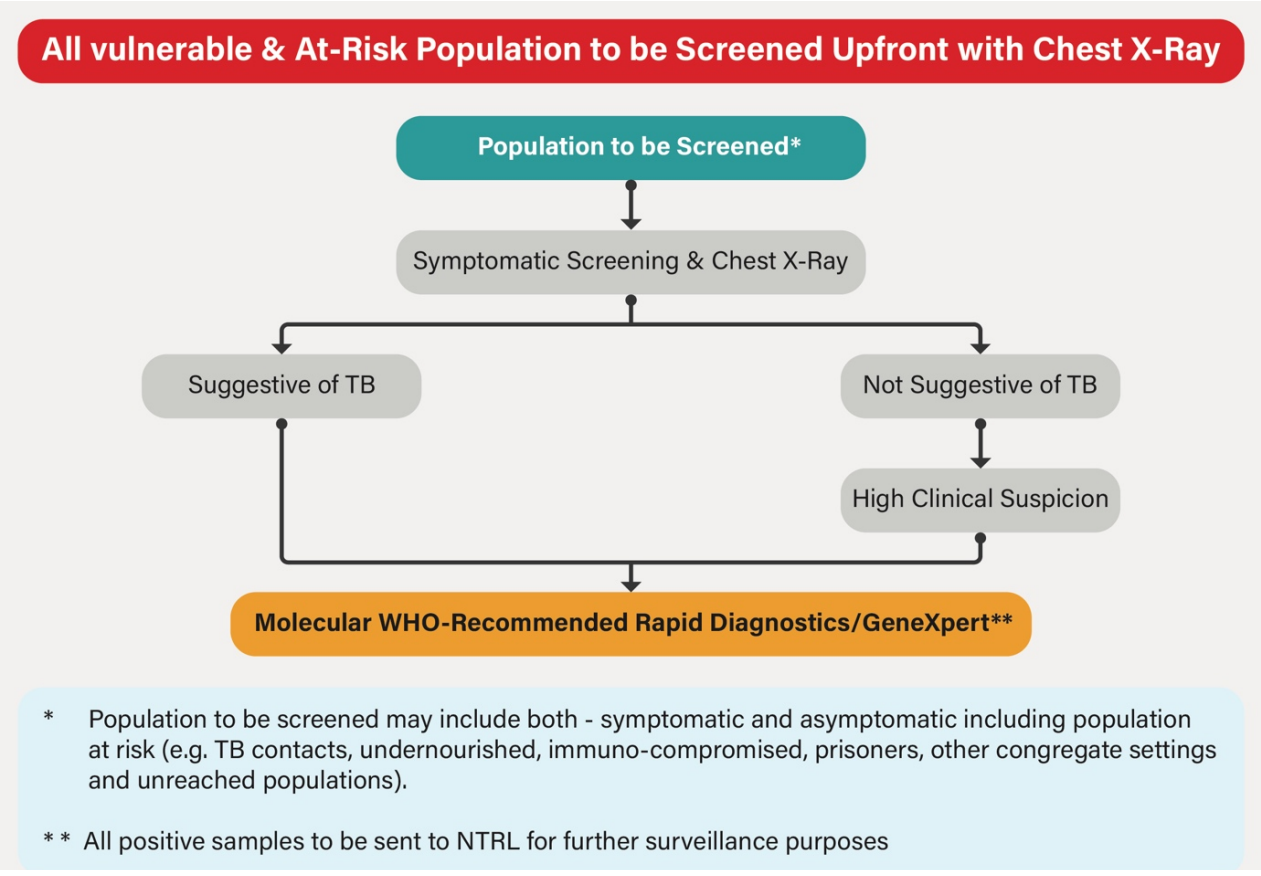


Figure 3.1: Algorithm for TB screening among high-risk groups

3.3. Active screening

Active case finding is a provider-initiated activity with the primary objective of detecting TB cases early by active case finding in targeted groups and to initiate treatment promptly. It can target people who have sought health care with or without any signs and symptoms of TB and also people who do not seek care. Increased coverage can be achieved by focusing on the clinically, socially and occupationally vulnerable population groups who have greater risk for TB.

In view of recent data showcasing reasonably high sensitivity, **Chest X-rays as an initial screening tool will be used.** It can help in improving the pre-test probability of subsequent diagnostic tests and to reduce the number of further diagnostic evaluations.

Active case finding helps in early identification of asymptomatic TB cases. Screening using sensitive algorithms among close contacts of TB patients, high risk groups, congregate settings and unreached populations should be planned and carried out, **although mass screening is not recommended**. The main purposes of contact screening and management are:

- To identify close contacts of all ages with undiagnosed TB disease and
- To provide TB Preventive Therapy (TPT) for contacts without TB disease who are susceptible to developing the disease following recent infection.
- **Close contacts of all bacteriologically confirmed pulmonary TB patients irrespective of sputum findings should be screened for symptoms of TB.**

Groups as per WHO recommendations to be focused for ACF:

- Household contacts and other close contacts should be systematically screened for active TB.
- People living with the human immunodeficiency virus (HIV should be systematically screened for active TB at each visit to a health facility.
- Current and former workers in workplaces with silica exposure should be systematically screened for active TB.
- Systematic screening for active TB should be considered in prisons and other penitentiary institutions.
- Systematic screening for active TB should be considered in people with an untreated fibrotic chest X-ray lesion.

Tools for screening TB

- Among adults and adolescents living with HIV, C-reactive protein using a cut-off of >5mg/L may be used to screen for TB disease (shift to HIV)

Those who have **symptoms suggestive of TB** should be **investigated upfront with GeneXpert if they can produce sputum. Chest X Ray needs to be used in high-risk groups who could be asymptomatic.**

In order to achieve the End TB target, NTCP will be starting ACF among high-risk communities using mobile vehicles. The screening will be based by applying a symptom questionnaire, digital X-ray with AI enabled software. Based on symptoms and/or X-ray finding, the presumptive TB patients will undergo GeneXpert MTB/RIF testing. Areas and Districts will be selected based on risk mapping exercises focusing on notification rates, hard-to-reach areas with limited access to health care and with poor universal access to diagnostic services. ACF among all close contacts of TB patients will be coordinated by the health facility where the index case is diagnosed.

Contact investigation should be conducted as part of active case finding following the protocol mentioned in Chapter 12.

3.4 TB diagnostic algorithm using Xpert MTB/RIF as first line test

All presumptive TB will be subjected to Xpert MTB/RIF in GeneXpert sites as initial test of diagnosis along with chest X-Ray. **Smear microscopy will be done only for the follow-up cases at the GeneXpert sites.** In non-GeneXpert sites, chest X-ray and sputum microscopy will be performed and sputum sample for Xpert MTB/RIF will be shipped to the nearest GeneXpert sites.

- In adults with signs and symptoms of pulmonary TB, Xpert MTB/RIF should be used as an initial diagnostic test for TB and rifampicin-resistance detection in sputum rather than smear microscopy/culture and phenotypic DST.

- In children with signs and symptoms of pulmonary TB, Xpert MTB/RIF should be used as an initial diagnostic test for TB and rifampicin-resistance detection in sputum, gastric aspirate, nasopharyngeal aspirate and stool rather than smear microscopy/ culture and phenotypic DST.

Sputum microscopy will be done on **2 samples instead of 3 samples** for initial diagnosis**. If expectoration is not possible or difficult then Bronchoscopy can be done and Bronchoalveolar Lavage (BAL) samples can be tested for Xpert MTB/RIF and MTB culture/DST**.

In adults and children with signs and symptoms of extra-pulmonary TB, Xpert MTB/RIF Ultra will be used in lymph node aspirate, lymph node biopsy, pleural fluid, peritoneal fluid, pericardial fluid, and synovial fluid or urine specimens as the initial diagnostic test rather than smear microscopy/culture.

In HIV-positive adults and children with signs and symptoms of disseminated TB, Xpert Ultra MTB/RIF may be used in blood, as an initial diagnostic test for disseminated TB.

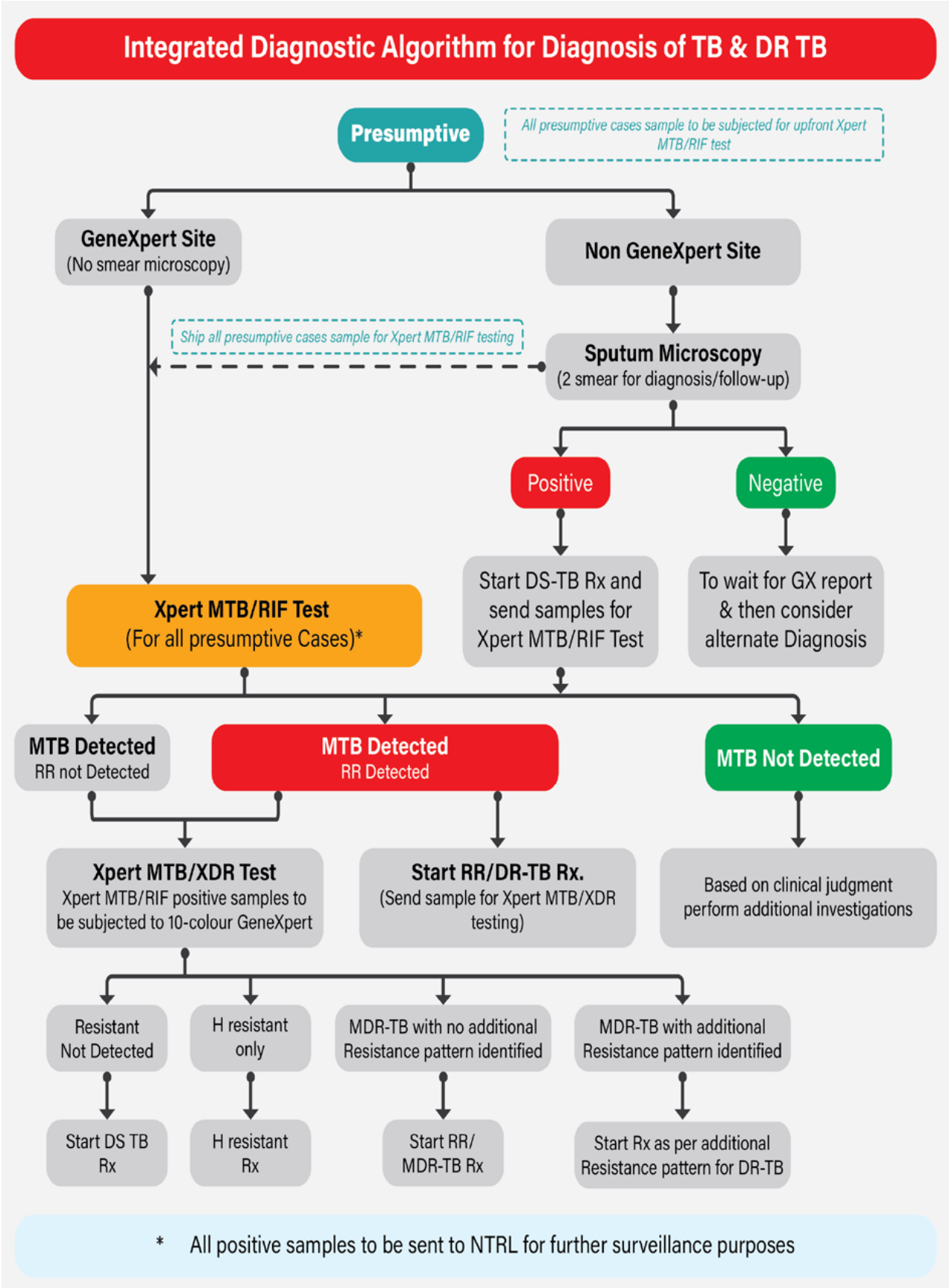


Figure 3.2 Integrated diagnostic algorithm DS-TB and DR-TB

CHAPTER 4

DIAGNOSTICS

With advancement in TB diagnostics, new diagnostic tools evaluated and validated by WHO especially Nucleic Acid Amplification Tests (NAAT) such as GeneXpert are now available at 14 GeneXpert sites with 17 machines, including 6 machines with 10 colour modules.

- **These GeneXpert machines will be used as the primary tool for diagnosis** of all forms of TB along with Chest X Ray in line with the algorithm provided in Chapter 3 above. Sites not having GeneXpert will strengthen sample transportation mechanism for early and accurate diagnosis.

- **Smear microscopy will consciously not be used for diagnosis and will only be used for follow-up examination.**

- **The newer 10 colour GeneXpert machines which have been strategically placed will be used for detecting resistance to isoniazid (INH), fluoroquinolones (FLQ), ethionamide (ETH), and second-line injectable drugs (SLIDs) on all bacteriologically positive cases**. The available diagnostic tools/technology in the country is listed in the Table 4.1.

4.1 Tuberculosis diagnosis Laboratory Network

There is a three-tier laboratory network in the country to support the diagnosis of TB and drug resistant TB (Figure 4.1).

- **Dzongkhag Hospitals and Hospitals-10 Bedded** – All samples to be tested on GeneXpert as the primary diagnostic tool for TB. Hospitals not equipped with GeneXpert to ship sputum samples to the nearest linked GeneXpert site. All positive samples to be sent to NTRL, RCDC for surveillance purpose for further culture and DST.

- **National and Regional Referral Hospitals** – To perform rapid DST using Xpert MTB/RIF and all the samples found positive on GeneXpert either MTB detected with or without Rif Resistance to be tested on 10 colour GeneXpert module for further resistance pattern. All positive cases sample to be shipped to NTRL, RCDC for culture and DST for other resistance pattern and surveillance purposes.

- **National TB Reference Laboratory** – identification of MTBC, rapid molecular detection of MDR/XDR-TB, 1st line drug phenotypic susceptibility testing for TB and plans to introduce 2nd line drug susceptibility testing for newer and genotyping soon. Organize NEQAS for TB microscopy and Xpert MTB/RIF assay.

The collection and transportation of sputum from all screening categories should be done within 48 hours from the time of collection to the nearest GeneXpert site. **In case of a delay in transportation beyond 48 hours, the sample should be kept in freezer (<0°C). The sample shipment should not be delayed for more than 3 days.**

The transportation of the sputum specimen should be done through Bhutan Postal Services, hospital utility vehicle/ambulance/in person. The transportation should be facilitated by the hospital management.

Laboratory technician at the GeneXpert site will be responsible for ensuring the availability of Xpert MTB/RIF results within 2 days of receipt of samples from referred hospitals**.**

Table 4.1 List of diagnostic tool/technology available in the country and its turn-around time (TAT)

Sl. No.	Tools / Technology		Description	Lab TAT	Overall TAT	Advantages	Disadvantages
1	Smear Microscopy	Ziehl Neelsen	Time between receipt of specimens for smear at the laboratory and result reporting	24-48 hrs	2 days	Simple, cost effective	Less sensitive
		Auramine-O				Sensitive compare to ZN	Expensive
2	Xpert MTB/RIF		Time between testing and result reporting	24 hours	5 days for non-Xpert sites 48 hours for Xpert sites	Sensitive, detects MTB and Resistance to Rif	Expensive and cannot be used for treatment follow up
3	10 coloured GeneXpert module (Xpert MTB/XDR) test		Time between receipt of specimens from other GeneXpert labs and result reporting	24 hours	5 days for sites which does not have 10 coloured modules 48 hours for sites with 10 coloured module	Detects resistance to isoniazid (INH), fluoroquinolones (FLQ), ethionamide (ETH), and second-line injectable drugs (SLIDs)	Expensive and cannot be used for treatment follow up
4	Culture	Solid	Time between receipt of specimens for culture at the laboratory and result reporting	2-8 weeks average for smear positive samples and 4–8 weeks average for smear-negative samples.	9 weeks	Sensitive, cost effective	Need trained-skilled person, tedious and biosafety issue
		Liquid		8-10 days for smear-positive samples and 2–6 weeks for smear-negative samples	2 months	More sensitive than solid	Need trained-skilled person, Tedious and biosafety issue
5	DST	Solid	Time between inoculation of DST and result reporting (mean, range and 90th percentile). For total DST TAT, add this value to culture TAT.	4-6 weeks	90 days/3 months	Cheaper and more widely available	Labour-intensive, less sensitive and slower than liquid culture.
		Liquid		After inoculation, 2 weeks	10 weeks	Reading of result automated. Facilitate processing of large numbers of specimens. Early TAT compared to solid DST.	Costly and more prone to contamination
6	TBST		Time between inoculation and result reporting	48-72 hrs	72 hrs	Rapid	Non-specific and cannot be used to diagnose TB disease.

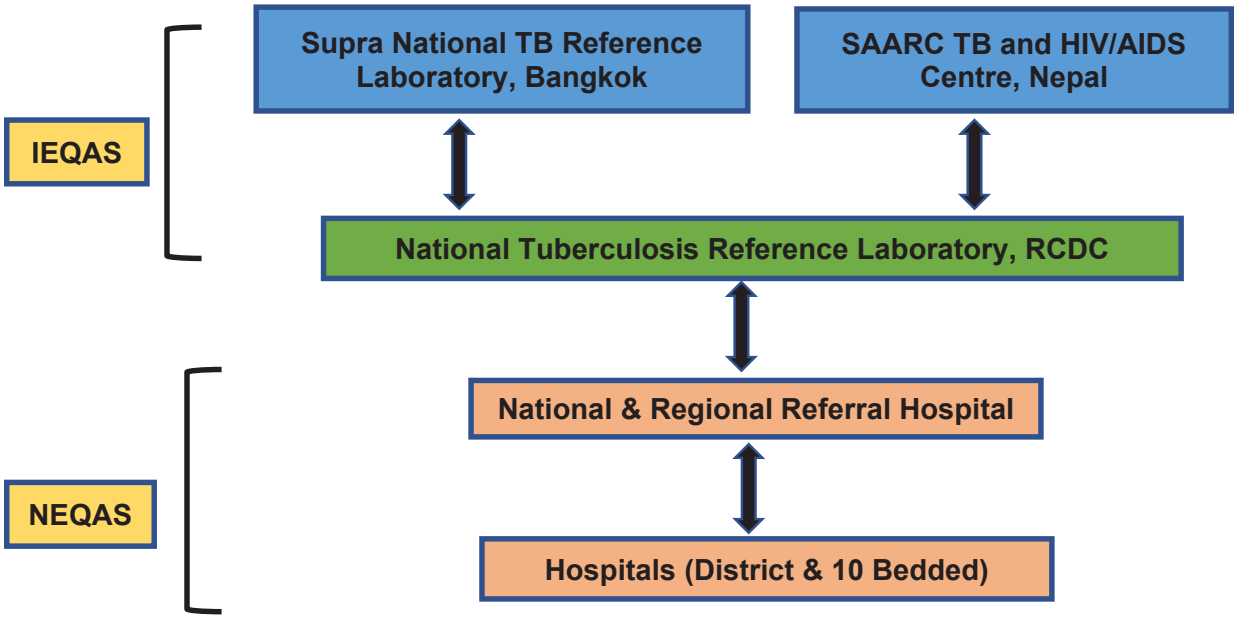


Figure 4.1 TB laboratory network

(***IEQAS***: *International external quality assurance scheme includes proficiency panel for TB microscopy and 1st line phenotypic DST;* ***NEQAS***: *National external quality assurance scheme, includes proficiency panel for TB microscopy, blinded rechecking of slides and on-site evaluation visit.)*

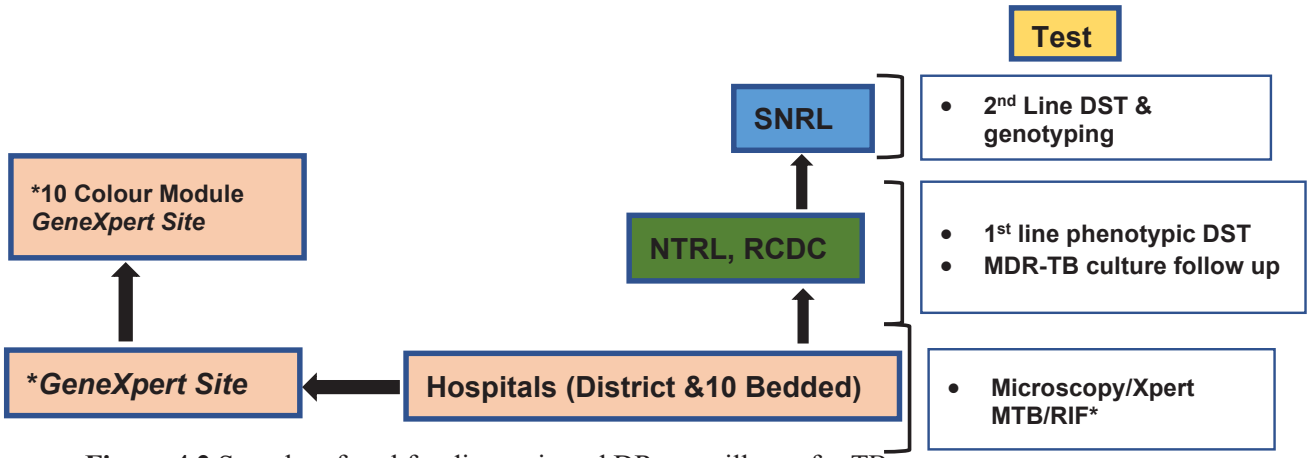


Figure 4.2 Sample referral for diagnosis and DR surveillance for TB.

4.2 Diagnostic tools and technology available in Health Facilities

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

machines are available including 6 machines with 10 coloured modules (Xpert MTB/XDR tests) placed at 13 sites. The program has plans to procure and install 3 more 10 colour machines at the Cluster Hospitals in the near future making GeneXpert services available at 16 strategic sites with 20 machines in the country.

Table 4.2: List of GeneXpert sites

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

**GeneXpert facilities will be expanded to Tsirang, Bumthang, Paro, Yebilaptsa and Pemagatshel Hospital*

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

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

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

4.3 Drug Susceptibility Testing (DST)

Drug susceptibility testing is conducted to find out if a TB patient has developed or has drug resistant TB (strains). This is essential to determine at the first contact to provide effective TB treatment. WHO now recommends universal DST for all TB patients with the objective to reduce the spread of drug resistant TB and amplification of resistance in the patient being treated with inappropriate regimen without DST. The country has geared towards providing universal DST with introduction of Xpert MTB/RIF in thirteen hospitals including 6 sites with 10 coloured module machines. These hospitals act as referral for rapid DST and test for rifampicin **resistance for all pulmonary and extra-pulmonary TB cases.** The 10 coloured modules GeneXpert machines using Xpert MTB/XDR tests will be used for further drug susceptibility testing for all confirmed MTB and MTB Rif resistant cases**.**

4.3.1 First line Drug Susceptibility Testing (FL-DST)

Upfront GeneXpert as the diagnostic tool will help in bacteriologically confirmation along with simultaneous Rif resistance detection. The hospitals and 10-bedded hospital which does not have GeneXpert will ship the samples to GeneXpert sites. to perform rapid drug susceptibility testing for rifampicin. Simultaneously, the hospitals and 10-bedded hospital including GeneXpert sites also refer samples to NTRL for surveillance as well as to perform phenotypic susceptibility testing using liquid culture.

4.3.2 Second line Drug Susceptibility Testing (SL-DST)

NTP has strategically placed 6 10-color GeneXpert machine which tests for MTB/XDR, located across the country will be used for early identification of drug resistance using Xpert MTB/XDR testing for all confirmed MTB and MTB Rif resistant cases. They will detect resistance to isoniazid (INH), fluoroquinolones (FLQ), ethionamide (ETH), and second-line injectable drugs (SLIDs). Furthermore, NTRL also has capability to perform genotypic susceptibly testing for Fluoroquinolones and injectables (Kanamycin, Amikacin, Capreomycin) using the same GeneXpert platform. NTRL will continue with phenotypic susceptibility testing for Kanamycin, Amikacin, Capreomycin, Moxifloxacin, and Ofloxacin using liquid culture and look into developing capacity for the newer drugs.

4.4 Diagnosis of extra-pulmonary TB

The common methodology to diagnose EPTB include (not limited to);

4.4.1 Lymph node tuberculosis

a. Tissue aspirate

Usually an adequate amount (at least 1 ml) of aspirate is obtained for Xpert MTB/RIF and culture for MTB. Cytology and direct smear for AFB can be done on aspirates from extra-pulmonary sites such as lymph nodes or collections of pus when Xpert MTB/RIF test is not available. However, conventional AFB stain has low sensitivity for the diagnosis of EPTB.

b. Tissue biopsy

Tissue biopsy is useful in the diagnosis of EPTB. A biopsy will also exclude other pathological processes like malignancy. A biopsy should be attempted in suspected EPTB cases if a lesion is amenable to biopsy and when a confirmed diagnosis cannot be made using Xpert MTB/RIF on tissue aspirate. In PTB, lung biopsy may be indicated in the diagnosis of miliary TB or in cases of lung lesions atypical of TB when the bacteriological confirmation can't be done. Histology will reveal granulomatous inflammation with central caseation and cell infiltration with lymphocytes, epithelioid cells, and Langerhan's giant cells. Biopsy specimens collected should be kept in normal saline and shipped using cold chain to RCDC for MTB culture. When an adequate amount of sample can be obtained, Xpert MTB/RIF to be conducted on biopsy samples. Xpert MTB/RIF is recommended in addition to MTB culture for diagnosis of EPTB cases including pleural effusion, blood, urine and stool. Presently the specimens can be processed only at JDWNRH for GeneXpert and RCDC for culture and NTP will expand to other GeneXpert sites after provisioning training and some lab upgradation.

4.4.2 Tuberculous pleural effusions

The presentation is usually with constitutional and local features. The fluid analysis can provide clue in the diagnosis of TB and GeneXpert needs to be offered upfront for diagnosis of TB. However, the absence of typical findings cannot rule out EPTB. Tuberculous fluid is invariably an exudate with lymphocytic predominance and Light's criteria is used for differential diagnosis (Figure 4.3). The gold standard for diagnosis of TB pleural effusion remains the detection of MTB in pleural fluid, either on GeneXpert and/or culture. TB pleural effusion with an ADA level > 40 U/L will further aid in tubercular etiology.

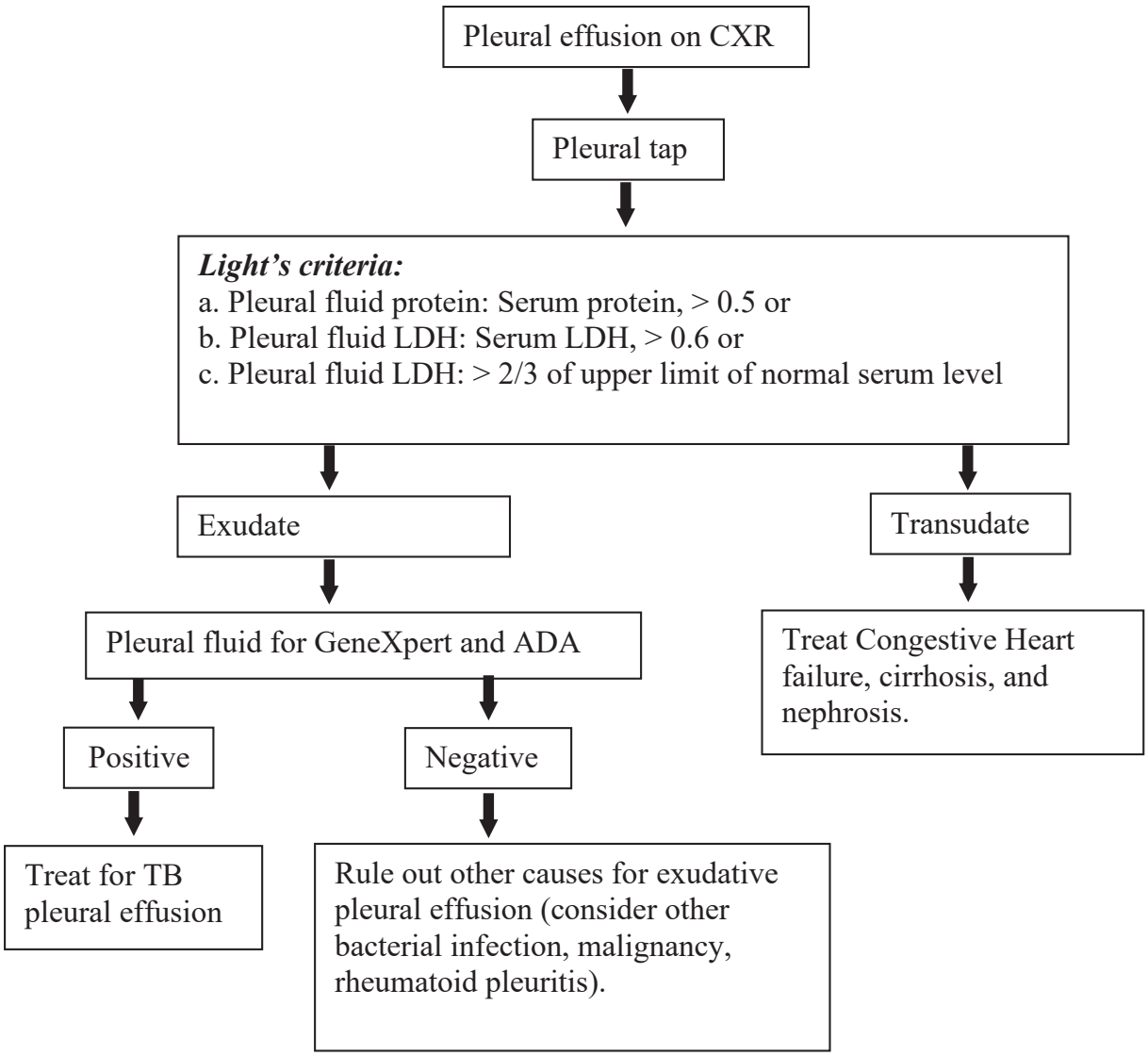


Figure 4.3 Diagnostic algorithm of pleural effusion

4.4.3 Tuberculous pericardial effusion:

The diagnosis and treatment of tuberculous pericarditis is important, as mean survival rate is 3.7 months, with a mortality rate approaching 85% at 6 months. The diagnosis usually rests on suggestive constitutional and cardiovascular features and investigation findings (ECG, chest CXR and echocardiography). For pericardial effusion to be visible radiologically, at least 200 ml of fluid is required. The chest x-ray shows globular enlargement of heart giving a water bottle appearance. However, 50% of the pericardial effusions also have pleural effusion due to concurrent tuberculous pleuritis. On echocardiography, pericardial thickening and detection of fibrinous strands is suggestive of tuberculous pericarditis. Invasive test like pericardiocentesis can be attempted to confirm the diagnosis (Source: Diagnosis of tuberculous aetiology in pericardial effusion-G Cherian).

4.4.4 Tuberculous ascites:

GeneXpert to be offered as the as initial tests in adults and children with signs and symptoms ascites suspecting extrapulmonary TB in the ascitic fluid. Even though WHO recommends GeneXpert with low certainty of evidence for test accuracy for peritoneal fluid. Further clinical judgement and a negative test result will not rule out the condition and in a high pre-test probability setting (>5%), should guide the treatment. Aspirated fluid is exudative with high protein content and leukocytosis with predominantly lymphocytes. The yield of even culture for AFB is relatively low; culture of a large volume ascitic fluid can increase the yield. Ultrasound may show features consistent with TB, including enlarged mesenteric or retroperitoneal lymph nodes. Definitive diagnosis rests on a peritoneal biopsy. Blind percutaneous needle biopsy of the peritoneum has a low pickup rate and a high complication rate. In experienced hands, laparoscopy under anaesthesia has a high pick-up rate. Laparoscopy enables direct visualization and biopsy of peritoneal TB lesions. Laparotomy will confirm the diagnosis in nearly every case but is too invasive for routine use. Adenosine Deaminase (ADA) from ascitic fluid could support in diagnosis of EPTB.

4.4.5 Gastrointestinal TB

Diagnostic options are; X-ray abdomen (features of obstruction), USG (mass at ileocecal junction), CT abdomen, barium contrast study of the small and large intestine, endoscopic biopsy, colonoscopy and laparoscopic biopsy.

4.4.6 Tuberculous meningitis

In all patients with signs and symptoms of TB meningitis, Xpert MTB/RIF is strongly recommended to be used in cerebrospinal fluid (CSF) as an initial diagnostic test for TB meningitis rather than smear microscopy/culture. MTB/RIF is a sensitive rapid molecular diagnostic test on CSF which should be performed as a first line investigation whenever neuro TB with meningeal involvement is suspected. At least 0.5 ml of CSF should be sent for the Xpert MTB/RIF test which has a high sensitivity and is the preferred initial diagnostic option. Mycobacterial culture can also be done which needs at least 1 ml of the specimen. Culture of CSF is diagnostic in up to 80% of cases and remains the gold standard and other supporting investigations with high suspicion like ADA from CSF could support in diagnosis of tuberculous meningitis.

4.4.7 Genito-urinary TB

Xpert MTB/RIF is recommended to be used in urine samples as an initial diagnostic test for renal TB rather than smear microscopy/culture. In addition to Urine analysis which does give abnormal result in 90% of cases, revealing pyuria and haematuria. Sterile pyuria first raises the suspicion of renal tuberculosis. An intravenous pyelography helps in the diagnosis. Calcification and ureteric stricture are also suggestive findings. Centrifuged urine specimen helps in the diagnosis. Culture of three morning urine specimens does yield a definitive diagnosis in nearly 90% cases but the time taken for diagnosis by culture warrants an upfront GeneXpert test.

4.5 Quality Assessment

External Quality Assessment is a process to identify laboratories with problems resulting in poor performance by an identified reference laboratory. The key activities under EQA include:

4.5.1. National External Quality Assurance Scheme (NEQAS)

a) TB microscopy

- Monitors the overall smear quality and results of AFB sputum microscopy in the district hospitals.
  NEQAS methods comprises of
- Panel testing: conducted once in a year
- Blinded Rechecking: conducted on quarterly basis
- Onsite evaluation: conducted once in a year

b) Xpert MTB/RIF

- Monitors the quality and proficiency of laboratory technician by sending the panel samples. It is conducted once in a year for all the GeneXpert sites.

4.5.2. International External Quality Assurance Scheme (IEQAS)

A program where a WHO identified Supranational Reference Laboratory (SNRL) evaluates and monitors quality of TB microscopy, culture and DST at NTRL. NTRL participates in following IEQAS:

a. Smear microscopy:
Proficiency testing for Sputum smear microscopy conducted by SAARC TB and HIV/AIDS Centre (STAC), Nepal.

b. Culture and 1st line DST:
Proficiency testing for culture and first line molecular and phenotypic DST for TB conducted by SNRL, Thailand. Annual assessment visit is also carried by SNRL, Thailand.

c. Xpert MTB/RIF:
Annual Maintenance and calibration of Xpert MTB/RIF machine by CEPHEID. NTRL facilitates the shipment of Xpert MTB/RIF calibration kits from CEPHEID to all the GeneXpert sites.

4.6 Quality indicators monitoring

Table 4.3 Laboratory quality indicators with targets.

Indicator	Target
Number of tests performed, by type of test	Solid culture/Liquid MGIT Culture- >90% of total sample received Solid/Liquid DST- > 80 % of culture positive samples GeneXpert MTB/RIF- >2400 test run per year
Service interruptions	No interruptions
Stock outs of reagents	No stock outs leading to service interruption
Equipment breakdown time	No equipment breakdown leading to service interruption
Turnaround time	
Test statistics (quality indicator) report	100% reports delivered by defined TAT
EQA results	>90% EQA panels are passed
QC results	>90% QC results meet expected criteria
Specimen rejection	<1% specimens rejected
Percentage of smear +ve, culture -ve	10-15% culture -ve
Technician productivity	Report average number of tests performed per month per technician

CHAPTER 5
MANAGEMENT OF DRUG-SUSCEPTIBLE TUBERCULOSIS (DS-TB)

Timely diagnosis and initiation of early effective treatment and cure of infectious cases of TB will interrupt transmission of TB infection in the community. Therefore, successful completion of treatment is the most effective way to prevent TB.

Basic Principles of TB treatment

The basic principles of good TB treatment are:

- Early diagnosis and initiation of effective treatment
- Right combination of drugs and duration to kill different bacterial populations
- Drugs are given in the right dosages for the right duration to achieve therapeutic effect but within minimum toxic effect
- Support and package of treatment adherence intervention may be offered for patients on TB treatment in conjunction with the selection of a suitable treatment administration option.
- Health education and counselling on the disease and treatment adherence should be provided to patients on TB treatment

5.1. Baseline investigations

It is important to undertake some baseline investigations apart from thorough general and systemic examination including comorbid conditions and pre-existing drug allergies. **The conditions to be screened at initial medical evaluation** include:

a. Baseline full blood count, random blood sugar, LFT, serum albumin, RFT, Uric acid, electrolytes,
b. HBsAg, anti-HCV
c. HIV testing. If HIV positive, the case will be referred for CD4 count. (CD4% in children and viral load testing)
d. Chest radiograph if not already conducted
e. Mycobacterial cultures for surveillance purposes and if needed DST to FLDs and SLDs and newer drugs
f. Pregnancy test for women of child bearing age

5.2 Start of treatment

Treatment should be started as soon as possible after a confirmed diagnosis has been made. **The treating doctor should categorize (PTB/EPTB) and mention the basis of diagnosis of the patient.** The TB in-charge should fill in the treatment card and TB register. They should also maintain other documents related to the diagnosis of the patients.

The TB In-charges should review and cross check the TB register weekly with the laboratory register to ensure that all patients diagnosed in the laboratory are registered and enrolled for treatment. Patients who are bacteriologically confirmed TB cases, according to the laboratory register, but did not begin treatment should be traced immediately after the laboratory results are available. For effective tracing of patients, proper address and contact numbers should be noted in the laboratory register during the first visit.

5.3 Treatment phases

Effective chemotherapy consists of two phases

- The **intensive phase (IP)** administered daily for two months in both new and retreatment cases found to not have resistance to the first line anti-TB drugs. The aim of this phase is to rapidly reduce and eliminate the multiplying bacilli without allowing the development of acquired resistance to the prescribed drugs. The infectious patients quickly become non-infectious (within approximately two weeks after initiation of appropriate treatment).

- The **continuation phase (CP)** is essential to eliminate the remaining bacterial population. Drugs are administered daily for the rest of the treatment duration according to treatment regimens.

Table 5.1 Case classification and recommended regimen

Case classification	Treatment Regimen	
	Intensive Phase	Continuation Phase
New cases • Pulmonary TB • Extra pulmonary TB	**2 (HRZE)**	**4 (HR)**
***Previously treated cases** • Relapse • Treatment after failure • Treatment after loss to follow up • Other previously treated cases		

**(if no resistance is found on GeneXpert/DST)*

5.4 Fixed-dose combinations (FDCs)

Tablets of fixed-dose drug combinations have several advantages compared to individual drugs:

a) Prescription errors are likely to occur less frequently because dosage recommendations are more straightforward and adjustment of dosage according to patient weight is easier.
b) The number of tablets to ingest is smaller and may thus encourage patient's adherence. A new TB patient of 35-54 kg body weight has to take three tablets of 4-FDC daily during the intensive phase of treatment.

c) Drug resistance is less likely to occur; patients swallow all drugs and cannot skip any particular drug.

FDCs have the disadvantage that if severe side-effects occur, all drugs have to be stopped and the patient has to continue treatment with single drugs, excluding the drug(s) which might be responsible for the side effect. In order to manage side effects, 5% of single drugs will be supplied together with FDCs.

FDC tablets are composed as follows:

4 FDC: isoniazid 75 mg + rifampicin 150 mg + pyrazinamide 400 mg + ethambutol 275 mg

2 FDC: isoniazid 75 mg + rifampicin 150 mg

5.5 Standardized Regimens

Standardized treatment means that all patients in a defined group receive the same treatment regimen. Standard regimens have the following advantages over individualized prescription of drugs:

- Reduce errors in prescription-thereby reducing the risk of development of drug resistance
- Facilitate estimates of drug needs, purchasing, distribution and monitoring
- Facilitate staff training
- Reduce costs
- Facilitate regular drug supply when patients move from one area to another
- Makes outcome evaluation convenient and comparable
- Convenient for the drug quantification and procurement

For assigning standard regimens, patients are grouped by the same patient registration groups used for recording and reporting. This differentiates new patients from those with prior treatment. Registration groups for previously treated patients are based on the outcome of their prior treatment course: failure, relapse, and loss to follow up.

5.6 New DS TB Regimen of 4 months

As per the new WHO recommendation, new treatment of drug-susceptible TB using 4-month regimens for people aged 12 years or older with body weight of more than 40 kg with drug-susceptible pulmonary TB, of isoniazid, rifapentine, moxifloxacin and pyrazinamide will be used.

(Source: WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-susceptible tuberculosis treatment. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO)

This regimen maybe initiated on special cases who fulfills above eligible criteria upon consultation with the specialist. However following group of patients should be excluded from this regimen:

- patients weighing less than 40 kg;
- patients with severe extrapulmonary TB (e.g. tuberculous meningitis, disseminated TB, osteoarticular TB or abdominal TB);
- PLHIV with a CD4 count of less than 100 cells/mm3 ;
- children and adolescents aged under 12 years; and
- pregnant, breastfeeding and postpartum women

This regimen consists of 8 weeks of daily (7 days per week) of isoniazid, rifapentine, moxifloxacin and pyrazinamide, followed by 9 weeks of daily isoniazid, rifapentine and moxifloxacin **(2HPMZ/2HPM).** The dose of rifapentine is fixed at 1200 mg and moxifloxacin at 400 mg and replacement of moxifloxacin by another fluoroquinolone is not recommended. Treatment duration has been fixed at 4 months and any prolongation beyond 4 months is not recommended.

As per WHO guidelines, unless clinically indicated no additional investigations are suggested, except the nationally recommended baseline monitoring similar to the existing 6-month regimen. Unless clinically indicated no additional EKG and/or cardiac monitoring is recommended and laboratory monitoring such as liver function tests would remain the same for both regimens. NTP needs to look into provisioning of treatment supporter in view of this new regimen being rolled out under the program.

Table 5.2 Management of TB meningitis

TB Meningitis	**Treatment**
ATT	2(HRZE) + 10(HR)
AND	
Dexamethasone	Week 1: IV 0.4mg/kg/day Week 2: IV 0.3mg/kg/day Week 3: IV 0.2mg/kg/day Week 4: IV 0.1mg/kg/day then Oral Week 5: 4 mg/day orally Week 6: 3mg/day orally Week 7: 2mg/day orally Week 8: 1mg/day orally

Table 5.3 Management of bone and joints TB

Bones and joints TB	Treatment
ATT	2(HRZE) + (HR) (total duration of treatment will be 12/18 months according to clinical response)

Sputum specimen from all cases would be subjected to Culture and DST (C & DST) apart from Xpert MTB/RIF testing and treatment will be modified according to results of DST.

Table 5.4 Number of FDC tablets used in TB treatment in adults according to body weight

Treatment regimen	Body weight (kg)		
	<35	**35-54**	**≥55**
HRZE tablet (4 FDC)	2	3	4
HR tablet (2 FDC)	2	3	4

For patients over 70 kg body weight, additional 400 mg Pyrazinamide may be added by the clinician in the intensive phase. Change the number of drugs if the weight band changes over time.
For detailed weight-based dosing of individual drugs see **(Annex 1).**

5.7 Important drug interactions

Many TB patients have concomitant illnesses. At the start of TB treatment, all patients should be asked about medicines they are currently taking. The most important interactions with anti-TB drugs are due to rifampicin. Rifampicin induces pathways that metabolize other drugs, thereby decreasing the concentration and effect of the other drugs. To maintain a therapeutic effect, dosages of the other drugs may need to be increased. When rifampicin is discontinued, its metabolism-inducing effect resolves within about two weeks, and dosages of the other drugs will need to be decreased again.

Commonly used drugs affected by rifampicin
Rifampicin substantially decreases the concentrations of certain drugs. They are:

- Anti-infective (including certain anti-retroviral drugs): mefloquine, clarithromycin, erythromycin, doxycycline, atovaquone, chloramphenicol
- Anti-fungal agents
- Hormone therapy including ethinylestradiol, norethindrone, tamoxifen, and levothyroxine
- Methadone

- **Warfarin** (patients on warfarin needs close monitoring of PTINR with frequent optimization of the warfarin dose and where possible rifampicin to be replaced with rifabutin)
- Cyclosporine
- Corticosteroids
- Anticonvulsant (including phenytoin)
- Cardiovascular agents including digoxin (among patients with renal insufficiency), verapamil, nifedipine, diltiazem, propranolol, metoprolol, enalapril, losartan, quinidine, mexiletine, tocainide, propafenone
- Theophylline
- Sulfonylurea
- Hypolipidemics including simvastatin and fluvastatin
- Nortriptyline, haloperidol, quetiapine, benzodiazepines (diazepam, triazolam, zolpidem, buspirone)

CHAPTER 6
MANAGEMENT OF DRUG RESISTANT TUBERCULOSIS (DR-TB)

6.1. Causes of drug resistance and prevention

There are two principal pathways leading to the development of drug-resistant TB:

Primary drug resistance

Primary or initial drug resistance means that a person has been infected with a drug-resistant TB strain among new TB patients, and among retreatment TB patients. Transmission of drug-resistant TB occurs exactly in the same way as transmission of drug susceptible TB. Environments conducive for TB transmission such as crowding, poor ventilation and poor infection control practices in health facilities and other congregate settings, also contribute to transmission of drug-resistant TB. Details of infection control measures to prevent infection with drug-resistant TB are discussed in Chapter 13.

Acquired drug resistance

Acquired drug resistance is the result of inadequate, incomplete or poor treatment quality that allows the selection of mutant resistant strains. If drug-susceptible TB is treated with a sub-optimal regimen based on lesser number of effective TB drugs than recommended, there is a risk that bacteria with drug-resistant mutations will multiply further during the course of treatment, eventually becoming the dominant strain. Therefore, appropriate treatment with a combination of several quality-assured TB medicines dramatically diminishes the risk of selection of resistant strains.

Poor treatment outcomes, including acquired drug-resistant TB, can be caused by inappropriate treatment; inadequate drug quality and supply; patient and social factors hampering adherence and treatment responses.

Interventions to prevent Drug-Resistant TB

There are five principles to prevent drug-resistant TB:

a) Early detection and high-quality treatment of drug-susceptible TB
b) Early detection and initiate effective treatment of drug-resistant TB
c) Effective implementation of infection control measures
d) Strengthening and regulation of healthcare systems
e) Addressing underlying risk factors and social determinants

6.2 Diagnosis and interpretation of results from Xpert MTB/RIF

All patients identified as having TB or rifampicin resistance by Xpert MTB/RIF should be initiated on treatment regimen as per the guidelines at the earliest possible.

A small proportion of tests may result in an error or invalid results, a repeat test needs to be performed while simultaneously sample to be sent for culture and expanded DST.

When the result of a second Xpert MTB/RIF test on a fresh specimen again shows rifampicin resistance, a standardized treatment regimen for RR/MDR-TB may be started without any further delay. In this case, the patient should be registered as having bacteriologically confirmed rifampicin-resistant TB, and an additional specimen should be taken for Xpert MTB/XDR to test for susceptibility to isoniazid, fluoroquinolones and second-line injectables. When DST results are available, the treatment regimen and patient registration should be adjusted as required. Additional sample for surveillance needs to be sent to NTRL.

6.2.1 Xpert MTB/RIF does not detect *M. tuberculosis*:
The disease can be ruled out in most cases unless there is a strong suspicion of TB that may require further investigation. However, the decision lies with the treating physician. The ability of any diagnostic test to detect TB depends on the quality of the specimen collected.

6.2.2 Xpert MTB/RIF detects M. tuberculosis without rifampicin resistance:
The patient should be started on first line TB treatment as per the guideline and registered as a case with drug susceptible bacteriologically confirmed TB. Another sample will be sent to Xpert MTB/XDR testing sites which detect resistance to isoniazid (INH), fluoroquinolones (FLQ), ethionamide (ETH), and second-line injectable drugs (SLIDs). The patients will be continued on drug-susceptible TB treatment until the results for INH resistance becomes available.

6.2.3 Xpert MTB/RIF detects M. tuberculosis with rifampicin resistance:
Patients will be promptly initiated on the new **bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM/BPaL)** regimen which is short 6-month MDR regimen after fulfilling the eligibility criteria. Another sample will be sent to Xpert MTB/XDR testing sites which detect resistance to isoniazid (INH), fluoroquinolones (FLQ), ethionamide (ETH), and second-line injectable drugs (SLIDs). In case of fluoroquinolone resistance, BPaL (without moxifloxacin) regimen will be continued for the patient. Additional sputum sample should be sent for culture and DST to RCDC for additional drug susceptibility testing.

When the DST results are available, treatment can be modified if necessary and the patient's registration can be updated accordingly. Treatment modifications may include changing the quinolone and/or second-line injectable, or, in the case of XDR-TB, placing the patient on an appropriately designed regimen. The patient's registration should be modified to reflect any new information, and the case should be notified according to national guidelines.

The Xpert MTB/RIF test is NOT to be used for monitoring a patient's response to treatment. Conventional microscopy and culture are required for monitoring MDR-TB patients during treatment.

6.3 Diagnosis of drug resistance among EPTB cases

For diagnosing drug-resistance in EPTB cases, Xpert MTB/RIF would be used in preference to conventional microscopy and culture as the initial diagnostic test for various EP TB specimens

from patients and for testing specific non-respiratory specimens (lymph nodes, other tissues and for pleural fluid) from patients suspected of having EPTB with drug-resistance.

6.4 Treatment initiation and process of enrolment

After the diagnosis of RR-/MDR-TB, person will be initiated on second-line treatment immediately at the National Referral Hospital or any of the regional referral hospitals (MDR-TB Treatment/Registration centers).

When the treatment is initiated at the regional referral hospitals and district hospitals (GeneXpert sites), the TB In-charges and the laboratory technicians will coordinate with the nearest Referral Hospital for pending baseline investigations (that may involve transportation of blood/sputum samples) and severe adverse drug reactions or complications that are not manageable at the regional/district hospital.

6.5 Baseline investigations

While initiating a case found to be RR/MDR-TB, it is important to undertake some baseline investigations apart from thorough general and systemic examination including comorbid conditions and pre-existing drug allergies. **The conditions to be screened at initial medical evaluation** include:

a. Mycobacterial cultures, DST to FLDs and SLDs
b. Baseline full blood count, glucose, LFT, serum albumin RFT, Uric acid, electrolytes,
c. Serum magnesium and calcium (where possible and in case of adverse drug effects)
d. Routine baseline thyroid function tests can be done on all patients.
e. HIV testing. If HIV positive, the case will be referred for CD4 count. (CD4% in children and viral load testing)
f. HBsAg, anti-HCV
g. Pregnancy test for women of child bearing age
h. Audiometry (required if second line injectables are used)
i. Chest radiograph
j. ECG
k. Visual assessment
l. Baseline psychosocial assessment

6.6 Treatment regimen for MDR-TB

A. The new 6-month bedaquiline, pretomanid, linezolid and moxifloxacin (BPaLM/BPaL) regimen for MDR/RR-TB

New 6-month MDR/RR-TB treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) The use of the 6-month treatment regimen BPaLM is suggested in MDR/RR-TB patients with or without resistance to fluoroquinolones, who have either had no previous exposure to bedaquiline and linezolid or have been exposed for less than 1 month.

(Source: WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.)

The rationale for this recommendation is based on the evidence and considerations linked to a phase 3 trial which showed much improved treatment success rates with the BPaLM regimen (89%) of 6 months duration compared with the current short course chemotherapy (SCC) regimens (52%), as well as lower levels of treatment failure, death and loss to follow-up. In addition, the trials also suggested fewer adverse events with a linezolid dose of 600 mg while maintaining high efficacy.

The comparison between patient groups receiving this regimen with those receiving currently recommended regimens lasting 9 months or longer too favored for the 6-month BPaLM regimen, suggesting it to be the regimen of choice for eligible patient groups.

The BPaLM/BPaL regimen consists of bedaquiline, pretomanid and linezolid, with or without moxifloxacin throughout the regimen duration. Bedaquiline dosing could be either daily throughout treatment: 200 mg once daily for 8 weeks followed by 100 mg once daily OR with a loading dose of 400 mg once daily for 2 weeks followed by 200 mg three times per week. Pretomanid is to be administered at 200 mg once daily for the duration of the regimen. Linezolid dosing at 600 mg/daily throughout the regimen, but the dose can be reduced to 300 mg/daily if necessary to mitigate toxicity. Moxifloxacin is to be dosed at 400 mg once daily throughout the treatment course. Replacement of moxifloxacin with levofloxacin or any other fluoroquinolone is not recommended.

6 Bdq-Pa-Lzd - Mfx

Table 6.1 Dosing of component drugs for adults and adolescents (aged ≥14 years) for BPaLM

Drug	Dose
Bedaquiline (100 mg tablet)	400 mg once daily for 2 weeks, then 200 mg 3 times per week afterwards OR 200 mg daily for 8 weeks, then 100 mg daily
Pretomanid (200 mg tablet)	200 mg once daily
Linezolid (600 mg tablet)	600 mg once daily
Moxifloxacin (400 mg tablet)	400 mg once daily

BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin.

MDR/RR-TB patient groups to be offered this new 6 months regimen:

- Pulmonary TB or all forms of extrapulmonary TB, except TB involving the CNS, osteoarticular TB and disseminated (miliary) TB
- 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 as defined above
- Patient is not pregnant or breastfeeding or, if the patient is a premenopausal woman, is willing

Furthermore, some major points to be considered with this new 6 monthly regimen is that Drug susceptibility testing (DST) for fluoroquinolones is strongly encouraged in people with MDR/RR-TB, and although it should not delay initiation of the BPaLM, results of the test should guide the decision on whether moxifloxacin can be retained or should be dropped from the regimen – in cases of documented resistance to fluoroquinolones, BPaL without moxifloxacin would be initiated or continued.

These recommendations below need to be looked into before starting the regimen:

- History of cardiac disease, syncopal episodes, significant symptomatic or asymptomatic arrhythmias (with the exception of sinus arrhythmia), people with prolonged corrected QT interval of more than 500 ms.
- People with currently having severe peripheral neuropathy or with BMI less than 17 kg/m^2
- Laboratory Abnormalities:
    a) Haemoglobin level < 8.0 g/dl
    b) Platelets grade 2 or greater(<75,000/mm3);
    c) Absolute neutrophil count (ANC) < 1000/ mm3;
    d) Alanine aminotransferase Grade 3 or greater (> 3.0 x ULN) to be excluded
    e) Serum creatinine level greater than 2 times upper limit of the normal laboratory reference range.

- Similarly, patients taking any medications contraindicated with the medicines in the BPaLM/BPaL regimen like zidovudine, stavudine or didanosine, among PLHIV and use of MAO Inhibitors as antidepressants and among Parkinson's etc.
- The preferred ART regimens for co-administration with BPaLM/BPaL are dolutegravir-based regimens in combination with two nucleoside reverse transcriptase inhibitors.
- Treatment duration of BPaLM is 6 months (26 weeks) during programmatic implementation but for BPaL is is suggested an extension to a total of 9 months (39 weeks) if sputum cultures are positive between months 4 and 6.
- In cases where treatment was interrupted and treatment duration was extended to make up for missed doses, it was necessary for patients to complete 6 months of the regimen (i.e. 26 weeks of prescribed doses) within 8 months.
- Patients who start a 6-month BPaLM/BPaL regimen may switch to the 9-month all-oral regimen, if required, provided they meet the necessary eligibility criteria for the 9-month regimen. This may be warranted when toxicity to linezolid develops early in the BPaLM/BPaL regimen and necessitates a linezolid-sparing regimen, such as the 9-month regimen with ethionamide.

If a patient starts the 9-month all-oral MDR/RR-TB regimen but is later found to be ineligible following detection of M. tuberculosis resistance to fluoroquinolones, the

If either bedaquiline or Pretomanid Tablets are discontinued, the entire combination regimen should also be discontinued. If linezolid is permanently discontinued during the initial four consecutive weeks of treatment, bedaquiline and Pretomanid Tablets should also be discontinued. If linezolid is discontinued after the initial four weeks of consecutive treatment, continue administering bedaquiline and Pretomanid tablets

Monitoring of patients who receive BPaLM/BPaL need to be tested at baseline and then monitored during treatment using schedules of relevant clinical and laboratory testing. If feasible, it is also important to follow up patients 12 months after the completion of treatment for possible relapse, including with sputum culture and smear.

It is recommended to monitor patients with MDR/RR-TB while on treatment using monthly sputum cultures. Failure to convert sputum culture at or after the fourth month on treatment is a potential sign of a failing treatment regimen.

DST for fluoroquinolones is important to support prescription of the relevant combination, BPaLM or BPaL, to maximize the efficacy and prevent unnecessary potential toxicity. NTP needs to look into establishing DST capacity to test for resistance to bedaquiline and linezolid at baseline (particularly in cases demonstrating fluoroquinolone resistance) and to test samples from patients with no bacteriological conversion after month 4 while on the BPaLM/BPaL regimen.

Active TB drug-safety monitoring and management (aDSM) - Close monitoring of adverse effects of treatment is particularly important for the shorter treatment regimens and for regimens including new medicines (e.g. this regimen includes a novel compound – pretomanid), to ensure relapse-free cure. Active pharmacovigilance and proper management of adverse drug reactions and prevention of complications from drug–drug interactions will ensure proper patient care; and systems need to be established for reporting any adverse drug reactions to the responsible drug-safety authority.

B. The 9-month all-oral regimen for MDR/RR-TB

In the new 2022 guideline WHO further suggests the use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded, when BPaLM is either not available or cannot be administered for clinical reasons.

(Source: WHO consolidated guidelines on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.)

This 9-month all-oral regimen consists of bedaquiline (used for 6 months or longer in specific cases), in combination with levofloxacin/moxifloxacin, ethionamide, ethambutol, isoniazid (high-dose), pyrazinamide and clofazimine (for 4 months, with the possibility of extending to 6 months if the patient remains sputum smear positive at the end of 4 months), followed by treatment with levofloxacin/moxifloxacin, clofazimine, ethambutol and pyrazinamide (for 5 months). Ethionamide may be replaced by 2 months of linezolid (600 mg daily).

The regimen comprises an intensive phase (IP) of 4 months and a continuation phase (CP) of 5 months with the duration of bedaquiline and linezolid was restricted to 6 and 2 months, respectively. IP may be extended to 6 months when no bacteriological conversion is seen at the end of the fourth month of treatment, and a continuation phase of 5 months; hence, if extended, the regimens may last 11 months and NTP needs to look into patient support to enable full adherence to treatment.

The 9-month all-oral regimen (with either ethionamide or linezolid) may be offered to the following
patients with MDR/RR-TB (where resistance to at least rifampicin has been confirmed and resistance to fluoroquinolones has been ruled out):

- those with no documented resistance or suspected ineffectiveness of bedaquiline, clofazimine, or ethionamide or linezolid (whichever is considered for inclusion in the regimen)
- those with no exposure to previous treatment with bedaquiline, fluoroquinolones,4 clofazimine, or ethionamide or linezolid (whichever is considered for inclusion in the regimen) for more than 1 month – when prior drug exposure is greater than 1 month, patients may still receive this regimen if resistance to the specific medicine with such exposure has been ruled out
- those with no extensive or severe TB disease and no severe extrapulmonary TB. The extent of a patient's TB disease is important in determining appropriate regimen options, in addition to the drug susceptibility of the M. tuberculosis and other considerations mentioned above. Patients with extensive disease are not eligible for the 9-month all-oral regimen with either linezolid or ethionamide.
- all people living with or without HIV
- **women who are pregnant or breastfeeding: these patients may be considered eligible for the linezolid-containing 9-month regimen, but they should not receive the 9-month regimen containing ethionamide**
- children and adults without bacteriological confirmation of TB or resistance patterns but who require MDR/RR-TB treatment based on clinical signs and symptoms of TB (including radiological findings) and history of contact with someone with confirmed MDR/RR-TB: these patients may be eligible for this regimen based on the drug resistance profile of the isolate obtained from the most likely index case.

This 9-month regimen is to be used in patients not eligible for the shorter, 6-month BPaLM regimens; also, they represent a preferred treatment option over the longer regimens. With an intention to have a relatively shorter duration of treatment for patients with forms of DR-TB or other eligibility criteria which is not compatible with the 6-month regimen detailed above. This 9-month regimen has options with either linezolid or with ethionamide, and that both regimens can be used in preference to the longer (18-month) regimens in eligible patients. This regimen has been suggested for various subgroups including PLHIV and Paediatric population. Among the pregnant and lactating mothers, linezolid-based regimen instead of Ethionamide is suggested but the regimen is not recommended with severe forms of EP TB.

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 (see above regarding severe and non-severe TB disease in children). This highlights the importance of chest radiography as part of the diagnostic work-up for patients, along with the usual patient–clinician interaction. Patients with extensive MDR/RR-TB disease should not be treated with the 9-month all-oral regimen with either linezolid or ethionamide because of the lack of evidence on the impact of this regimen in this subgroup of patients.

Among the PLHIV population, co-administration of zidovudine and linezolid should be avoided because of the increased risk of myelosuppression. Boosted protease inhibitors can increase bedaquiline exposure, thereby increasing the risk of bedaquiline-related adverse drug reactions

(e.g. QT interval prolongation), which may require closer monitoring. Efavirenz can reduce the concentration of bedaquiline; therefore, this antiretroviral drug should be avoided in patients receiving the 9-month all-oral regimen. There are no overlapping toxicities or drug–drug interactions with dolutegravir in patients receiving the shorter regimen with either linezolid or ethionamide. PLHIV receiving the 9-month all-oral bedaquiline-containing regimen will need prophylactic medication for opportunistic infections, support for adherence to TB and antiretroviral medication, and close monitoring of the biomarkers of immune status.
Child-friendly formulations are now available for all second-line drugs and should be provided to children whenever possible. When these are not available, practical instructions for use of adult formulations for administration are available, so lack of formulation should not be a hindrance to treating children of all ages. Extent of disease is defined slightly differently for children than for adults, and most children with TB have less severe forms of the disease than adults. Pulmonary TB disease should be classified as severe (which may include extensive, advanced and complicated disease) or non-severe in children. Despite the lack of comparable data among children with MDR/RR-TB disease specifically, the same definitions for severity of disease are likely to be appropriate when considering the use of a shorter regimen for children with MDR/RR-TB. Non-severe disease in children is defined as peripheral lymph node TB; intrathoracic lymph node TB without airway obstruction; uncomplicated TB pleural effusion (without empyema or pneumothorax); or paucibacillary, noncavitary disease confined to one lobe of the lungs and without a miliary pattern post evaluation on chest X-ray.

Ethionamide variation

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

Initial phase: 4–6 Bdq(6 m)-Lfx/Mfx-Cfz-Z-E-Hh-Eto
Continuation phase: 5 Lfx/Mfx-Cfz-Z-E

Linezolid variation

4–6 Bdq(6 m)-Lzd(2 m)-Lfx/Mfx-Cfz-Z-E-Hh / 5 Lfx/Mfx-Cfz-Z-E

Initial phase: 4–6 Bdq(6 m)-Lzd(2 m)-Lfx/Mfx-Cfz-Z-E-Hh
Continuation phase: 5 Lfx/Mfx-Cfz-Z-E

Regimen selection at RR-TB diagnosis – no initial linezolid contraindications

MDR-TB with no previous treatment with second-line TB drugs, no extensive or severe pulmonary disease, no severe extrapulmonary TB, and no contact with pre-XDR-TB or XDR-TB; thus, there are no contraindications to linezolid.

- **Diagnosis of RR-TB only or RR-TB with isoniazid susceptibility, pending results of fluoroquinolone DST**.
  This patient could start the 9-month regimen with linezolid (but preferably not with ethionamide) while DST results are awaited. This patient has the option to switch from the linezolid-containing regimen to the ethionamide-containing regimen if preferred (and if not

pregnant) once fluoroquinolone susceptibility is confirmed on DST and if no mutation was detected in the inhA promoter region.

- **Diagnosis of RR-TB with isoniazid resistance conferred by mutations in the inhA promoter region only, and pending results of fluoroquinolone DST or susceptibility to fluoroquinolones is confirmed.**
  This patient could start the 9-month regimen with linezolid (but not with ethionamide owing to the inhA mutation).
- **Diagnosis of RR-TB with isoniazid resistance conferred by mutations in the katG gene only, and pending results of fluoroquinolone DST**.
  This patient could start the 9-month regimen with linezolid (but preferably not with ethionamide) while DST results are awaited.This patient has the option to switch from the linezolid-containing regimen to the ethionamide-containing regimen if preferred (and if not pregnant) once fluoroquinolone susceptibility is confirmed.
- **Diagnosis of RR-TB with isoniazid resistance conferred by mutations in the katG gene only and confirmed susceptibility to fluoroquinolones**.
  This patient could start the 9-month regimen with either ethionamide (if not pregnant) or linezolid.

Regimen selection at RR-TB diagnosis – linezolid contraindications

MDR-TB with no previous treatment with second-line TB drugs, no extensive or severe pulmonary disease, no severe extrapulmonary TB, and no contact with pre-XDR-TB or XDR-TB, but with contraindications to linezolid.

- **Diagnosis of RR-TB only, or RR-TB with isoniazid susceptibility, pending results of fluoroquinolone DST.**
  This patient could start a longer regimen initially, but with the option to switch to a 9-month regimen with ethionamide (not linezolid because contraindicated) within the first month of treatment once fluoroquinolone susceptibility is confirmed on DST, no mutation is detected in the inhA promoter region and the patient is not pregnant.
- **Diagnosis of RR-TB with isoniazid resistance conferred by mutations in the inhA promoter region only, and pending results of fluoroquinolone DST or susceptibility to fluoroquinolones is confirmed.**
  This patient should preferably not receive the 9-month regimen with either ethionamide (owing to the inhA mutation) or linezolid (contraindicated) and should instead be considered for a longer regimen.
- **Diagnosis of RR-TB with isoniazid resistance conferred by mutations in the katG gene only, and pending results of fluoroquinolone DST.**
  This patient could start a longer regimen initially while DST results are awaited, but with the option to switch to a 9-month regimen with ethionamide (not linezolid because contraindicated) if fluoroquinolone susceptibility is confirmed and the patient is not pregnant.
- **Diagnosis of RR-TB with isoniazid resistance conferred by mutations in the katG gene only and confirmed susceptibility to fluoroquinolones.**
  This patient is eligible to start the shorter regimen with ethionamide (not linezolid) if not pregnant.

Overall NTP needs to implement aDSM in all patients enrolled on treatment of DR-TB although the current available data has not shown any major signs of risk. aDSM systems must be functional to conduct rigorous active monitoring of adverse events and to detect, manage and report suspected or confirmed drug toxicities in a timely manner.

The patients need to be monitored for both clinical and laboratory testing including both smear and culture on a monthly basis for the shorter MDR-TB treatment regimen. This is similar to the schedule of bacteriological monitoring recommended for the longer regimens.
In view of wider applicability and including paediatric populations in the 9-month regimens highlights the need for paediatric formulations. NTP will look into the sustained availability of modern paediatric formulations to ensure smooth implementation in this subgroup of patients.

NTP to strengthen and increase access to DST, and the need to monitor and undertake surveillance for emerging drug resistance, including for bedaquiline and for all second-line medicines in the shorter regimen. DST is needed for bedaquiline and linezolid when no bacteriological conversion is seen at the end of the fourth month of treatment and following the 2 months of prolongation. If feasible, it is also important to follow up patients 12 months after the completion of treatment, for possible relapse, including with sputum culture and smear.

Regimen modifications:

The 9-month all-oral MDR/RR-TB regimen should be implemented as a standardized package. It
is not advisable to change the composition of the regimen or the duration of either the initial or continuation phase, with a few exceptions, as follows:

- Bedaquiline is usually given for 6 months but may be extended to 9 months if the initial phase of the regimen is extended from 4 to 6 months because of positive sputum smears at month 4 of treatment.
- Linezolid is only given for 2 months (instead of 4–6 months of ethionamide). If occasional doses of linezolid are missed during that time, the missed doses can be added on to the end of the 2-month period if the patient is tolerating the drug well; however, once fluoroquinolone resistance has been definitively ruled out, it may not be strictly necessary to make up the missed doses. The linezolid dose should not be reduced to less than the recommended dose to reduce the severity of adverse effects. If the full dose of linezolid (600 mg in adults) is not tolerated for the first full 2 months of treatment (apart from occasionally missed doses, which can be added to the end of the 2-month period), then the patient must either switch to an ethionamide-containing 9-month regimen (provided fluoroquinolone susceptibility is confirmed and the patient is not pregnant) or to an individualized longer regimen without linezolid. In selected cases where the risk of undetected resistance to fluoroquinolones and other second-line TB drugs is very low and the patient is unable to tolerate linezolid but would greatly benefit from a shorter regimen (e.g. migrant populations and children), the treating clinician may, after weighing up the risks and benefits, choose to stop linezolid

before 2 months and continue the 9-month all-oral regimen, with close monitoring for relapse or recurrence.

- Prothionamide may be used instead of ethionamide.
- Moxifloxacin may be used instead of levofloxacin, provided close ECG monitoring is feasible (should this be required).
- If, for any reason, a patient is unable to tolerate pyrazinamide or ethambutol within the 9-month regimen, then one (but only one) of these drugs may be dropped during the continuation phase without necessitating a switch to a longer regimen. If two or more of these drugs are not tolerated within the 9-month regimen, the treatment will have to switch to a longer regimen. If any of the other drugs within the 9-month regimen (bedaquiline, levofloxacin/moxifloxacin, linezolid/ethionamide or clofazimine) are stopped early because of toxicity or intolerance then the patient will also have to switch to a new regimen. Patients switching to a new regimen due to toxicity or intolerance need to be reported as "treatment failed".
- At the fourth month of treatment on the 9-month regimen, the decision to extend the initial phase from 4 to 6 months is based on the bacteriological sputum smear status of the patient's sputum specimen. If the specimen is smear negative at month 4 (regardless of smear status at the start of treatment), the patient may move to the continuation phase of treatment. If the specimen is smear positive at month 4, the initial phase is prolonged to 6 months. The duration of the continuation phase remains fixed at 5 months.
- At the sixth month of treatment, the culture result from the specimen taken at month 4 and possibly month 5 should be available, as well as the smear results from the specimens taken at months 5 and 6. If the culture from the 4-month specimen is positive for M. tuberculosis, the clinician should undertake a full work-up to assess for treatment failure – this involves a comprehensive clinical assessment, review of treatment adherence to address specific challenges, radiological assessment and collection of another respiratory sample for bacteriological assessment, as well as repeat DST of the most recent positive culture to test for emerging resistance to second-line TB drugs. Similarly, if the month 5 and 6 culture results remain persistently positive, treatment failure should be suspected, particularly if the patient has had suboptimal adherence to treatment or shows other signs of poor clinical or radiological response to treatment.
- If a patient starts the 9-month all-oral MDR/RR-TB regimen but is later found to be ineligible following detection of M. tuberculosis resistance to fluoroquinolones, the patient must switch to a different regimen. Such patients might be eligible for a 6-month BPaL regimen if their prior exposure to bedaquiline and linezolid was for less than 1 month and there is no demonstrated resistance to any components of the BPaL regimen.
- Patients who start on a longer regimen but are subsequently found to be eligible for the 9-month all-oral regimen may switch to the 9-month regimen if this is done within the first month of starting treatment. There is little experience in switching from longer to shorter

regimens in this way; hence, clinical monitoring and adequate data collection are important to inform future treatment recommendations.

- Patients who are lost to follow-up after starting the 9-month all-oral regimen are likely to have had more than 1 month of exposure to key drugs within the 9-month regimen. Should such patients return to care and require MDR/RR-TB treatment in future, the 9-month all-oral regimen may still be considered as a treatment option if resistance to bedaquiline, fluoroquinolones, clofazimine, and ethionamide or linezolid (whichever is considered for inclusion in the regimen) is ruled out and all other relevant eligibility criteria are met. In such cases, DST for the key drugs in this regimen is likely to take some time; therefore, patients may have to initiate a longer individualized regimen while awaiting DST results.

Although the 9-month all-oral MDR/RR-TB regimen is taken for much less time than the longer regimens, this regimen still has a high pill burden and includes medications with multiple overlapping toxicities. The most common adverse events associated with the 9-month all-oral regimen are anaemia (among patients receiving the linezolid-containing regimen), hepatotoxicity, QT prolongation, nausea and vomiting. Treatment monitoring schedules must include relevant clinical and laboratory parameters to detect, manage and prevent common and significant adverse events in a timely manner.

C. Longer regimens for MDR/RR-TB

A longer treatment regimen should be proposed mainly when the BpaLM/BpaL or 9-month all-oral regimen cannot be used. In MDR/RR-TB patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included. If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.

- Kanamycin and capreomycin are not to be included in the treatment of MDR/RR-TB patients on longer regimens
- Levofloxacin or moxifloxacin should be included in the treatment of MDR/RR-TB patients on longer regimens.
- Based on newer findings it is suggested that Bedaquiline should be included in longer multidrug-resistant TB (MDR-TB) regimens for both adults and paediatric age group
- Based on newer findings it is suggested that Delamanid may be included in the treatment of MDR/RR-TB both adult and paediatric patients
- Linezolid should be included in the treatment of MDR/RR-TB patients on longer regimens.
- Clofazimine and cycloserine or terizidone may be included in the treatment of MDR/RR-TB patients on longer regimens.
- Ethambutol may be included in the treatment of MDR/RR-TB patients on longer regimens.

Table 6.2 Grouping of medicines recommended for use in longer MDR-TB regimens.

Groups & steps	**Medicine**	
Group A: Include all three medicines	levofloxacin *OR* moxifloxacin	Lfx Mfx
	bedaquiline [2,3]	Bdq
	linezolid [4]	Lzd
Group B: Add one or both medicines	clofazimine	Cfz
	cycloserine *OR* terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	ethambutol	E
	delamanid [3,5]	Dlm
	pyrazinamide [6]	Z
	imipenem–cilastatin *OR* meropenem [7]	Ipm–Cln Mpm
	Amikacin (*OR* streptomycin)	Am (S)
	ethionamide *OR* prothionamide [9]	Eto Pto
	p-aminosalicylic acid [9]	PAS

1. This table is intended to guide the design of individualized, longer MDR-TB regimens (the composition of the recommended shorter MDR-TB regimen is largely standardized; see section 6.6). Medicines in Group C are ranked by decreasing order of usual preference for use subject to other considerations. The 2018 IPD-MA for longer

regimens included no patients on thioacetazone and too few patients on gatifloxacin and high-dose isoniazid for a meaningful analysis. No recommendation on perchlozone, interferon gamma or sutezolid was possible owing to the absence of final patient treatment outcome data from appropriate studies.
2. Evidence on the safety and effectiveness of bedaquiline use beyond 6 months and below the age of 6 years was insufficient for review. Use of bedaquiline beyond these limits should follow best practices in "off-label" use (48).
3. Evidence on the concurrent use of bedaquiline and delamanid was insufficient for review.
4. Use of linezolid for at least 6 months was shown to increase effectiveness, although toxicity may limit use. The analysis suggested that using linezolid for the whole duration of treatment would optimize its effect (about 70% of patients on linezolid with data received it for more than 6 months and 30% for 18 months or the whole duration). No patient predictors for early cessation of linezolid could be inferred from the IPD subanalysis.
5. Evidence on the safety and effectiveness of delamanid beyond 6 months and below the age of 3 years was insufficient for review. Use of delamanid beyond these limits should follow best practices in "off-label" use (48).
6. Pyrazinamide is counted as an effective agent only when DST results confirm susceptibility.
7. Every dose of imipenem–cilastatin and meropenem is administered with clavulanic acid, which is available only in formulations combined with amoxicillin. Amoxicillin–clavulanic acid is not counted as an additional effective TB agent and should not be used without imipenem–cilastatin or meropenem.
8. Amikacin and streptomycin are to be considered only if DST results confirm susceptibility and high-quality audiometry monitoring for hearing loss can be ensured. Streptomycin is to be considered only if amikacin cannot be used (unavailable or documented resistance) and if DST results confirm susceptibility (resistance to streptomycin is not detectable with second-line molecular assays and phenotypic DST is required). Kanamycin and capreomycin are no longer recommended for use in MDR-TB regimens.
9. These agents showed effectiveness only in regimens without bedaquiline, linezolid, clofazimine or delamanid, and are thus proposed only when other options to compose a regimen are not possible.

In MDR/RR-TB patients on longer regimens, a total treatment duration of 18–20 months including a treatment duration of 15–17 months after culture conversion is suggested for most patients; the duration may be modified according to the patient's response to therapy.

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

Any patient eligible for a longer regimen should undergo a pretreatment assessment to optimize the drug selection, reduce the chances of adverse events and thus increase the probability of the favourable treatment outcomes.

The pretreatment assessment includes:
- a detailed clinical history (including all comorbidities, medications and known intolerances), a physical examination, a blood test, chest X-ray or other imaging and bacteriological tests; and

- a list of current effective TB medicines available based on a clinical history of drugs taken before this treatment episode and guided by the DST results or sequencing of the most recent sample from the patient (or the index case).

In addition to the eligibility criteria and preclinical assessment, a clinician should also consider:

- development of a personalized treatment approach (patient-centred approach) and close follow-up, including food support if needed, to increase bioavailability of drugs, improve nutritional status and facilitate adherence;
- provision of advice on contraception for women of childbearing age;
- availability of ancillary medications (e.g. corticosteroids in the case of disseminated TB or TB meningitis or pericarditis, pretreatment blood transfusion in the case of severe anaemia and nutritional support) and other interventions (e.g. intravenous [IV] medication in the case of severe malnutrition and malabsorption, insertion of peripherally inserted central catheter, or surgery in the case of restricted options and meeting criteria for intervention); and
- Provision of counselling, depending on the patient's comorbidities (e.g. HIV or diabetes) or pre-existing conditions needing to be treated to optimize TB treatment outcomes.

Implementation considerations and eligibility

- Quinolone susceptible or resistant
- Patient not eligible for the shorter regimen (according to shorter regimen criteria)
- Careful regimen design in case of use in pregnancy
- Children or adults

The regimen is as below

18-20 Bdq (6m)-Lfx-Lzd-Cfz

***Based on the patient's response to the treatment, Bdq can be given more than 6 months.**

The total duration of treatment in the longer regimen for RR/MDR-TB patients is **18-20 months.** Treatment duration has to be at least a minimum of 15 months after culture conversion. Since the longer regimen doesn't contain any injectable, the term intensive phase and continuation phase is not used for this regimen.

Justification for choosing the above regimen:
It is recommended that all three group A agents and at least one group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective and at least three agents are included for the rest of the treatment after bedaquiline is stopped.
If only one or 2 group A agents are used, both group B agents are to be used. If the regimen cannot be composed with agents from groups A and B alone, group C agents are added to complete it.

After stopping bedaquiline at 6 months, the regimen needs to have at least three effective agents. However, in certain situations where the benefit outweighs the risk, bedaquiline may be used for longer than 6 months as per the guidelines for 'off-label' use of the drug. If another agent needs to be stopped because of toxicity, then it needs to be replaced by another medicine either from group B or C.

The dosages of the drugs according to weight for adults are given in **Annexure 2.** Regimen options and factors to be considered for selection of treatment regimens for patients with MDR/RR-TB (Source: WHO operational handbook on tuberculosis. Module 4: treatment - drug-resistant tuberculosis treatment, 2022 update. Geneva: World Health Organization; 2022. Licence: CC BY-NC-SA 3.0 IGO.)

Table 6.3 Summary of BpaL/BpaLM regimen

Regimen	MDR/RR-TB fluoroquinolone susceptible	Pre-XDR-TB	XDR-TB	Extensive pulmonary TB	Extrapulmonary TB	Age <14 years
6-month BPaLM/BPaL	Yes (BPaLM)	Yes (BPaL)	No	Yes	Yes – except TB involving CNS, miliary TB and osteoarticular TB	No
9-month all-oral	Yes	No	No	No	Yes – except TB meningitis, miliary TB, osteoarticular TB and pericardial TB	Yes
Longer individualized 18-month	Yes[a]/No	Yes[a]/No	Yes	Yes	Yes	Yes
Additional factors to be considered if several regimens are possible	Drug intolerance or adverse events					
	Treatment history, previous exposure to regimen component drugs or likelihood of drug effectiveness					
	Patient or family preference					
	Access to and cost of regimen component drugs					

BPaL: bedaquiline, pretomanid and linezolid; BPaLM: bedaquiline, pretomanid, linezolid and moxifloxacin; CNS: central nervous system; MDR/RR-TB: multidrug- or rifampicin-resistant TB; TB: tuberculosis; XDR-TB: extensively drug-resistant TB.

[a] When 6-month BPaLM/BPaL and 9-month regimens could not be used.

Summary of DR-TB management based on WHO recommendations:

- The use of a 6-month treatment regimen composed of bedaquiline, pretomanid, linezolid (600 mg) and moxifloxacin (BPaLM) rather than the 9-month or longer (18-month) regimens in MDR/RR-TB patients.
- The use of the 9-month all-oral regimen rather than longer (18-month) regimens in patients with MDR/RR-TB and in whom resistance to fluoroquinolones has been excluded.
- In MDR/RR-TB patients on longer regimens, all three Group A agents and at least one Group B agent should be included to ensure that treatment starts with at least four TB agents likely to be effective, and that at least three agents are included for the rest of the treatment if bedaquiline is stopped. If only one or two Group A agents are used, both Group B agents are to be included.
- If the regimen cannot be composed with agents from Groups A and B alone, Group C agents are added to complete it.

6.7 Pre-XDR and XDR-TB treatment regimens

For Pre-XDR cases, fulfilling the eligibility criteria, 6-month BPaL will be the preferred option.

The recommended regimen for Pre-XDR and XDR-TB will be:

Option 1 (Pre-XDR-TB only)
BPaL: 6 Bdq+Pa+Lzd

Option 2 (Pre-XDR and XDR-TB)
Initial phase: 6 Bdq+Lzd+Cfz+Cs+E+Z
Continuation phase: 14 Lzd+Cfz+Cs+E+Z

Bdq-bedaquiline; Lzd-linezolid; Cfz-clofazimine; Cs-cycloserine; E-ethambutol; Z-pyrazinamide.

6.8 Treatment regimens for the management of mono and poly resistant TB

Table 6.4 Pattern of resistance and recommended regimen

Pattern of drug resistance	Regimen	Minimum duration Rx (Month)	Comments
H	R, Z, E and levofloxacin OR 4FDC and Lfx	6	**If smear is positive, use Xpert MTB/RIF at month 2 and 3** if rifampicin resistance is found; switch to full MDR-TB treatment.
H & E	R, Z and FQ	9–12	**If smear is positive, u**se Xpert MTB/RIF at month 2 and 3 if rifampicin resistance is found; switch to full MDR-TB treatment. Some experts recommend using a second-line injectable agent for the first three months.
H, E, Z,	R, FQ, plus ethionamide, plus a second-line injectable agent for the first 2-3 months (+/- Z)	18	A longer course (6 months) of the second-line injectable may strengthen regimen for patients with extensive disease. Z should be added if resistance is uncertain. **If smear is positive,** use Xpert MTB/RIF at month 2 and 3 if Rifampicin resistance is found; switch to full MDR-TB treatment and check DST to second-line anti-TB drugs. If culture positive after month 2, repeat DST to first- and second-line anti-TB drugs.
R mono- or poly-drug resistance	Full MDR-TB regimen	20	shorter or oral longer regimen

***Culture follow up to be done at 2, 5 and 6-month for all INH resistance.**

The use of Xpert MTB/RIF at month 2 and 3 is NOT intended for monitoring response to therapy as the test may be positive for M. tuberculosis for patients with a positive response and even after cure. Rather, it is intended only to detect rifampicin amplification during therapy.

Regimen for rifampicin susceptible and isoniazid resistant TB

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

All medicines in this regimen are to be used daily for 6 months. 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.

For logistics simplicity, H containing 4 FDC may be used in the regimen along with FQ without counting H as an effective drug.

6.9 Newer drugs for treatment of drug-resistant TB in the country

New medicines: Novel medicines

i. Bedaquiline
ii. Delamanid
iii. Pretomanid

Repurpose medicines: Old medicines for new indications

i. Linezolid

6.9.1 Bedaquiline

This is a new class of drug, diarylquinoline that specifically targets mycobacterial ATP synthase, a crucial enzyme for mycobacterium tuberculosis growth.

i. Dose

Adults: dosing could be either daily throughout treatment: 200 mg once daily for 8 weeks followed by 100 mg once daily or daily 400 mg once daily for 2 weeks for loading dose and 200 mg three times per week following up

Children (Refer pediatric TB management guideline for details)

If a dose is missed during the first 2 weeks of treatment, patients should not make up the missed dose but should continue the usual dosing schedule. From week 3 onwards, if a 200 mg dose is missed, patients should take the missed dose as soon as possible and then resume the 3 times a week regimen.

Special circumstances

Use in pregnancy/breastfeeding: new findings recommended during pregnancy or breastfeeding. Reproduction studies performed in rats and rabbits have revealed no evidence of harm to the foetus.

Use in renal disease: No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution).

Use in hepatic disease: No dosage adjustment is required in patients with mild to moderate hepatic impairment. Dosing and toxicity not well established in severe hepatic impairment, use with caution and only when the benefits outweigh the risks.

ii. Adverse reactions

Common: Gastrointestinal distress (nausea, vomiting, abdominal pain, loss of appetite), joint pain (arthralgia), headache. (Note: haemoptysis and chest pain were also more frequently reported in the group receiving bedaquiline than in the placebo treatment group).

Less common: QT prolongation, hyperuricaemia, phospholipidosis (the accumulation of phospholipids in the body's tissues), elevated aminotransferases. Possibly, an increased risk of pancreatitis.

iii. Contraindications/Caution

Do not use or discontinue bedaquiline

- Clinically significant ventricular arrhythmia.
- A QTcF interval of >500 ms (confirmed by repeat ECG).
- Severe liver disease
- Abnormal electrolytes

Use with caution in the following situations (with more frequent ECG monitoring and evaluation of risk versus benefit):

- Use with other QT prolonging drugs (see drug interactions)
- A history of torsade de pointes
- A history of congenital long QT syndrome
- A history of hypothyroidism and bradyarrhythmias
- A history of uncompensated heart failure
- Serum calcium, magnesium or potassium levels below the lower limits of normal

iv. Monitoring

An ECG should be obtained before initiation of treatment, and at least 2, 4, 8, 12 and 24 weeks after starting treatment. More frequently if heart conditions, hypothyroidism or electrolyte disturbances are present. Liver function tests should be done monthly.

Baseline potassium, calcium, magnesium needs to be done.

6.9.2 Pretomanid

Pretomanid is a new chemical entity and a member of a class of compounds known as nitroimidazooxazines. Novel compounds are important in pursuing new TB treatments because resistance to drugs and drug classes currently used to treat TB is widespread. During early development, pretomanid was referred to as PA-824. Pretomanid was developed by TB Alliance as an oral tablet formulation for the treatment of tuberculosis in combination with other anti-tuberculosis agents.

Dose: Pretomanid Tablet 200 mg orally once daily for 26 weeks to be swallow whole with water. Only to be used as part of the BPaLM/BPaL regimen, together with bedaquiline and linezolid

Most common adverse reactions (≥10%) **are peripheral neuropathy, acne, anemia, nausea, vomiting, headache, increased transaminases, dyspepsia, decreased appetite, rash, pruritus, abdominal pain, pleuritic pain, increased gamma-glutamyltransferase, lower respiratory tract infection, hyperamylasemia, hemoptysis, back pain, cough, visual impairment, hypoglycemia, abnormal loss of weight, and diarrhea.**

The addition of pretomanid to antituberculosis drug regimens has been linked to an increased rate of transient **serum liver test abnormalities during treatment and to several instances of mild, clinically apparent liver injury**.

Myelosuppression was reported with the use of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid. Monitor complete blood counts. Decrease or interrupt linezolid dosing if significant myelosuppression develops or worsens.

Peripheral and optic neuropathy were reported with the use of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid. Monitor visual function. Obtain an ophthalmologic evaluation if there are symptoms of visual impairment. Decrease or interrupt linezolid dosing if neuropathy develops or worsens.

QT prolongation was reported with the use of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid. Use with drugs that prolong the QT interval may cause additive QT prolongation. Monitor ECGs. Discontinue the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid if significant ventricular arrhythmia or if QTcF interval prolongation of greater than 500 ms develops.

Reproductive effects: Pretomanid caused testicular atrophy and impaired fertility in male rats. Advise patients of reproductive toxicities seen in animal studies and that the potential effects on human male fertility have not been adequately evaluated.

Lactic acidosis was reported with the use of the combination regimen of Pretomanid Tablets, bedaquiline, and linezolid. Consider interrupting linezolid or the entire combination regimen of Pretomanid Tablets, bedaquiline, and linezolid dosing if significant lactic acidosis develops.

6.9.3 Delamanid

Delamanid has a potent in vitro bactericidal activity and potential sterilizing activity; it is thought that nitroimidazooxazole derivatives generate reactive nitrogen species, including nitrogen oxide, which are responsible for cell poisoning in low metabolic states. There is no age restriction for use of delamanid and there are currently dispersible formulations that are preferred over crushing and dispersing adult tablets. Delamanid is strongly bound to plasma proteins, resulting in low CNS penetration; however, studies in humans and animals with CNS TB suggest that delamanid could potentially play a beneficial role when other options are not available.

The recent data review for the WHO guidelines suggested that there are no additional safety concerns for concurrent use of delamanid with bedaquiline. Studies undertaken between 2020 and 2022 had shown no increased toxicity with the use of delamanid beyond 6 months; they showed safety on the concomitant use of delamanid with bedaquiline, while increasing rates of survival of patients with restricted therapeutic options.

Animal data show no evidence of teratogenicity. Although the case series of pregnant women on delamanid are small, all children had excellent birth outcomes, suggesting that pregnant women in need should not be denied access to delamanid. It can be considered for the treatment of DR-TB in pregnant women with restricted therapeutic options.

i. Dose

Adults: 100 mg twice daily for 24 weeks.

Children: The recommended dose of delamanid in children aged >2 years (25 mg bd in 3–5 years; 50 mg bd in 6–11 years; 100 mg bd in 12–17 years) for 6 months.

Special circumstances

Use in renal disease: No dosage adjustment is required in patients with mild to moderate renal impairment. Dosing not established in severe renal impairment, use with caution and only when the benefits outweigh the risks.

Use in hepatic disease: No dosage adjustment is required in patients with mild to moderate hepatic impairment. Dosing and toxicity not well established in severe hepatic impairment, use with caution and only when the benefits outweigh the risks.

ii. Adverse reactions

Common: The most frequently observed adverse drug reactions in patients treated with delamanid (i.e. incidence > 10%) are nausea (38.3%), vomiting (33%), and dizziness (30.2%).
Less common: QT prolongation.

iii. Contraindications/caution

Do not use or discontinue delamanid

• Clinically significant ventricular arrhythmia.

- A QTcF interval of > 500 ms (confirmed by repeat ECG).
- Severe liver disease.
- Serum Albumin less than 2.8.
- Abnormal electrolytes.

Use with caution in the following situations (with more frequent ECG monitoring and evaluation of risk versus benefit):

- Use with other QT prolonging drugs (see drug interactions).
- A history of torsade de pointes.
- A history of congenital long QT syndrome.
- A history of hypothyroidism and bradyarrhythmias.
- A history of uncompensated heart failure.
- Serum calcium, magnesium, or potassium levels below the lower limits of normal.
- Use with caution in patients sensitive to lactose.

iv. Monitoring:

An ECG should be obtained before initiation of treatment, and at least 2, 4, 8, 12, and 24 weeks after starting treatment with delamanid. Monitoring ECGs should be done monthly if taking other QT prolonging drugs (i.e moxifloxacin, clofazimine, etc).

6.9.4 Linezolid

Linezolid is a synthetic antibiotic of the class oxazolidinones useful in the treatment of gram-positive including Methicillin-resistant Staphylococcus aureus (MRSA), Vancomycin-resistant Enterococci (VRE) and penicillin resistant strains of streptococcus pneumonia. Linezolid should be reserved for infections caused by multidrug resistant bacteria.
It inhibits the bacterial protein synthesis by acting at early step. Linezolid is a weak monoamine oxidase inhibitor so it significantly interacts with some foods and drugs.

i. **Dose:** 600mg daily and in patients with toxicity it can be reduced to 300 mg daily.

ii. **Adverse effects**: diarrhoea, nausea, vomiting, headaches, visual disturbances, discolored tongue, anaemia, peripheral neuropathy, bone marrow suppression and lactic acidosis.

Peripheral neuropathy is quite common after prolonged use and if occurs it should be stopped and not reintroduced.

iii. **Important drug interactions:** Patients with selective serotonin reuptake inhibitors (SSRIs) have been reported to cause serotonin syndrome when taken concurrently with linezolid.

Lactic acidosis has been associated with the use of linezolid.

iv. **Contraindication**: Hypersensitivity and within 14 days of monoamine oxidase (MAO) inhibitors.

CHAPTER 7

MANAGEMENT OF DS-TB & DR-TB WITH CO-MORBIDITIES/SPECIAL SITUATION

7.1 TB and HIV Co-infection

The Human Immunodeficiency Virus (HIV) destroys the immune system of an individual. HIV-positive individual infected with TB bacilli is more likely to become sick with TB than HIV-negative individuals infected with TB bacilli. HIV and TB form a lethal combination, each speeding the progress of the other. TB is a leading cause of death among people who are HIV-positive. HIV is the most potent factor known to increase the risk of progressing from latent tuberculous infection to tuberculous disease. In an HIV negative patient infected with *M. tuberculosis*, the life time risk of developing tuberculosis is only 10%, whereas in person dually infected with TB and HIV is 50%.

Tuberculosis is the most life-threatening opportunistic infection associated with HIV infection. It is the leading cause of death among people who are HIV positive and accounts for more than one-third of AIDS deaths worldwide.

7.2 Features of HIV related TB

TB usually occurs earlier in the course of HIV infection compared to other opportunistic infections associated with HIV. It may, however, occur at any stage of HIV infection as the result of a rapid progression of a recently acquired or latent infection. Among HIV infected people, TB infection results in a transient drop in CD4 count and a progression of the HIV infection.
As the HIV infection progresses, the CD4 lymphocyte count declines and the immune system is less efficient in preventing the growth and spread of *M. tuberculosis*. As a result, disseminated and extra-pulmonary disease is more common in HIV positive patients than in HIV negative patients. Nevertheless, pulmonary TB is still the most common form of TB seen in HIV infected patients, with or without concomitant EPTB.

7.3 Pulmonary TB in HIV

The presentation of pulmonary TB in HIV infected individuals depends on the stage and the degree of immune-suppression. The clinical picture, sputum result, and chest X-ray appearance often differ in early and late HIV infection.

Table 7.1 Features of PTB in HIV infection depending on the stage

Features of PTB	**Stages of HIV infection**	
	Early (CD4 > 350)	Late (CD4 < 350)
Clinical picture	Often resembles post primary PTB	Often resembles primary TB
Sputum smear result	Often positive	Often negative
Chest X-ray	• Often rare cavities • Lymphadenopathy usually absent • Pleural effusion rare	• Rare cavities • Often infiltrates • Lymphadenopathy and pleural effusion often present

7.4 Diagnosis

The diagnosis of TB in HIV infected patients is often difficult because:

- The sputum smear examinations tend to be more often negative, particularly in the late stages of HIV infection
- X-ray abnormalities are often atypical
- The Tuberculin Skin Test (TBST) is often negative due to immune-suppression

If TB is suspected in HIV infected people, their sputum should be tested using Xpert MTB/RIF and followed by culture & DST. Other investigations include CXR, tissue biopsy, aspirations from suspected extra-pulmonary sites for cytology, histology, direct smear, and culture for mycobacteria and Xpert MTB/RIF.

7.5 TB Treatment and Anti-retro viral therapy (ART)

- In a TB/HIV co-infection, the priority is to treat TB. When patients on anti-TB drugs are started on anti-retroviral drugs, paradoxical exacerbation of symptoms, signs, and radiographic manifestations of TB may be seen. **This is known as Immune Reconstitution Inflammatory Syndrome (IRIS). To prevent IRIS, the** current WHO guidelines recommend that TB treatment should be commenced first, and ART should be commenced within;
    - 2 weeks of starting anti-TB treatment irrespective of CD4 count
    - In the case of TB meningitis, delay the initiation of ART by minimum of 4 weeks after ATT is initiated.
    - If patients with HIV who are already on ART gets TB, continue ART and start anti-TB treatment at the earliest.

Immune Reconstitution Inflammatory Syndrome (IRIS)

Adverse effects and drug-drug interactions are much more common in PLHIV. The multiple medicines involved in drug-resistant TB with recognized high toxicity risks, often combined with ART, results in a high incidence of adverse effects. Such patients are at increased risk of immune response inflammatory syndrome (IRIS).

IRIS is relatively common in mild to moderate forms in patients with TB started on ART (seen in up to one third of patients in some studies); however, it is relatively rare in its severe forms. This syndrome can present as a paradoxical worsening of the patient's clinical status, often due to a previously subclinical and unrecognized opportunistic infection. These reactions may present as fever, enlarging lymph nodes, worsening pulmonary infiltrates, respiratory distress, or exacerbation of inflammatory changes at other sites. It generally presents within three months of the initiation of ART and is more common with a low CD4 cell count (<50 cells/mm3). Patients with advanced AIDS may show clinical deterioration for a number of other reasons. New opportunistic infections or previously subclinical infections may be unmasked following immune reconstitution and cause clinical worsening. The management of IRIS is complex and depends on the clinical status of the patient and the site and extent of involvement. Various treatment modalities have been employed, including non-steroidal anti-inflammatory drugs (NSAIDs) in mild disease and corticosteroids in moderate to severe disease. Most patients can be treated without interruption of ART.

Anti-TB treatment regimen in HIV positive TB patients is the same as for HIV negative TB patients. However, for patients whose ART regimen contains protease inhibitor, rifabutin is preferred over rifampicin.

It is more common for adverse reactions to occur in HIV positive patients due to anti-TB drugs and for drug interactions to occur between anti-TB and anti-retroviral drugs.

For Bhutan, the first line ART consists of 3TC+TDF+ DTG. Tenofovir Dixoproxil Fumerate (TDF) and Lamuvidine does not have substantial interaction with Rifampicin, so can be co-administered with Rifampicin. **However, coadministration of Rifampicin with Dolutegravir (DTG) will decrease the concentration of Dolutegravir and therefore dose adjustment of Dolutegravir is needed (50 mg twice daily).**

For patients whose ART regimen contains protease inhibitor, rifabutin is preferred over rifampicin. Rifampicin stimulates the activity of cytochrome P450 which metabolizes protease inhibitors (PIs) e.g. saquinavir, ritonavir, indinavir, nelfinavir, amprenavir), non-nucleoside reverse transcriptase inhibitors (NNRTI), except for efavirenz (EFV).

ART regimen for TB-HIV Co-infection:

- **First line:**
  3TC+TDF+ DTG (50mg q12h)
- **Alternative regimen:**
  3TC+TDF+ EFV (600mg q24h)

- The rate of recurrence of TB after completion of treatment is higher in HIV positive patients than in HIV negative TB patients.
- The case fatality rate is higher in HIV positive TB patients than in HIV negative TB patients. The excess deaths in TB/HIV patients are partly due to the tuberculosis disease itself and partly due to other HIV related problems.
- For TPT prophylaxis refer chapter 11 on TB Infection (Table 11.4)
- **Co-trimoxazole Preventive Therapy (CPT), (Co-trimoxazole 960 mg OD, should be provided for all patients with active TB and HIV irrespective of CD4 count and should be continued till the completion of ATT treatment. Thereafter CPT will be administered as per CD4 criteria.**

7.6 Screening of TB patients for HIV

All TB patients should be screened for risk behaviour that may lead to HIV infection at the time of diagnosis or, if not screened at the initial visit, at a subsequent visit. Screening should be done as provider-initiated counseling and testing.

Counseling should be done by the Medical Officer or by the Nursing staff. In case a patient is detected to be HIV positive, he/she should be referred to the VCT/HIV treatment and care unit for a confirmatory test or for HIV care services. After taking informed consent from the patient, pre- and post-test counseling should be conducted. This also should be recorded in the standard Treatment Card that is kept in the patient's file.

7.7 Screening of HIV patients for TB

All HIV infected patients should be screened for TB at the time of the diagnosis and whenever it is suspected. **All HIV positive cases should undergo chest X-ray and Xpert MTB/RIF as an initial test.** For those patients who are found to have tuberculous disease, anti-TB treatment should be commenced immediately. HIV patients who are already on ART and diagnosed subsequently with TB may need a change in ART regimen when they start anti-TB drugs.

To strengthen collaborations between NTCP and NACP, the following activities will be undertaken:

- Joint review of the programmes at National and sub-national level twice a year

- TB training modules will have a section on TB-HIV co-infection and vice-versa. The training on relevant section will be held in coordination with both programmes.
- Both programmes will plan joint supervisory visits, once a year from the national level and twice a year at the dzongkhag level
- Offer VCT to all TB patients and record TB-HIV activities such as ART, CPT and IPT for HIV positive patients

7.8 MDR-TB with HIV Co-Infection

Drug-resistant TB is often associated with higher mortality rates in people living with HIV (PLHIV). Moreover, HIV co-infection is common among DR-TB. Therefore, management of HIV and DR-TB should be integrated. Early diagnosis of drug-resistant TB and HIV, prompt initiation of appropriate second line anti-TB drugs and antiretroviral treatment (ART), sound patient support, and strong infection control measures are all essential components in the management of drug-resistant TB in PLHIV.
A provider-initiated HIV testing and counselling in all patients with presumed or diagnosed drug-resistant TB should be performed. Mycobacterial cultures will also be used in HIV-positive TB symptomatic who are Xpert MTB/RIF negative but have strong suspicion of TB.

ART should be started promptly in all HIV-infected patients with MDR-TB regardless of CD4 cell count. Second-line anti-TB drugs should be initiated first, followed by ART as soon as second-line anti-TB drugs are well tolerated. **Generally, this should be within the first 8 weeks of initiating MDR-TB treatment and within 2 weeks if CD4 counts are less than 50/mm^3**.
The composition of the treatment regimen for MDR-TB does not usually differ substantially for people living with HIV. A few drug-drug interactions may be avoided with careful attention (e.g. bedaquiline and efavirenz).

The shorter regimen for MDR-TB is not recommended for treatment of extra-pulmonary disease in PLHIV.

Table 7.2 Potential overlapping and additive toxicities of ART and anti-TB treatment

Toxicity	Antiretroviral agent	Anti-TB antigen	Comments
Skin rash	ABC, NVP, EFV, d4Tand others	H, R, Z, PAS, Fluoroquinolones, and others	Don't re-challenge with ABC (can result in life-threatening anaphylaxis). Do not re-challenge with any agent that may have caused Stevens-Johnson syndrome. Also consider co-trimoxazole as a cause of skin rash if the patient is receiving this medication. thioacetazone is contraindicated in HIV because of the risk of life-threatening rash.

Peripheral neuropathy	d4T, ddI	Lzd, Cs, H, aminoglycosides Eto/Pto, E	Avoid use of D4T or ddI in combination with Cs or Lzd because of an increased risk of peripheral neuropathy; If these agents must be used in combination and peripheral neuropathy does develop, replace anti-retrovirals with a less neurotoxic agent. Patients taking H, Cs or Lzd should receive prophylactic pyridoxine.
Central nervous system (CNS) toxicity	EFV	Cs, H, Eto/Pto, FQ	EFV has a high rate of CNS side effects (dizziness, impaired concentration, depersonalization, abnormal dreams, insomnia and confusion) in the first 2–3 weeks of use, but typically resolve on their own. If these effects do not resolve, consider substitution of the agent. At present, there are limited data on the use of EFV with Cs; concurrent use is the accepted practice as long as there is frequent monitoring for central nervous system toxicity. Frank psychosis can occur with Cs but is rare with EFV alone; other causes should always be ruled out.
Depression	EFV	Cs, FQ, H, Eto/Pto	Severe depression can be seen in 2.4% of patients receiving EFV. Consider substitution of EFV if severe depression develops.
Headache	AZT, EFV	Cs, Bdq	Rule out more serious causes of headache, such as bacterial meningitis, cryptococcal meningitis, central nervous system toxoplasmosis, etc. Use of analgesics (ibuprofen, paracetamol) and good hydration may help. Headaches secondary to AZT, EFV and Cs are usually self-limited.
Nausea and vomiting	RTV, d4T, NVP, and most others	Eto/Pto, PAS, H, Bdq, E, Z and others	Persistent vomiting and abdominal pain may be a result of developing lactic acidosis (especially common with long-term d4T use) and/or hepatitis secondary to medications.
Abdominal pain	All antiretroviral have been associated with abdominal pain	Eto/Pto, PAS	Abdominal pain is a common adverse effect and often benign; however, abdominal pain may be an early symptom of severe side effects, such as pancreatitis, hepatitis or lactic acidosis (especially common with long-term d4T use.
Pancreatitis	d4T, ddI	Lzd	Avoid use of these agents together. If an agent causes pancreatitis, suspend it permanently and do not use any of the potentially pancreatitis-producing antiretrovirals (d4T or ddI) in the future. Also consider gallstones or excessive alcohol use as potential causes of pancreatitis.
Diarrhoea	All protease inhibitors, ddI (buffered formulation)	Eto/Pto, PAS, FQ	Diarrhoea is a common adverse effect. Also consider opportunistic infections as a cause of diarrhoea, or Clostridium difficile (pseudomembranous colitis).

Hepatotoxicity	NVP, EFV, all protease inhibitors (RTV > others), all NRTIs	H, R, E, Z, Bdq, PAS, Eto/ Pto, FQ	Also see Section on hepatotoxicity treatment related to second-line anti-TB drugs. When severe, stop both the ART and TB medications, and restart the TB medications first. Also consider co-trimoxazole as a cause of hepatotoxicity if the patient is receiving this medication. Also rule out viral etiologies as cause of hepatitis (hepatitis A, B, C, and CMV).
Lactic acidosis	d4T, ddI, AZT, 3TC	Lzd	If an agent has caused hyperlactataemia (i.e. high lactate) or lactic acidosis, replace it with an agent less likely to cause lactic acidosis. Note: the goal should always be early detection and management of hyperlactataemia to prevent development of lactic acidosis.
Renal toxicity	TDF (rare)	Aminogly cosides, Cm	TDF may cause renal injury with the characteristic features of Fanconi syndrome, hypophosphataemia, hypouricaemia, proteinuria, normoglycaemic glycosuria and, in some cases, acute renal failure. Avoid TDF in patients receiving aminoglycosides or Cm. If TDF is absolutely necessary, serum creatinine and electrolytes should be monitored frequently (at least every two weeks). Even without the concurrent use of TDF, HIV-infected patients have an increased risk of renal toxicity secondary to aminoglycosides and Cm. Frequent creatinine and electrolyte monitoring is recommended. In the presence of renal insufficiency, antiretrovirals and anti-TB medications need to have their doses adjusted.
Nephrolithiasis	IDV	None	No overlapping toxicities regarding nephrolithiasis have been documented between ART and anti-TB medications. Adequate hydration prevents nephrolithiasis in patients taking IDV. If nephrolithiasis develops while on IDV, substitute with another protease inhibitor.
Electrolyte disturbances	TDF (rare)	Cm, amino-glycosides	Diarrhoea and/or vomiting can contribute to electrolyte disturbances. Even without the concurrent use of TDF, HIV-infected patients have an increased risk of both renal toxicity and electrolyte disturbances secondary to aminoglycosides and Cm.
Bone marrow suppression	AZT	Lzd, R, RFB, H	Monitor blood counts regularly. Replace AZT if bone marrow suppression develops. Consider suspension of Lzd. Also consider co-trimoxazole as a cause if the patient is receiving this medication. Consider adding folinic acid supplements, especially if the patient is receiving co-trimoxazole.

Optic neuritis	ddI	E, Eto/Pto (rare)	Suspend agent responsible for optic neuritis permanently and replace with an agent that does not cause optic neuritis.
Hyperlipidaemia	Protease inhibitors, EFV	None	No overlapping toxicities regarding hyperlipidaemia have been documented between antiretrovirals and anti-TB drugs.
Lipodystrophy	NRTIs (especially d4T and ddI	None	No overlapping toxicities regarding lipodystrophy have been documented between antiretrovirals and anti-TB drugs.
Dysglycaemia (disturbed blood sugar regulation)	Protease inhibitors	Gfx, Eto/Pto	Protease inhibitors tend to cause insulin resistance and hyperglycaemia. Eto/Pto tends to make insulin control in diabetics more difficult, and can result in hypoglycaemia and poor glucose regulation.
Hypothyroidism	d4T	Eto/Pto, PAS	There is potential for overlying toxicity, but evidence is mixed. Several studies show subclinical hypothyroidism associated with some antiretrovirals, particularly stavudine (d4T). PAS and Eto/ Pto, especially in combination, can commonly cause hypothyroidism.
Arthralgia	Indinavir, other protease inhibitors	Z, BDQ	Protease inhibitors can cause arthralgia and there have been case reports of more severe rheumatologic pathology. Arthralgias are very common with Z and has been reported as one of the most frequent adverse effects (>10%) in controlled clinical trials with Bdq.
QT Prolongation	ART has been associated with QTc prolongation	Bdq, Mfx, Gfx, Cfz, Lfx, Ofx	ARV therapy does appear to confer a significant increased risk of QTc prolongation in HIV-positive patients but data is sparse. The additive effects of combining ART with the known second-line anti-TB drugs in respect to QTc prolongation is not known

Monitoring needs to be more intense for both responses to therapy and adverse effects. **Co-trimoxazole Preventive Therapy (CPT), (Co-trimoxazole 960 mg OD, should be provided for all patients with active MDR-TB and HIV irrespective of CD4 count and should be continued till the completion of ATT treatment. Thereafter CPT will be administered as per CD4 criteria.** There are overlapping toxicities between ART, second-line anti-TB drugs, and co-trimoxazole, so patients should be monitored closely.

7.9 Management of DS-TB in special situations

The treatment of TB in pregnancy and breastfeeding, liver disorders, and renal failure is discussed below:

7.9.1 Pregnancy and breastfeeding

Women of childbearing age should be asked about current or planned pregnancy before starting TB treatment. A pregnant woman should be advised that successful treatment of TB with the standard regimen is important for a successful pregnancy outcome. First line anti-TB drugs are safe for use in pregnancy.

A breastfeeding woman who has TB should receive a full course of TB treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to the baby. Mother and baby should possibly be isolated; however, the baby should continue to breastfeed.

After active TB in the baby has been ruled out, the baby should be given 6 months of TB Preventive Treatment (TPT) and BCG vaccination. Mother should use face mask while breastfeeding and breast feed in a well-ventilated room. Pyridoxine supplementation (25mg) is recommended for all pregnant or breastfeeding women taking isoniazid.

Pregnant women are to be treated and started on ATT regimen similar to new

Breast feeding

Breast milk is not contraindicated in all circumstances of TB exposure in newborns. The **WHO recommends to breast feed all the neonates irrespective of tuberculosis status in mother.** However, TB infection control practices must be adhered to all the times. If mother is sputum positive, continue breast feeding and all efforts should be made to reduce transmission by letting mother use facemask with normal surgical mask, cough etiquette and hand hygiene. If mother is MDR-TB, give expressed breast milk or formula feed if mother is unable to produce breast milk.

7.9.2 Liver disorders/Drug induced liver injury (DILI)

Isoniazid, rifampicin and pyrazinamide may cause hepatotoxicity with Pyrazinamide being the most hepatotoxic.

After the initiation of ATT, in cases where aminotransferase are five or more times higher than the upper limit of normal (with or without symptoms), or three or more times higher in the presence of symptoms or jaundice (i.e. bilirubin >3 mg/dL), the treatment should immediately be withdrawn. The responsible drugs should be identified, and a sequential reintroduction implemented once enzyme levels have returned to normal. The drug reintroduction should be performed one drug at a time, starting with the drug considered to be the least hepatotoxic, as follows:

- when aminotransferases return to less than two times the upper limit of normal, rifampicin may be restarted with ethambutol;
- after 3–7 days, after checking aminotransferases, isoniazid may be reintroduced, with subsequent rechecking of liver enzymes; and
- if symptoms recur or aminotransferases increase again, the last drug added should be stopped and replaced with another from the list of the recommended drugs. If the clinical pattern indicates cholestasis, rifampicin may be the responsible drug. If the patient has prolonged or severe hepatotoxicity but tolerates isoniazid and rifampicin, a re-challenge with pyrazinamide may be hazardous. In this situation, pyrazinamide may be permanently discontinued, with treatment eventually extended to 9 months.

Chronic liver disease (CLD)

In people with DS-TB and Chronic liver disease (CLD), evaluation of the degree of impairment of the liver function is necessary, to design the best possible regimen that is sufficiently effective while not being aggressive for the liver. The NTP should ensure a stock of individual formulations to manage patients with CLD who are unable to tolerate the standard recommended regimens. Experts recommend monitoring aminotransferases (i.e. alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) on a weekly basis initially, and fortnightly after the second month of treatment in patients with CLD. Expert consultation is advised in treating patients with advanced or unstable liver disease. TB itself may involve the liver and cause abnormal liver function.

The Child–Turcotte–Pugh (CTP) score is based on albumin, bilirubin, prothrombin time/international normalized ratio (PT/INR), ascites and encephalopathy. The CTP score can be used as a predictor of tolerance to anti-TB drugs and the treatment outcome, as shown in the Table below

Table 7.3 CTP score parameters

	1 point	2 points	3 points
Ascitis	None	Mild	Moderate to severe
Serum albumin (g/dl)	>3.5	2.8–3.5	<2.8
Bilirubin, total (mg/dl)	<2	2–3	>3
Hepatic encephalopathy	No	Grade I–II	Grade III–IV
Prothrombin time (INR)	<1.7	1.7–2.3	>2.3

CTP: Child–Turcotte–Pugh; INR: international normalized ratio.

Table 7.4 Estimated survival at 1 and 2 years based on CTP

Class	Score points	Survival after 1 year (%)	Survival after 2 years (%)
A	5–6	100	85
B	7–9	80	60
C	10–15	45	35

CTP: Child–Turcotte–Pugh.

In people with DS-TB with

- mild CLD (CTP ≤7 or Child class A), a treatment regimen containing two hepatotoxic drugs can be given that includes Isoniazid, Rifampicin and Ethambutol. In this situation

two months of intensive phase with Isoniazid, Rifampicin and Ethambutol followed by seven months of Isoniazid and Rifampicin should be given

- more severe CLD (CTP 8–10 or Child class B), a treatment regimen containing one hepatotoxic drug (Rifampicin, Ethambutol and Levofloxacin OR Isoniazid, Ethambutol and Levofloxacin for 12 to 18 months) should be given.
- very advanced (CTP ≥11 or Child class C), a treatment regimen containing no hepatotoxic drug (Ethambutol, Fluoroquinolone (Lfx) and injectable aminoglycoside for 18-24 months should be given.

Table 7.5 Recommended TB regimens for patients with Chronic liver disease

Regimens	Initial phase	Continuation phase
Two hepatotoxic drugs	HRE 2 months	HR 7 months
One hepatotoxic drug	Lfx-HE OR Lfx-RE 12 -18 months	
No hepatotoxic drugs	18-24 months ethambutol and fluoroquinolone (Lfx) (note: aminoglycoside can be given for a minimum of 18-24 months)	

7.9.3 Renal failure and severe renal insufficiency

The recommended initial TB treatment regimen for patients with renal failure or severe renal insufficiency is 2 months of isoniazid, rifampicin, pyrazinamide and ethambutol, followed by 4 months of isoniazid and rifampicin. No change in dosing is necessary because Isoniazid and rifampicin are eliminated by biliary excretion. There is significant renal excretion of ethambutol and metabolites of pyrazinamide, and therefore doses should be adjusted.

Patients with DS-TB on dialysis, a thrice-weekly dosing of pyrazinamide and ethambutol should be administered after the dialysis cycle. Dose adjustments in adults with creatinine clearance below 30 mL/minute are as follows (unless otherwise indicated):

- Pyrazinamide: 25–35 mg/kg per dose, three times per week after dialysis.
- Ethambutol: 15–25 mg/kg per dose, three times per week after dialysis.
- Rifapentine and moxifloxacin, which are both used in regimens for DS-TB, do not require renal dose adjustment.

Given the risk of QT prolongation (particularly due to moxifloxacin) and electrolyte imbalance, an ECG should be performed. Electrolyte imbalance particularly hypokalaemia and hypomagnesaemia should be corrected.

In order to prevent peripheral neuropathy in renal insufficient patients receiving isoniazid, pyridoxine should be given.

7.9.4 Tuberculosis and Diabetes

Patients with diabetes specifically uncontrolled diabetes is more vulnerable to develop TB. Studies have shown that there is increased morbidity and mortality in patients who have TB diabetes co-morbidity. Poorly controlled diabetes can lead to multiple complications, including vascular disease, neuropathy and increased susceptibility to infection. For this reason, early diagnosis of TB in diabetics, exclusion of diabetes and proper control of diabetes in patients with TB is important to improve the outcome of TB treatment.

Treatment of TB in those suffering from diabetes is the same as for non-diabetics. It is important to assess renal function. Patients with renal function impairment should be managed in consultation with an expert.

Although TB can cause glucose intolerance and might predispose patients to diabetes mellitus, the drugs used to treat tuberculosis might also worsen glycaemic control in patients with diabetes. Overlapping toxicities, such as peripheral neuropathy caused by treatment with isoniazid, must also be considered when co-managing tuberculosis and diabetes. Given the risk of peripheral neuropathy, pyridoxine should be given with isoniazid for tuberculosis treatment in diabetic patients.

Just as tuberculosis drug treatment affects diabetes treatment, anti-diabetics might alter the pharmacokinetics of anti-tuberculosis drugs. Diabetes can also cause changes in oral absorption, decreased protein binding of drugs, renal insufficiency, or a fatty liver with impaired drug clearance. Its effect on tuberculosis drug concentrations has not been formally studied. Therapeutic drug monitoring might be considered in cases with poor response to treatment in diabetic patients with tuberculosis.

Oral hypoglycaemic agents are not contraindicated during the treatment of tuberculosis but may require increase in the dosage due to drug interactions; shift to insulin might be required in some cases.

7.10 Management of drug-resistant TB in special populations and situations

This topic outlines the management of drug-resistant TB in selected special conditions and situations including HIV co-infection. The special conditions would generally entail careful administration of drugs as well as monitoring of response. Some of the situations may call for altered doses or regimen of drugs.

7.10.1. Pregnancy

Most pregnant patients should be started on treatment as soon as the diagnosis is made. However, treatment may be delayed until the second trimester when the patient is very stable with minimum disease to minimize teratogenic effects of second line drugs**. The 9 month all oral RR/MDR regimen with Linezolid can be offered during pregnancy whereas ethionamide containing 9 month all oral RR/MDR regimen is contraindicated during pregnancy**. The

longer regimen devised for non-pregnant adults earlier may be used or individualized regimen may be constructed.
It is also recommended to avoid **ethionamide** as it can increase the risk of nausea and vomiting associated with pregnancy, and teratogenic effects have been observed in animal studies.

7.10.2. Lactating mothers

It is preferable to provide infant formula options as an alternative to breastfeeding. The infant formula should be available free of charge for the patient, especially in resource-poor settings. The concerned hospital administration should provide formula milk from the regular patient diet budget.
A woman who is breastfeeding and has active drug-resistant TB should receive a full course of anti-TB treatment. **The 9 month all oral RR/MDR regimen with Linezolid can be offered or individualized regimen may be constructed. Ethionamide containing 9 month all oral RR/MDR regimen is contraindicated during breastfeeding.**

The mother and her baby should not be completely separated. However, if the mother is sputum smear positive, the care of the infant should be left to the family members until she becomes sputum smear negative, if feasible. When the mother and infant are together, they should be in well-ventilated areas or outdoors. The mother should use a surgical mask until she becomes sputum smear negative.

7.10.3 Hepatic Insufficiency

All first line drugs–isoniazid, rifampicin and pyrazinamide – are associated with hepatotoxicity. 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 fluoroquinolones.
Patients with history of liver disease can receive the usual anti-TB drug regimens provided there is no clinical evidence of severe chronic or liver disease, hepatitis virus carriage, and recent history of acute hepatitis or excessive alcohol consumption. 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 there is evidence of any significant liver inflammation, the drug(s) suspected to be responsible have to be stopped. **In a patient on treatment for drug resistant TB, simultaneous treatment for both MDR-TB and Viral hepatitis is recommended if medically indicated.**

7.10.4 Diabetes Mellitus

Diabetes mellitus may potentiate the adverse effects of anti-TB drugs, especially renal dysfunction and peripheral neuropathy. Diabetes must be managed closely throughout the treatment of drug-resistant TB. Oral hypoglycaemic agents are not contraindicated during the treatment of drug-resistant TB but may require the patient to increase the dosage as the use of ethionamide or prothionamide may make it more difficult to control blood glucose levels. Creatinine and potassium levels should be monitored more frequently, often weekly for the first month and then at least monthly there-after in view of the renal toxicity of aminoglycosides.

7.10.5 Renal Insufficiency

Renal insufficiency caused by longstanding TB infection itself or previous use of aminoglycosides is not uncommon. Great 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. The dosing is based on the patient's creatinine clearance.
Refer to annex 6 for dose adjustments for second-line drugs in patients with renal insufficiency.

7.10.6 Seizure Disorder

If a patient has a history of seizure disorder, then the physician needs to evaluate such patients to determine whether the seizure disorder is under control and whether the patient is taking anti-epileptic medication(s). If the seizures are not under control, initiation or adjustment of anti-seizure medication will be needed before the start of drug-resistant TB therapy.

Cycloserine should be avoided in patients with active seizure disorder. However, in cases where cycloserine is a crucial component of the treatment regimen, it can be given and the anti-epileptic medication adjusted as needed to control the seizures.
Prophylactic oral pyridoxine (vitamin B6) will be used in patients with seizure disorder to protect against the neurological adverse effects of cycloserine. The dose for at-risk patients on cycloserine is 25 mg of pyridoxine for every 250 mg of cycloserine daily. Prophylactic dose of 1–2 mg/kg/day of pyridoxine for children will be used for patients at risk for neurological sequelae.
Drug interactions should be checked before their use and the treating physician will work in close contact with physician managing the seizure disorder. Seizures that happen for the first time during anti-TB therapy could be due to adverse effect of one of the anti-TB drugs and should be evaluated accordingly.

7.10.7 Substance Dependence

Patients with substance use disorders will be offered treatment for their addiction. Complete abstinence from alcohol or other substances should be strongly encouraged but should not be pursued at the expense of compromising adherence to treatment. If the treatment is repeatedly interrupted because of the patient's dependence, therapy should be suspended until measures to ensure adherence has been established.
Patient-centered directly observed therapy gives the patient contact with and support from healthcare providers, which often allows complete treatment even in patients with substance dependence.

Cycloserine will have a higher incidence of adverse effects as in psychiatric patients, in patients dependent on alcohol or other substances, including a higher incidence of seizures. The drug is contraindicated in severe central nervous system disease. However, if central nervous system disease is not severe and cycloserine is considered important to the regimen, it can be used in these patients under close observation for adverse effects and prompt treatment initiation.

CHAPTER 8
MONITORING TREATMENT

In order to evaluate the result of treatment, sputum smear examinations should be performed at defined intervals.

8.1 Monitoring PTB patients

The follow-up is done with a sputum examination both for new and retreatment cases and they should be screened for resistance at the start of the treatment as well as at any point during the treatment follow-up, when the sputum is positive on microscopy. However, retreatment cases are considered to be at greater risk for drug resistance.

- **Sputum examination should be done after 2 months of completing the intensive phase. If the smear is positive, confirm patient's compliance to treatment and trace report of culture and DST sent at baseline**
- If results of DST are not available, shift the treatment to continuation phase. Perform Xpert MTB/RIF test as well as culture and DST examination on sputum.
- To document the outcome as Cure, sputum smear negative should be documented after the completion of ATT or at least one previous occasion.
- **Positive sputum at any stage during the treatment should call for Xpert MTB/RIF tests and if found MTB Positive to conduct Xpert MTB/XDR for further resistance pattern.**
- **For 6 months regime: Follow-up sputum examination should be done on 2nd month, 4th month, and at the end of 6th month. However, if the sputum remains positive at 4th month, a follow up sputum must be done at the end of 5th month.**
- **If the sputum still remains positive at the end of 5 month, after ruling out drug resistance, classify as treatment failure and start retreatment while also considering the new DS TB treatment option (4-month regime) available under the Programme in consultation with Specialist.**
- **For 4 months regime: Follow-up sputum examination should be done on 2nd month, 3rd month and at the end of 4th month. However, if the sputum remains positive at 2nd month, a follow up sputum test for Xpert MTB/XDR must be to rule out drug resistance and send sample for culture.**

- In case there is persistent smear positivity but no resistance being detected on the rapid tests, consult the TAG committee for further management.

8.2 Monitoring Extra-pulmonary patients

In case of EPTB, CXR should be done. Sputum examination is not required if CXR is normal. Sputum smear examination is not necessary during follow up and the patients should be assessed clinically. The weight of the patient is a useful indicator. **However, if the patient develops any chest symptoms at any time during the course of treatment, a sputum examination may be requested to rule out pulmonary involvement.**

8.3 Actions in case of interruption of TB treatment

If a patient misses an arranged appointment to receive treatment, the DOT provider should ensure that the patient is contacted within a day after missing treatment. The patient can be traced using the location information previously obtained. In order to take appropriate action and continue treatment it is important to find out the cause of the patient's absence. For managing patients who have interrupted treatment, multiple factors need to be considered. All possible support should be provided to able patient to adhere to treatment. At no point should confrontation be used as health system and care delivery are equally responsible for patient non-adherence. In general, long absence of a patient who has already started treatment puts them at greater risk of developing drug resistance.

8.3.1 Principles in management of new patients who interrupt treatment

- A patient must complete all 60 doses of the intensive phase. If the treatment interruption is short, the patient has to continue his previous treatment. For example, if the patient took one month of treatment (30 doses before interruption), he will have one more month (30 doses) of the intensive phase to take. He/She will then, depending on follow-up sputum results, take the continuation phase of the treatment till completion.
- A patient who needs to "start again" will restart from the beginning and take complete duration irrespective of doses taken before the interruption.

Table 8.1 Management of treatment interruption among new cases

Length of treatment	Length of interruption	Do a smear?	Result of smear	Register again as	Treatment
< 1 month	< 2 weeks	No	-	-	Continue new patient regimen*
	2-8 weeks	No	-	-	Start again on new patient regimen**
	> 8 weeks	Yes	Positive	- Treatment after loss to follow-up	Start on first-line regimen** after Xpert MTB/RIF test found negative for rifampicin resistance
			Negative	-	Continue new patient regimen*
1-2 months	< 2 weeks	No	-	-	Continue new patient regimen*
	2-8 weeks	Yes	Positive	-	1 extra month of intensive phase of new patient regimen after Xpert MTB/RIF testing if RR not found
			Negative	-	Continue new patient regimen*
	> 8 weeks	Yes	Positive	Retreatment case - treatment after loss to follow up	Start on first-line regimen after a Xpert MTB/RIF test found negative for rifampicin resistance and Culture & DST
			Negative	-	Continue new patient regimen*
2 months or more	<2 weeks	No	-	-	Continue new patient regimen*
	2-8 weeks	Yes	Positive With no RR	Retreatment case – treatment after loss to follow up	Start on first-line regimen after a Xpert MTB/RIF test found negative for rifampicin resistance and Culture & DST
			Negative	-	Continue new patient regimen*
	> 8 weeks	Yes	Positive with no RR	Retreatment case – treatment after loss to follow up	Start on first-line regimen after a Xpert MTB/RIF test found negative for rifampicin resistance and Culture & DST
			Negative	-	Continue new patient regimen*

Note: *A patient must complete all 60 doses of the initial intensive phase. Treatment taken before interruption is also counted.

** Such patients should re-start treatment from the beginning

***** Xpert MTB/XDR test may be used in smear positive patients to test for both H and R sensitivity. In certain cases, it can also be done on culture positive samples.**

8.4 Monitoring treatment response in MDR-TB

This section focuses on monitoring the progress of treatment and identifying failure of treatment that indicates the need for a change in treatment strategy. **Performing monthly culture tests till the end of the treatment is the best strategy in identifying response to treatment**. Sputum smear microscopy alone results in delayed detection of failure. Initial culture conversion is not always maintained and hence repeated tests should be performed as per the guidelines, as often as prescribed. **Molecular tests such as Xpert MTB/RIF should not be used to monitor response to treatment in all cases.** However, Xpert MTB/RIF can be used to detect Rifampicin resistance in mono and poly drug resistance during follow up.
While monitoring treatment progress, it is also important to proactively detect and manage adverse effects to drugs. Table 8.3 defines various treatment outcomes as well as the process of assigning the treatment outcomes.

8.4.1 Progress of treatment

All patients on second-line treatment should be monitored closely for progress. Monitoring response to treatment is done through regular history taking, physical examination, chest radiograph and laboratory monitoring. The classic symptoms of TB include cough, sputum production, fever and weight loss which generally improves within the first few weeks. Cough and sputum production can persist after sputum conversion in patients with extensive lung damage, but even in those with extensive lung damage improvement is often seen within a month or two of effective treatment.

Persistent fever, weight loss or recurrence of any of the classic symptoms of TB should prompt investigation of treatment failure or untreated co-morbidities. **The recurrence of TB symptoms after sputum conversion may be the first sign of treatment failure**. For children, height and weight should be measured monthly to ensure that they are growing normally. Normal growth rate usually resumes after a few months of successful treatment. For adults too, weight should be recorded monthly. The most important evidence of improvement is conversion of the sputum culture to negative. While sputum smear is useful because of its much shorter turnaround time, sputum culture is much more sensitive to detect ongoing active disease and or treatment failure.

Table 8.2 Monitoring schedule of RR-/MDR-TB patients on treatment

MONITORING EVALUATION	RECOMMENDED FREQUENCY
Evaluation by clinician	*During the initial phase*: Every week during their stay in the hospital and every month if treated as outpatient, until the treatment is well tolerated.
Treatment adherence and tolerance	Daily by the treatment supporter.
Sputum smears and culture	Monitoring smears and culture throughout treatment –sputum smear and culture monthly till the end of treatment.
Weight	At baseline and then monthly thereafter till the end of the treatment.
Height	At the start of treatment for all (to be able to assess BMI throughout treatment); monthly for children (to assess growth).
Drug susceptibility testing	At baseline for first and second-line anti-TB drugs. Repeat DST when/if indicated.
Chest radiograph	At baseline, at the end of 4 months, thereafter 6 monthly and then at the end of treatment.
Blood test	As per Annex 5.

Routine Checklist for follow up and monitoring MDR-TB/XDR-TB patients

The checklist should be attached with the TB Treatment card of the patient so that the TB In-charge could regularly monitor and do necessary follow up investigations as per the defined schedule.

To ensure regular follow up and monitor treatment of MDR-TB/XDR-TB, MDR-TB register and MDR-TB lab register will be distributed to all the TB Reporting Centres. Similarly, a card for aDSM recording and porting to be made part and distributed to all TB reporting centers. The TB In-charge of the MDR-TB treatment center will notify the TB In-charge where the patient wishes to receive his/her treatment and TB In-charge of that particular health facility will have to register the patient (referring to the MDR-TB patient card) and do necessary follow up investigations till the treatment outcome is determined.

Routine Checklist for follow up and monitoring MDR-TB/XDR-TB patients including aDSM (Annexure 5)

In case a dose of medicine is missed, the VHW/treatment supporter /PHC staff (whoever is directly responsible for administering treatment to the patient) will contact the patient and the

family within 2 days of missed dose and counsel patients to restart treatment. Mobile phones may be used but visiting patients' home is necessary if counselling is not successful over the phone. If the VHW/ treatment supporter /PHC staffs are not able to convince patient, local community members/leaders may be involved along with the TB In-charge.

8.5 Indications for suspending treatment

If the patient continues to deteriorate despite the relevant measures being taken, treatment failure could be considered in consultation with TAG. Signs suggesting treatment failure with no further options to available cure includes the concurrence of several of the following:

- Persistent positive smears or cultures in the past 8 to 10 months of treatment together with clinical judgement
- Progressive extensive and bilateral lung disease on chest radiography with no option for surgery
- High-grade resistance (often extensively drug-resistant TB (XDR-TB) with additional resistance) with no option to add at least two additional effective agents
- Severe drug intolerance that does not respond to all existing measures to prevent and alleviate it
- Overall deteriorating clinical condition that usually includes weight loss and respiratory insufficiency

Under criminal Penal Code of Bhutan, Section 410 – If a person refuses to take treatment for a disease which poses a threat to Public Health, he/she is liable to be prosecuted.

CHAPTER 9
ACTIVE TB DRUG SAFETY MONITORING AND MANAGEMENT (aDSM)

Active TB drug-safety monitoring and management (aDSM) is the active and systematic, clinical and laboratory assessment of patients on treatment with new anti-TB drugs, novel MDR-TB regimens, or XDR-TB regimens, to detect, manage and report suspected or confirmed drug toxicities. While all detected adverse events (AEs) need to be managed, the core package of aDSM requires the reporting of serious AEs (SAEs) only. MDR/XDR-TB treatment sites with additional resources may also monitor other AEs that are of clinical significance or of special interest to the programme (Annex 5) as part of comprehensive aDSM.

9.1 Important terminologies

i. **Pharmacovigilance:** the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.
ii. **Adverse events (AE):** Any untoward medical occurrence that may present during treatment with a pharmaceutical product, but which does not necessarily have a causal relationship with this treatment.
iii. **Adverse drug reactions (ADR):** a response to a medicine which is noxious and unintended, and which occurs at doses normally used in humans.
iv. **Serious adverse event (SAE):** an AE which either leads to death or a life-threatening experience; to hospitalization or prolongation of hospitalization; persistent or significant disability; or to a congenital anomaly. An SAE that does not immediately result in one of these outcomes but that requires an intervention to prevent it from happening is included.
v. **Severe adverse event:** an AE of maximal intensity as judged by the patient and/or the clinician; at times this assessment is based on laboratory or clinical tests. Different scales exist to determine the degree of severity, the simplest being “mild," “moderate”, or “severe”.
vi. **Adverse event of clinical significance:** an AE that is either (i) serious, (ii) of special interest, (iii) leads to a discontinuation or change in the treatment, or (iv) is judged as otherwise clinically significant by the clinician.
vii. **Adverse event of special interest:** an AE documented to have occurred during clinical trials and for which the monitoring programme is specifically sensitized to report regardless of its seriousness, severity or causal relationship to the TB treatment.

The recording and reporting of aDSM primarily target serious adverse events (SAEs) as a core requirement. Treatment initiation sites with additional resources may also monitor other AEs, which are of clinical significance or of special interest to the NTCP, as part of an extended aDSM approach.
An appropriate and timely management of all AEs and ADRs is an integral component of aDSM and patient care. Further details on the management of ADRs are included.

Setting up aDSM for patients on treatment for drug-resistant TB implies additional responsibilities and resource needs. In contrast to the surveillance of drug resistance and

treatment outcomes, the active systematic monitoring of the occurrence of SAEs is relatively new to TB programmes. The program has decided to introduce a simple card format which will be used along with the treatment cards for DR TB patients which will help in early identification of unidentified ADRs, risk factors for the occurrence of ADRs, drug safety issues and risk benefit comparisons. This is a cost-effective method to monitor safe use of drugs.

9.2 Objectives of aDSM

The overall objectives of aDSM are to reduce risks from drug-related harms in patients on second line treatment for drug-resistant TB and to generate standardized aDSM data to inform future policy updates on the use of such medicines. aDSM includes three essential activities to achieve these objectives:

a. All AEs detected should be managed in a timely manner in order to deliver the best possible patient care.
b. Standardized data should be systematically collected and reported for any detected SAE. These will eventually be used to characterize the types of SAEs, assess the safety of the treatment, and inform future policy on the use of these medicines.
c. All SAEs detected should be reported to the pharmacovigilance centres and regularly assessed for causality.

Patients targeted for aDSM should undergo active and systematic clinical and laboratory assessment during treatment to detect drug toxicity and AEs. Proposed schedules have been developed for use in patients on shorter regimens or on new medications.

There are three levels of monitoring in aDSM:

i. Core package: requiring monitoring for and reporting of all SAEs.
ii. Intermediate package: includes SAEs as well as AEs of special interest.
iii. Advanced package: includes all AEs of clinical significance.

All PMDT sites treating eligible patients with new anti-TB drugs, novel MDR-TB regimens or for XDR-TB require the core package. These treatment centres should, as a minimum, also take part in spontaneous reporting of ADRs as required by local regulations. Expansion of aDSM will be implemented in a phased approach while all resources needed are mobilized.

Implementation, management and supervision necessary for aDSM would be systematically built into the Treatment initiation sites component of the TB programme and conducted in step with other activities related to patient care and monitoring

All TB initiation sites treating eligible patients with new anti-TB drugs, novel MDR-TB regimens or for XDR-TB requires the core package.
Expansion of aDSM should be implemented in a phased approach while all resources needed are mobilized.

Key steps to implementing aDSM:

1) Create a national coordinating mechanism for aDSM
2) Develop a plan for aDSM
3) Define management and supervision roles and responsibilities
4) Create standard data collection materials
5) Train staff for collection of data
6) Define schedules and routes for data collection and reporting
7) Consolidate aDSM data electronically
8) Develop (or use existing) capacity for signal detection and causality assessment.

Summary of aDSM activities

- Active TB drug-safety monitoring and management (aDSM) refers to active and systematic clinical and laboratory assessment of patients on treatment with new anti-TB drugs, novel MDR-TB regimens or XDR-TB regimens to detect, manage and report suspected or confirmed drug toxicities.
- While all detected adverse events (AEs) need to be managed clinically, the core package of aDSM will also require the reporting of only serious AEs (SAEs). Treatment sites with additional resources will also monitor other AEs that are of clinical significance or of special interest to the programme, as part of comprehensive aDSM. aDSM will also be expanded in a phased approach to eventually cover TB patients on treatment with any second-line drugs with simple aDSM acrds along with the TB treatment cards.
- aDSM is intended to be an integral component of the programmatic management of drug-resistant TB (PMDT). Its rationale is based on recent developments in MDR-TB treatment, particularly the approval for use of new medicines ahead of the completion of Phase III trials, increased use of repurposed drugs for XDR-TB treatment and the development of novel second-line anti-TB regimens. Such approaches need careful monitoring for drug-related harms, some of which may not have been described as yet.
- aDSM is not aimed at replacing or duplicating efforts of national pharmacovigilance units but to complement current capacities and address barriers to undertake active pharmacovigilance within the context of TB care. 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. This monitoring and management need to be adapted to the realities of TB programmes that are often under-resourced.
- For national TB programmes (NTPs) to undertake aDSM effectively, a series of activities need to be coordinated to ensure that: the right expertise is developed through interaction with local and external drug-safety experts; sufficient funds are made available so that clinical monitoring activities are performed, data gets collected, reported and analysed; and decisions are made on the basis of new knowledge gained.

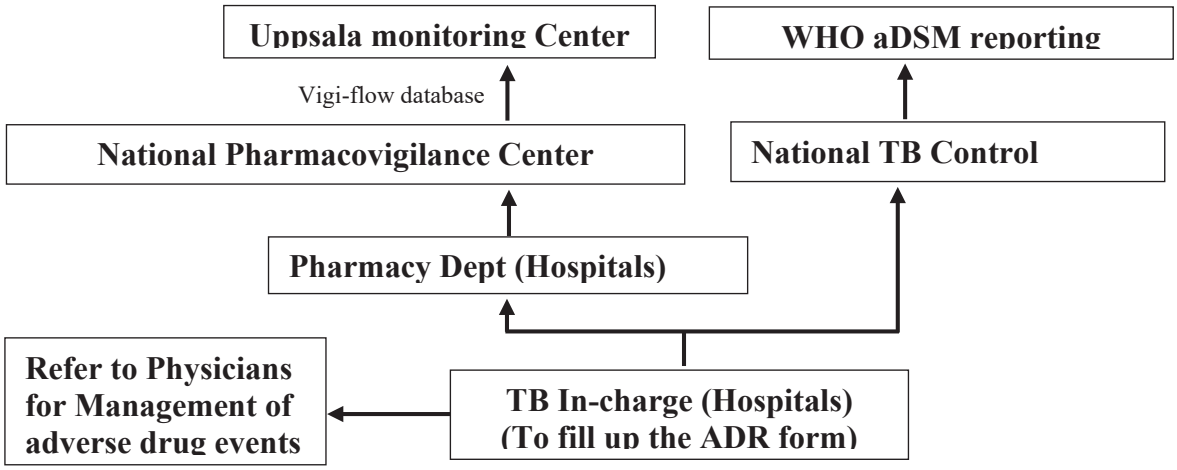


Figure 9.1 National coordinating mechanism for aDSM

The responsibility for the coordination and management of aDSM at the national level shall be done by the existing TAG.

In the core package of aDSM, clinical and laboratory test records at baseline (treatment initiation) and during regular reviews (e.g. monthly intervals) should be integrated into an expanded version of the programmatic MDR-TB (second-line TB) Treatment Card. The treatment initiation form should be completed before the start of treatment (to document any abnormality that could later be confused with a drug-related SAE) and the review form should be completed at scheduled encounters with the patient. In addition, information on SAEs occurring in-between visits should also be captured using the same forms. The content of the form could be similar to the one used by the national pharmacovigilance centre for spontaneous reporting.

Staff at the different levels of health services should be informed and trained on the use of new anti-TB drugs or novel regimens ahead of any patient enrolment. This training should include instruction on the completion of aDSM forms. It is important that this activity is completed ahead of any patient enrolment to ensure timely identification of AEs that need to be managed, and proper and complete collection and reporting of information.

All AEs detected during routine clinical patient care should lead to an appropriate and timely management response in order to limit potential harm to the patient. In terms of monitoring, 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.

Monitoring Registry for aDSM

1) All serious adverse events (SAEs).
2) All AEs of special interest (suggested list):
    i. Peripheral neuropathy (paraesthesia)

ii. Psychiatric disorders and central nervous system toxicity (e.g. depression, psychosis, suicidal intention, seizures)
iii. Optic nerve disorder (optic neuritis) or retinopathy
iv. Ototoxicity (hearing impairment, hearing loss)
v. Myelosuppression (manifested as anaemia, thrombocytopenia, neutropenia or leukopenia)
vi. Prolonged QT interval (Fridericia correction)
vii. Lactic acidosis
viii. Hepatitis (defined as increases in alanine aminotransferase (ALT) ≥5x the upper limit of normal (ULN), or increases in ALT ≥3x ULN with clinical manifestations, or increases in ALT ≥3x ULN with concomitant increase in bilirubin ≥1.5x ULN)
ix. Hypothyroidism
x. Hypokalaemia
xi. Pancreatitis
xii. Phospholipidosis
xiii. Acute kidney injury (acute renal failure).

3) Adverse events leading to treatment discontinuation or change in drug dosage.
4) Adverse events not listed above but judged as otherwise clinically significant by the clinician.

Clinical and laboratory testing for active tuberculosis drug-safety monitoring and management (aDSM) (Annex 5).

Basic principles to be followed:

- Timely recognition and management of AEs are important for adherence, treatment outcome, overall treatment tolerance and well-being of patients.
- Ensure patients have access to diagnostics and treatment for AEs, including ancillary drugs.
- Implement baseline examinations at initiation of treatment and monitoring during treatment for all MDR-TB patients.
- Assess availability of clinical examinations tools required. Seek funds to procure if not available.
- Ensure quick test result feedback, to allow for timely clinical decision making.
- Most AEs can be identified clinically, and are usually volunteered by patients themselves. This underlines the importance of close patient follow-up to ensure a more complete reporting of AEs.
- Laboratory evaluation is an integral part of aDSM, to detect potential harms early and before they manifest themselves clinically.
- Nonetheless, management of AEs is primarily aimed at the patient and not at the laboratory result.
- Patients should be counselled early and often about AEs.

For ADR to TB drugs, the TB In-charge will liaise with pharmacist/pharmacy unit to send report to the Pharmacy department at the JDWNRH with a copy to the National TB Control programme.

9.3 Management of Adverse Drug Effects

First line anti-TB drugs are generally considered safe. Most TB patients complete their treatment without any significant adverse drugs effects. A few patients, however, experience adverse effects although most of them are minor. Occasionally patients discontinue treatment due to major or even minor adverse effects. For this reason, it is important that patients are clinically monitored during the treatment so that adverse effects can be detected promptly and managed properly. Liver function tests should be done at the beginning and monthly after initiation of ATT.

Health workers and DOT providers can monitor side effects of drugs by teaching patients how to recognize symptoms of common side effects, to encourage patients to report if they develop such symptoms, and to ask about symptoms when the patients report to collect drugs.

All cases of severe adverse effects will have to be referred to the Regional Referral Hospitals (RRH) for management. Some of these cases may need single formulations for treatment. Hence, the RRH will be stocked with single formulation drugs.
For management of adverse effects of second line drugs, refer annex 3.

Table 9.1 Symptom based management of side-effects of Anti-TB drugs

Side-effects	Drug(s) responsible	Management
MINOR SIDE-EFFECTS - CONTINUE DRUGS		
1. Anorexia, nausea, abdominal pain	Rifampicin, INH, Pyrazinamide	Give drugs with small meals or last thing at night. If patient doesn't get better, exclude hepatitis.
2. Joint pain	Pyrazinamide	Give paracetamol or Aspirin/NSAIDs like ibuprofen
3. Burning, numbness or tingling sensation in the hands or feet	Isoniazid	Pyridoxine 50-75 mg daily*.
4. Orange/red urine	Rifampicin	Reassurance
5. Minor rash with itching	Any drug	Anti-histamines like cetrizine, promethazine.
MAJOR SIDE-EFFECTS - STOP DRUGS RESPONSIBLE, REFER FOR EVALUATION		
1. Itching of skin, severe rash	Any drug	Stop anti-TB drugs
2. Nausea, vomiting, deterioration of appetite +/-Jaundice (other causes of hepatitis excluded)	INH, Rifampicin and Pyrazinamide	Stop anti-TB drugs. Perform liver function test
4. Visual impairment	Ethambutol	Stop ethambutol
5. Shock, purpura, acute renal failure, haemolytic anaemia	Rifampicin	Stop rifampicin (***Never give again***)

Pyridoxine should not be given along with anti -TB drugs at the same time. Give at least 12 hours apart from anti -TB drugs.

CHAPTER 10
PEOPLE CENTERED CARE AND TREATMENT ADHERENCE

Patient adherence to treatment is a key factor in treatment success. For various reasons a proportion of patients stop treatment before completion. However, strict adherence to treatment should be ensured to cure the disease and to prevent the development of drug-resistant TB.

Supported treatment is an important component for TB control especially for shorter regimens. The treatment provider watches till the patient swallows his/her drugs. This is essential for the completion of treatment and recovery from TB. DOT ensures that the patient takes the right anti-TB drugs, in the right doses, at the right intervals and for the right time period. All patients, irrespective of their treatment category, should receive all doses of the anti-TB drugs under DOT. Seeing the advantages of using Video Observed Treatment (VOT) as adherence to treatment can be observed from distance even when people travel and cannot be visited, incorporating VOT as a part of ambulatory care will be explored as it is more flexible to people's schedules.

TB patients can be treated using ambulatory care as hospitalization itself has little or no effect on the outcome of the treatment.

Reasons for ambulatory care:

The reasons for moving to an ambulatory care are:

i. Studies have shown that MDR-TB patients become rapidly non-infectious after start of effective therapy
ii. The country will need to invest lots of resources in infection control in hospitals if longer stay for such patients is maintained
iii. It may not be convenient for all patients to stay long duration away from families and some of them may risk losing their jobs

10.1 Ambulatory care and treatment for DS-TB

It is important to know that the infectivity rate reduces once ATT is initiated. Therefore, after minimum of 2 weeks of self-isolation, the patients can return to their work place/ daily activities.

Hospitalization may be necessary if the patient cannot receive ambulatory treatment under direct observation. In-patient treatment may also be necessary (often only for a short period) for severely ill patients, e.g. spontaneous pneumothorax (air in the inter-pleural space resulting in collapse of the lung) or for those with other associated serious diseases.

10.2 Ambulatory care and treatment for MDR-TB

The MDR-TB patient will be admitted for a minimum of 2 months for the purpose of monitoring adverse drug reactions, conducting initial investigations, and providing counseling to the patients on DOT and will be discharged based on the clinical judgement.

The decision to discharge patient will be taken based on:

i. **Clinical assessment and improvement in the condition of the patient** in terms of general well-being, improvement in symptoms like cough, shortness of breath, weight gain and appetite gain etc. Generally, the patients will have seen improvement much earlier. However, in cases where there is no significant clinical improvement, the clinician may decide to wait for culture conversion (i.e. two consecutive cultures showing negative results after the start of the treatment).

ii. **Patient convenience and willingness**- In occasional cases the patient himself or herself may wish to continue treatment within the hospital because of socio-economic conditions. In such cases the clinician and nurses will discuss pros and cons of staying in the hospital with the patient and arrive at a mutually acceptable decision.

10.3 Treatment supporters

To ensure adherence to treatment, DOT should be provided as conveniently as possible to the patient. This often means as close to the patient's home or workplace as possible. The treatment supporter may be a facility-based or community-based health worker or a trained and supervised community member.

Medical officer, TB in-charge in consultation with local health workers and along with patients should identify the treatment supporter. The name and address of the treatment supporter should be recorded on the patient's treatment card. The treatment supporter should be mutually acceptable, accessible to the patient and should agree to be accountable to the health system. The medical officer or TB in-charge has to ensure that the treatment supporter diligently observes the treatment as per schedule.

10.4 Drug supplies to treatment supporter

If DOT is provided at the health centre where the patient is registered, the patient's drugs should be kept at a place that is secure and suitable in that centre for the whole course of the treatment. For other health facilities and community-based treatment supporter, a one-month supply of drugs should be provided for each of the patients. This will be refilled at the PHC during his/her monthly visits along with the patient. However, this does not mean the drugs will be handed over to the patients.

10.5 Regularity of treatment

DOT providers should make sure that the patients swallow the drugs according to prescription. They should trace absentees and prevent patients from becoming defaulters.
If a patient misses a dose of the treatment, he/she must be traced immediately to resume DOT without delay. To ensure easy tracing of patients, the detailed address should be filled in the Tuberculosis Treatment Card and TB Register. Mobile number of the patient should be included if available.

10.6 Education and Counselling

Education and counselling have an important role in the treatment of MDR/XDR-TB. They not only help in sharing proper information with the patient but also provide an opportunity to allay fears in the mind of patient and family, clarify doubts regarding the treatment and inform about options available so as to help patients take complete course of the treatment. The process of counselling a patient will be started right from the time she/ he is referred for DST and continues after the diagnosis is made. It is important to involve the family and or close relatives of the patient during the counselling process. Counselling shall be done by the TB in-charge, health staff who caters to the patients (nurses) and doctors involved in treatment and monitoring at every point of contact.

Essential points for counselling during referral for diagnosis will include:

- Reasons for referral
- Possibility of having drug resistance
- Infection control
- Need for follow-up and complete treatment depending on the results of the test.

Essential points at the start of treatment will include:

- Consequences of the diagnosis
- Limited options for treatment and medicine availability
- Treatment schedule and duration
- Counselling for HIV testing
- Need for DOT and follow-up
- Possible side effects and reporting
- Linking with social and community support during the treatment
- Infection control
- Contact screening

10.7 Financial security

In Bhutan, a person on TB or MDR-TB treatment receives job security as per the national policy (Labour Act). The person cannot be removed from the job. Therefore, such patients on treatment can continue treatment even in hospital without the fear of losing their job. Patients will also receive rehabilitation support in the form of recommendation for lighter duties if such cases are involved in manual labour or other similar strenuous duties.

10.8 Nutrition

Undernutrition is a major risk factor for TB along with diabetes, smoking, alcohol and HIV. Undernutrition and tuberculosis are closely linked with both being public health problems. Many infectious diseases including TB, has a bidirectional interaction between nutritional status and active disease and undernutrition is associated with an increased frequency, severity and fatality of TB. Undernutrition increases the risk of TB infection progressing to active TB.

The first three Sustainable Development Goals (SDGs 1, 2 and 3) deal with action on poverty, hunger and ensuring healthy lives and well-being of people. Action on chronic undernutrition and nutritional support to TB affected households are consistent with the SDGs and have a potential for a significant impact on TB incidence, especially in poor and marginalised communities.

Evidence suggests that nutritional interventions are associated with better outcomes in TB patients including reduced mortality, improved weight gain and body composition, earlier sputum conversion, improved pharmacokinetics of key drugs, improved functional status and adherence to therapy. Recent studies from the region on Nutritional support to household contacts of patients with PTB reduced TB incidence rates significantly in communities with high prevalence of undernutrition. In addition, nutritional support to TB patients was associated with lower death rates, increased weight gain, higher treatment success, lower loss to follow up, and high rates of return to work.

NTP would look into including:

(i) clinical assessment of nutritional status including Anthropometric measurements in children and adults and classification of nutritional status

(ii) Nutritional counselling based on the clinical assessment helping include concept of healthy balanced diet and advice on increasing energy intake of diet by using locally available nutrient-rich food

(iii) Nutritional management of severe undernutrition requiring hospitalization – initial stabilization phase and rehabilitation phase, and scope for additional food ration & nutritional supplementation of moderate to severe undernutrition patients

Even a small proportion of investments in social protection could contribute to a reduced TB burden. As per studies, social protection coverage could result in 76% drop in TB incidence by 2035

All patients will undergo a nutrition status assessment at the beginning of treatment and any time during the treatment, as considered appropriate (Box 3). **Weight is required to be measured at diagnosis and during follow up and should be recorded properly. It is also critical to record the height of the patient.** All in-patients will be evaluated and counseled by the nutritionist/dietician. A high protein diet and any additional supportive measures considered appropriate after the evaluation. While in the hospital, additional nutritional support to TB patients shall be met from the regular patients' diet budget of the concerned hospital.

The number of children notified with TB is considerably low in Bhutan. In 2022 only 3.9% of cases were in children while 5-15% is expected. The ratio of cases in the 0–4 age group to those in the 5–14 age group was 0.19 (5/27) in 2022, which is not within the desired range between 1.5-3.0, further indicating under-diagnosis particularly among younger children. Moreover, under-nutrition persists and stunting rates is still around 21% in the under 5s in the Nutrition Survey, 2015.

There are 10 hospitals in the country which provide basic counselling to the mothers on feeding practices, and additional nutritious food for children, but routine TB screening among malnourished children is not conducted systematically. Therefore, hospitals with NRUs should ensure that TB screening is conducted systematically in all malnourished children.

BOX 3: Nutritional Assessment and Support

Tuberculosis and undernutrition have bi-directional association and often TB causes weight-loss, macro and micro-nutritional deficiencies. Nutritional deficiencies do not occur in isolation, therefore deficiency of one nutrient also suggests of deficiency of related nutrients in body functions. All individuals with active TB should receive an assessment of their nutritional status and appropriate counselling based on their nutritional status at diagnosis and throughout treatment.

A complete nutritional assessment can be done by using the ABCD method (Anthropometry, Biochemical, Clinical and Dietary). This approach will provide complete and accurate information that enables a clinician to provide patient centered nutritional support.

Anthropometry

Anthropometric measurements are useful and commonly used criteria form assessing nutritional status. Body Mass Index (BMI) is a widely used anthropometric assessment. It is important to note that BMI cannot be used in pregnant women, patients with severe edema and body builders.

Assessing BMI

- Measure and record height and weight of the patients (weight in kg and height in m2)
- Assess the BMI (BMI= weight in kg / height in m2)

Although same method is used to calculate the BMI, its interpretation differs with age and gender. For children 5-19 years the BMI is plotted on a WHO BMI for age chart and interpreted accordingly. There are different charts for boys and girls (Annexure I and II).

For adults over 20 years old the following criteria is used for both the sexes (Table 9.1).

Table 10.1 Criteria for BMI and its interpretation in adults.

BMI (kg/m^2)	Classification
< 18.5	Underweight
18.5-24.9	Normal
25 – 29.9	Pre- Obesity
30 – 34.9	Obesity Class I
35 – 39.9	Obesity Class II
40 and above	Obesity Class III

Mid-Upper Arm Circumference (MUAC)

Measurement of mid-upper arm circumference is useful means of assessing protein-energy malnutrition. MUAC is the only anthropometric measure for assessing nutritional status among pregnant women. The MUAC is the circumference of the upper arm at the mid-point between the shoulder tip and the elbow tip on the left arm. The mid-arm point is determined by measuring the distance from the shoulder tip to the elbow and dividing it by two. A low reading indicates a loss of muscle mass.

To measure:

- Mark the mid-point between olecranon process and acromion.
- With the arm hanging straight down, wrap a MUAC tape around the arm at the midpoint mark.
- Measure to the nearest 1 mm.

Table 10.2 MUAC tape cut-off points

Children under five		
Range	**Classification**	**Color Coding**
0 - 115 mm	Severe Acute Malnutrition	Red
115 -125 mm	Moderate Acute Malnutrition	Yellow
>125 mm	Normal	Green
Adults		
0 - 210 mm	Severe Wasting	Red
210 -230 mm	Moderate Wasting	Yellow
>230 mm	Normal	Green

Management of severe acute malnutrition

Children less than 5 years of age with active TB and severe acute malnutrition should be treated in accordance with the WHO recommendations for the management of severe acute malnutrition in children less than five years. School age children and adolescents (5 to 19 years), and adults, including pregnant and lactating women, with active TB and severe acute malnutrition, should be treated in accordance with the WHO recommendations for management of severe acute malnutrition.

Biochemical Assessment

Biochemical or laboratory assessment is the most widely used and accurate method of nutritional assessment. Laboratory tests are used to determine the levels of micro-nutrients in the body.

Clinical Assessment

Clinical examination is essential component all nutritional assessments. Some clinical signs and symptoms of deficiency signs and symptoms are presence of pallor, edema, glossitis, stomatitis, etc.

Dietary Assessment

A detailed history of the patient's past or current food consumption pattern can be useful in determining the nutritional status. Dietary assessments can be done using 24-hour recall method and estimate the nutrient intake. Information on dietary diversity can be obtained by food frequency assessments.

Dietary Guidelines

Tuberculosis patients are likely to have increased requirement of proteins. The higher requirement of protein is in view of the metabolic stress related to the active infectious disease. The requirements of protein would be 1.2-1.5 g/kg ideal body weight per day. Thus it is important to increase the intake of proteins of high biological value such as meat, eggs and milk. Intake of fruits and vegetables should be also increased. If the patient has poor / reduced appetite, small frequent feedings 5 - 6 times per day is advised. This feeding patter is also useful for tuberculosis patients with comorbidities such as diabetes and HIV/AIDS.

10.9 Palliative care

WHO defines palliative care as an "approach that improves the quality of life of patients and their families facing problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems such as physical, psychosocial and spiritual"

End-of-life supportive measures

- **Relief from dyspnea**-Oxygen may be used to alleviate shortness of breath. Morphine provides significant relief from respiratory insufficiency and should be offered according to established clinical protocols.
- **Relief from pain and other symptoms**-Paracetamol, or codeine with paracetamol, gives relief from moderate pain.
- **Infection control measures**-Infection control measures should be continued with reinforcement of environmental and personal measures, including N-95 mask use for caregivers.
- **Nutritional support-**Small and frequent meals are often best for a person at the end of life. Nausea and vomiting may need to be treated.
- **Regular medical visits.** Regular visits by health-care providers and the support team should be continued.

Continuation of ancillary medicines- All necessary ancillary medications should be continued as needed. Codeine helps control cough, as well as pain. Bronchospasms can be controlled with a metered-dose inhaler with a spacer or mask. Depression and anxiety, if present, should be addressed.

10.9.1 Hospitalization care or home-based care

Home-based care can be offered to patients and families who want to keep the patient at home, with appropriate infection control practices. Institution based end-of-life care should be available to those for whom home care is not feasible or desirable

- **Preventive measures-** Oral care, prevention of bedsores, bathing and prevention of muscle contractures are indicated in all patients.
- **Provide psychosocial support.** Psychological counselling to the patient and family caregivers is critical.
- **Respect for patient's beliefs and values at the end of life.** It is common for the patient and family caregivers to develop or increase their interest in spiritual and religious matters once they perceive that the end of life is approaching.

10.10 Tobacco Smoking and Tuberculosis

The diagnosis of TB disease is an opportune moment for imparting behaviour change in a patient's smoking habit. A patient will be likely to accept the behaviour change necessary to improve their health. Tobacco smoking may lead to delayed sputum conversion in sputum smear-

positive PTB cases, lower treatment success rates and higher rates of relapse of TB disease or death. Hence, the past and present history of tobacco smoking in any form should be elicited from each TB case at the time they initiate treatment. Smoking cessation advice to current smokers should become an integral part of TB case management. Such interventions may help improve outcomes of anti-TB treatment and reduce transmission of infection in the short term. It will also improve the quality of life in the long term of TB patients by preventing chronic respiratory diseases or other diseases associated with smoking. Patients who smoke should be motivated to make an informed decision to stop smoking. All cases should be informed personally about the harmful effects of smoking on health in general and the potential for poorer outcomes of anti-TB treatment if smoking is continued. Patients should also be advised not to smoke in the presence of others, since increased frequency of coughing due to smoking increases the risk of TB infection among their household and other contacts.

10.11 Ethics in Management of Drug-resistant TB

TB particularly affects vulnerable population and therefore social justice and equity must be at the heart of the response. Prevention, diagnosis, care and treatment of TB, including drug-resistant TB, raise important ethical and human rights issues that must be addressed. It is therefore important to ensure balance of individual responsibilities, rights and liberties of those affected by the disease with the protection of those who are at risk of infection. In 2010, the WHO published a guidance document entitled *Guidance on ethics of TB prevention, care and control*.

Treatment of MDR-TB patients will be based on the principles of ethics as laid down in WHO guidance. This chapter presents the key ethical guidance points developed in the WHO guidance. The key elements include:

- **Social justice/equity** –redistribute resources to compensate for existing inequalities, and take further actions to prevent their perpetuation.
- **Solidarity** –a moral obligation to stand together as a group, community or nation when facing a crisis.
- **Common good** –The removal or reduction of a threat of infection from a society is something that everyone can benefit from.
- **Autonomy** – When possible, patients generally should have the right to choose among treatment options.
- **Reciprocity** –Reciprocity seeks to express the idea that those individuals who put themselves at risk of harm for the sake of others deserve benefits in exchange for running such risks.
- **Electiveness –** We have a duty to avoid doing things that are clearly not working, and a positive obligation to implement proven measures that are likely to succeed. Limited resources must be used in the most productive manner possible.
- **Subsidiarity –** Decisions should be made as close to the individual and communities, at local level, as possible.
- **Participation** – The public should be encouraged to participate in the decision-making process and reasons should be provided for decisions.

- **Transparency and accountability** – Decisions must be made in an open manner, and the decision-making process must be fair, responsive and evidence-based.

10.12 Social and psychosocial support

In its most recent TB Treatment Guidelines, the WHO notes that treatment supervision is not always sufficient to guarantee better treatment outcomes while the combination of treatment supervision with other treatment adherence interventions (incl. social support, digital health interventions etc.) significantly improves treatment outcomes for TB patients. Therefore, the WHO recommends the use of a package of treatment adherence interventions in addition to health education and counselling as a means to improve patient adherence to treatment.

A comprehensive patient-centred approach that include social & psychosocial support is especially needed in the patients and had been shown to improve outcomes. MDR-TB treatment can be successful with high overall rates of adherence when adequate support measures are provided. These measures include enablers and incentives for delivery of DOT to ensure adherence to treatment and may include the following: emotional/psychological support; patient, family and peer education on MDR-TB treatment; early and effective management of adverse drug reactions; and incentives to the DOT providers and reimbursement of travel expenses to patient and attendants for visits to health facilities and treatment centers. Socio-economic problems should, as far as possible, be addressed to enable patients and their families to adhere to the MDR-TB treatment. NTP will explore different possibilities for coming to the health facility for monthly follow up patients to be provided a monthly incentive for nutritional support or transport allowance from both government as well as non-government resources generation.

The NTP will use a mixture of types of adherence interventions depending on the specific patient situation. These include different combinations of patient education, staff education, material support (e.g. food, financial incentives, transport fees, bonuses for reaching treatment goals), psychological support and counselling. The interventions will be selected on the basis of the assessment of an individual patient's needs, the NTP's financial resources and conditions for implementation in specific locations throughout the country.

CHAPTER 11
TB PREVENTIVE TREATMENT (TPT)

11.1 Introduction to TBI

(South-East Asia Regional Action Plan on Programmatic Management of Latent Tuberculosis Infection. New Delhi: World Health Organization, Regional Office for South-East Asia; 2018. Licence: CC BY-NC-SA 3.0 IGO)

The control of an infectious disease epidemic requires active case detection, treatment where possible, interruption of transmission, and enhancement of immunity for the susceptible. If elimination is desired, containment of the reservoirs, or seedbeds of infection is essential. tuberculosis infection (TBI) is defined as a state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens with no evidence of clinically manifest active TB.

TB is a disease characterized by a period of asymptomatic subclinical infection that may last for weeks to decades; as a result, a large reservoir of infected human beings exist among whom new cases may arise at any time. A small number of viable tuberculosis bacilli can reside in an individual with TB infection (TB INFECTION) without obvious clinical symptoms or abnormal chest radiographs. Contemporary understanding of what has long been called "latent tuberculosis infection" has evolved. Rather than a binary distinction between "latent" and "active" states, TB infection is now understood as a dynamic multi-state gradient of latent subclinical infection to clinically active disease; a process that is imperfectly represented by the dichotomous classification. After more than three decades of policy that focused only on the detection and treatment of active cases of tuberculosis, a better understanding of the epidemiology and population dynamics of the disease has emerged, and the essential role of controlling the reservoir of disease-asymptomatic TB infections is now understood (Lee, 2015; Rangaka et al., 2015).
In 2014, the global burden of TB INFECTION was 23.0%, amounting to approximately 1.7 billion people. WHO South-East Asia, Western-Pacific, and Africa regions had the highest prevalence and accounted for around 80% of those with LTBI.

Studies suggest that active TB will develop in 5 to 15% of persons with latent infection during their lifetimes and (higher % if persons are immuno-compromised); thus, persons with latent infection serve, according to Osler, as the "seedbeds" of TB in the community (Getahun, Matteelli, Chaisson, & Raviglione, 2015).

The risk of transmission of *Mycobacterium tuberculosis* from patients to health-care workers is a neglected problem in many low- and middle-income countries (LMICs). Most health-care facilities in these countries lack resources to prevent nosocomial transmission of TB (Joshi, Reingold, Menzies, & Pai, 2006).

As per WHO (Source: WHO consolidated guidelines on tuberculosis. Module 1: prevention – tuberculosis preventive treatment. Geneva: World Health Organization; 2020. Licence: CC BY-NC-SA 3.0 IGO), 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

11.2 Identification of populations for testing for TB Infection

Certain groups of people are known to be at elevated risk of progression to disease. These include close contacts of cases, young children, the elderly, and people with HIV infection or other immuno-deficiencies. In particularly vulnerable groups, such as people living with HIV (PLHIV), miners, and prisoners in areas with high transmission rates of TB, and other groups with a high risk of developing disease due to occupational (e.g. healthcare workers) or behavioural exposures (e.g. drug-users), extended or periodic schedules of preventive therapy should be implemented (Getahun, Matteelli, Abubakar, et al., 2015; Rangaka et al., 2015).
The 2019 updated and consolidated guidelines for programmatic management of TB INFECTION describes at-risk populations for whom systematic TB INFECTION testing and treatment is recommended.

11.2.1 At-risk populations that should receive TB preventive treatment (TPT)

Based on recommendations published in the recently updated WHO guidelines TPT, the NTP considers the following to be at-risk populations that should receive TPT:

1. Adults, adolescents, children and infants living with HIV

- Adults and adolescents living with HIV who are unlikely to have active TB should receive preventive treatment of TB as part of a comprehensive package of HIV care. Treatment should be given to these individuals irrespective of the degree of immunosuppression and also to those on antiretroviral treatment (ART), those who have previously been treated for TB and pregnant women.
- Infants aged <12 months living with HIV who are in contact with a case of TB and are investigated for TB should receive preventive treatment of TB if the investigation shows no TB disease.
- Children aged ≥12 months living with HIV who are considered unlikely to have TB disease on the basis of screening for symptoms and who have no contact with a case of TB should be offered preventive treatment of TB as part of a comprehensive package of HIV prevention and care.

2. HIV-negative household contacts

- HIV-negative 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 clinical evaluation should be given TB preventive treatment.
- 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 clinical evaluation may be given TB preventive treatment.
- The NTP has developed a vulnerability assessment tool to help identify people who are at risk for progressing to active TB with the concept of treating other at-risk target populations in a shorter timeframe in order to reach the desired level of incidence decline as per the end TB strategy shown on the following page.

3. Other HIV-negative at-risk groups

- Systematic testing for TB INFECTION is not recommended and treatment for TB INFECTION may be considered on a 'case to case basis' for the following HIV-negative at-risk groups - uncontrolled diabetes, people with harmful alcohol use, tobacco smokers and underweight (severely malnourished in mothers and adults, stunting in children). A close monitoring of such risk groups according to the vulnerability assessment tool is recommended.

- Patients on anti-TNF (tumour necrosis factor) treatment, patients receiving dialysis, patients preparing for an organ or haematological transplant and patients with silicosis should be systematically tested and treated for TB INFECTION.

Group to be started on TPT after ruling out active disease & not requiring test for TB infection

- Children < 5 years who are close contacts of PTB
- PLHIV adults and adolescents with any of current cough, fever, weight loss or night sweats should be evaluated for TB and other diseases
- PLHIV infants and children (<10 y) who have poor weight gain, fever or current cough or who have a history of contact with a person with TB should also be evaluated for TB and other diseases
- Chest radiography to be offered to PLHIV on ART and TPT given to those without abnormal radiographic findings

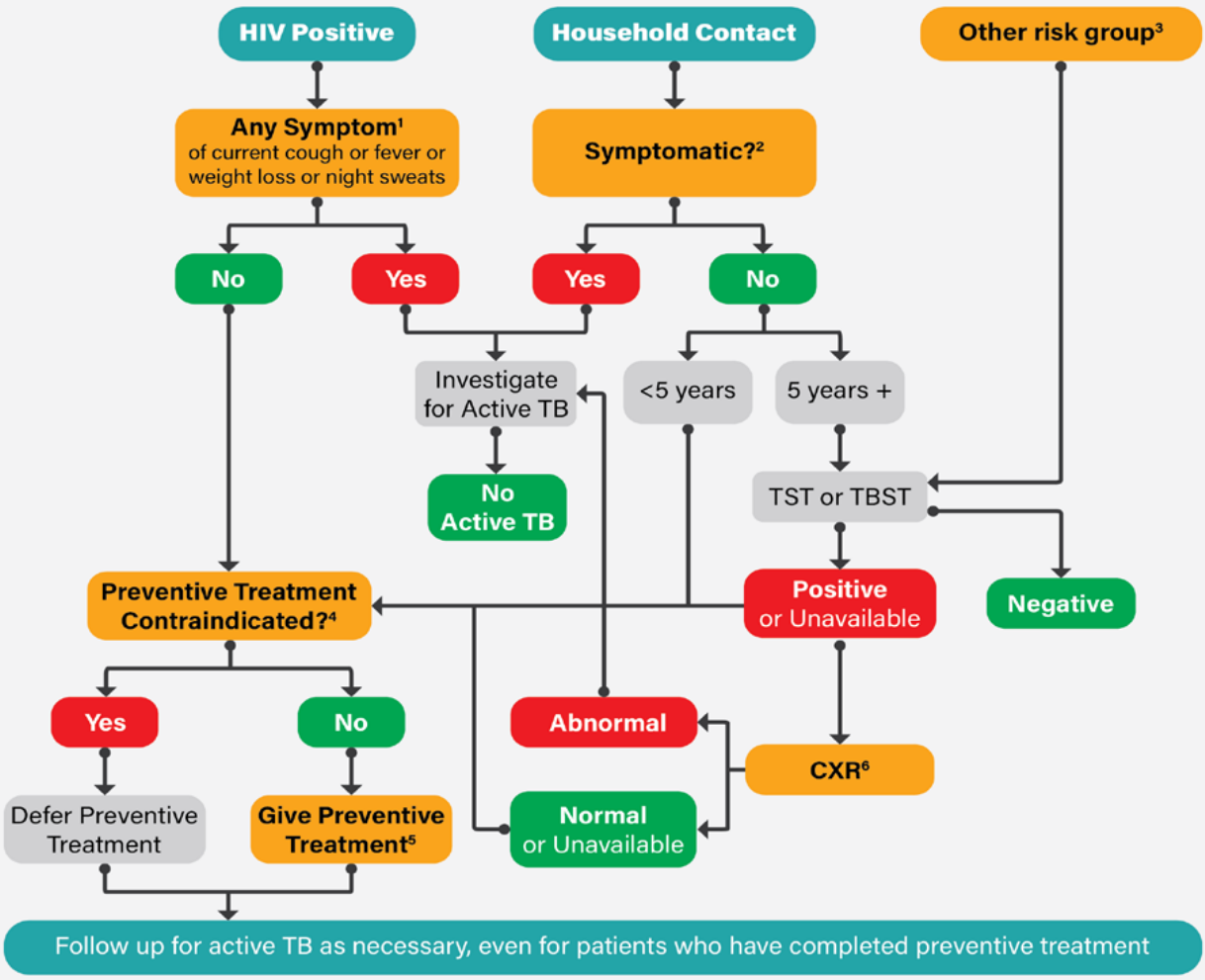
Group to be started on TPT after screening for TB infection with antigen-based skin test for TB infection (TBST till Antigen based Skin Test not available) Program to use TBST for the interim period till Antigen Skin Test is made available

- Adult household contacts of PTB cases (Both DS-TB and DR-TB)
- Patients undergoing hemodialysis
- Recipients of immunosuppressive therapy
- Patients receiving an organ transplant

Newer *Mtb* antigen-based skin tests (TBST) have been developed to measure the cell-mediated immunological response to *Mtb* specific antigens. Evidence suggests that these tests may offer similar specificity to IGRA, and when compared with TBST they may provide more reliable results in children and in people living with HIV. The TBST class is defined as skin tests for the detection of TB infection that use *Mtb* specific antigens

The program will aim towards focusing on vulnerable population groups on regular intervals and based on resources available. TBST will be introduced for identifying TB infection among vulnerable population who will then be initiated on TPT.

Algorithm for TB Preventive Treatment in Individuals at Risk



1. If <10 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 visit or growth curve flattening or weight for age <-2 Z-scores. As ymptomatic infants <1 year with HIV are only treated for TBI if they are household contacts of TB. TST or TBST may identify PLHIV who will benefit most from preventive treatment. Chest radiography (CXR) may be used in PLHIV on ART, before starting TBI treatment.

2. Any one of cough or fever or night sweats or haemoptysis or weight loss or chest pain or shortness of breath or fatigue. In children <5 years, they should also be free of anorexia, failure to thrive, not eating well, decreased activity or playfulnessto be considered asymptomatic.

3. Including silicosis, dialysis anti-TNF agent treatment, preparation for transplantation or other risks in national guidelines.

4. Including acute or chronic hepatitis; peripheral neuropathy (if isoniazid is used); regular and heavy alcohol consumption, pregnancy or a previous history of TB are not contrainfications.

5. Regimen chosen based on considerations od age, strain (drug susceptible ot oherwise), risk of toxixity and preferences.

6. CXR may have been carried out earlier on as part of intensified case finding.

Figure 11.1 Algorithm for diagnosis of tuberculosis infection (TBI) and TPT

11.3 Testing for tuberculosis infection

Testing for TB Infection increases the certainty that individuals targeted for treatment will benefit from it. However, there is no gold standard test to diagnose TB INFECTION. Earlier available tests (TST and IGRA) are indirect and require a competent immune response to identify people infected with TB. A positive test result by either method is not by itself a reliable indicator of the risk of progression to active disease.

New Antigen based skin test for TB infection Cy-Tb (formerly known as the C-Tb test, Serum Institute of India) contains a 1:1 ratio of two recombinant proteins of ESAT-6 and CFP-10 was previously produced by genetically modified Lactobacillus lactis, by Statens Serum Institute (Denmark). It amalgamates the cost-effectiveness and simplicity of a skin test with the accuracy of the traditional but high-cost lab based IGRA test and it remains unaffected by an individual's BCG vaccination status.

One single test dose of 0.1 mL contains 0.05 µg of rdESAT-6 and 0.05 µg of rCFP-10. The recommended administration is similar to the Mantoux (i.e. intradermal) method. If there is a resultant reaction, the transverse diameter of induration only should be measured and recorded in millimeters after 48–72 hours.

11.4 Treatment options for tuberculosis infection

The following are the treatment regimen options available:

Table 11.1 Treatment regimen options

Drug regimen	Dose per kg body weight	Maximum dose
3HP: Weekly Rifapentine plus Isoniazid for 3 months	Adult ≥30 Kg: HP 3 tabs weekly for 12 weeks. Individuals aged ≥ 14 years and weight 20–30 kg: HP 2 Tab weekly for 12 weeks	Rifapentine 900 mg Isoniazid 900 mg
Isoniazid alone, daily for 6 months	Adults, 5mg/kg	300 mg

Prophylactic Pyridoxine should be given to individuals at high risk of peripheral neuropathy, such as those with malnutrition, chronic alcohol dependence, HIV infection, renal failure, diabetes or who are **pregnant or breast feeding** when taking isoniazid containing regimens (Pyridoxine dose 25mg). **If Pyridoxine is given, it should be given at least 12 hours apart along with anti -TB drugs.**

11.5 Preventive treatment for contacts of patients with MDR-TB

In selected high-risk household or close contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualized risk assessment and a sound clinical justification.

- The preventive treatment should be individualized after a careful assessment of the intensity of exposure, the certainty of the source case, reliable information on the drug resistance pattern of the source case and potential adverse events.
- The preventive treatment should be given only to household contacts at high risk (e.g. children, people receiving immunosuppressive therapy and people living with HIV).
- **The drugs should be selected according to the drug susceptibility profile of the source case.**
- Confirmation of infection with TB Infection tests is required (TBST).
- Strict clinical observation and close monitoring for the development of active TB disease for at least 2 years is required, regardless of the provision of preventive treatment.

The regimen of preventive treatment of MDR-TB contacts should be based on reliable information on the drug resistance profile of the source case. Later-generation fluoroquinolones (e.g. levofloxacin) are considered to be important components of a preventive treatment regimen unless the strain of the source case is resistant to them. Although there has been concern about the use of fluoroquinolones in children because retardation of cartilage development was shown in animals, similar effects have not been demonstrated in humans.

For TPT among household contacts of MDR-TB patients, consider levofloxacin with or without ethionamide daily for six months *(The drugs should be selected according to the drug susceptibility profile of the source case and will be based on advice of specialists).*

The Levofloxacin dosage for TPT for MDR is as below:

- Age >14 years, by body weight: < 46 kg, 750 mg/day;
- ≥ 46 kg, 1g/day
- Age <15 years (range, approx. 15–20 mg/kg/day), by body weight:
- 5–9 kg: 150 mg/day;
- 10–15 kg: 200–300mg/day;
- 16–23 kg: 300–400mg/day;
- 24–34 kg: 500–750mg/day

CHAPTER 12
CONTACT INVESTIGATION

12.1 Rationale for Contact Investigation

The systematic evaluation of persons who have been exposed to potentially infectious cases of TB can be an efficient, targeted approach to intensify active TB case finding. This intervention method is termed as 'Tuberculosis Contact Investigations (CI)'. Systematic reviews of published studies from low and middle-income countries have shown that a pooled average of 3.5%-5.5% TB positivity rate among the household and close contacts of a person who had infectious TB. These findings suggest that CI may result in earlier case identification, possibly leading to decreased disease severity and reduction in transmission of *Mycobacterium tuberculosis* (WHO, 2019). With the ever-increasing incidence of TB, especially MDR-TB among the new TB patients in Bhutan, it is a wake-up call for us to design an appropriate and effective **"TB Contact Investigation Model for Bhutan"**, contextualizing the experiences and evidences of potential benefit in the countries that routinely perform CI.

This guideline emphasizes on importance of CI, priorities for evaluation, roles and responsibilities and the CI procedure through collecting and recording relevant data. Through this contact tracing design for Bhutan, it is expected to improve the efficiency and uniformity of CI, active case finding, diagnosis, treatment and evaluation.

CI has high potential to identify persons with TB Infection who are high priority candidates for preventive therapy whereby help to interrupt spread of TB and prevent outbreak of TB. It will also involve extensive follow-up, medical assessment of contacts, importance of communication and liaison. Effective interviewing skills are essential for eliciting information from cases and their contacts. CI Interview skills can be taught and improve with practice (WHO, 2012; Woodhouse et al., 2010).

12.2 Objectives

The Bhutan **"TB Contact Investigation Model"** is a systematic process with the overall objectives to:

- Identify and prioritize TB index cases around whom contact investigation should be focused
- Conduct systematic and prompt evaluation of close contacts and household contacts of all TB cases detected and put on treatment
- Investigate all the contacts of index positive cases immediately (within 72 hours) of the diagnosis
- Further reduce the spread of TB by timely diagnosis and initiation of early effective treatment of secondary cases
- Provide education and counselling to the contacts and to the community at large (Ireland, 2010; WHO, 2012).

Contact tracing activity should be supervised, monitored and audited periodically to ensure quality and consistency with guidelines. Screening should be concluded when levels of infection detected in the tiers of at risk contacts equate to those in the general community (Woodhouse et al., 2010).

12.3 Contact investigation team

All contact tracing exercises should be supervised by the CMO/MO of the reporting health centre in that district where the index case is notified. In this Bhutan Model of TB Contact Investigation, the nearest health care centres (PHCs, Hospitals and Referral Hospitals) will perform the contact tracing in their jurisdiction and file in the report to the NTCP.

Initial CI will be done by the TB In-Charge in consultation with the CMO. The VHW and PHCs will be involved as a key partner to bridge the gap between public health services and the communities. **IF REQUIRED**, a CI team will be decided by the TB In-charge, CMO & District Health Officer (DHO). The CI team may comprise of:

- **DS-TB**
    - TB In-charge
    - Laboratory technician
- **DR-TB**
    - Medical Officer
    - TB In-charge
    - Laboratory technician
- **Pre-XDR TB/XDR-TB**

Whenever a Pre-XDR-TB or XDR-TB is notified, the National TB Reference Laboratory (NTRL), RCDC will lead the CI at the earliest and NTCP team will provide support wherever required.

12.4 Tasks for the Contact Investigation Team (Roles and Responsibilities)

Initiate contact investigation by applying the following;

- Identify the index case eligible for CI and conduct detailed interview of the index case using the prescribed form
- Trace the contacts either systematically (door-to-door) or through social contacts using the information recorded with the index case
- Identify people with presumptive TB by applying the screening algorithm
- Perform TST/new CyTB test on the groups targeted on TB Infection treatment (TPT)
- Apply appropriate infection control measures when in contact with people with presumptive TB

- Ensure sputum samples collection in the community (SMS) to rule out active TB and transport to the nearest microscopy centre for testing and GeneXpert for all presumptive cases
- Complete contact tracing forms and follow-up with the investigation report and update the form in the TbISS
- Trace people with TB who are lost to follow-up
- Support and monitor treatment including TB Infection
- Organize awareness-raising activities in the community (WHO, 2018b)

12.5 Contact tracing method and establishing limits for contact investigations

The "TB Contact Investigation Model for Bhutan" will use the concept of the 'stone in the pond' or 'concentric circle' to limit contact investigations (Figure 12.1).

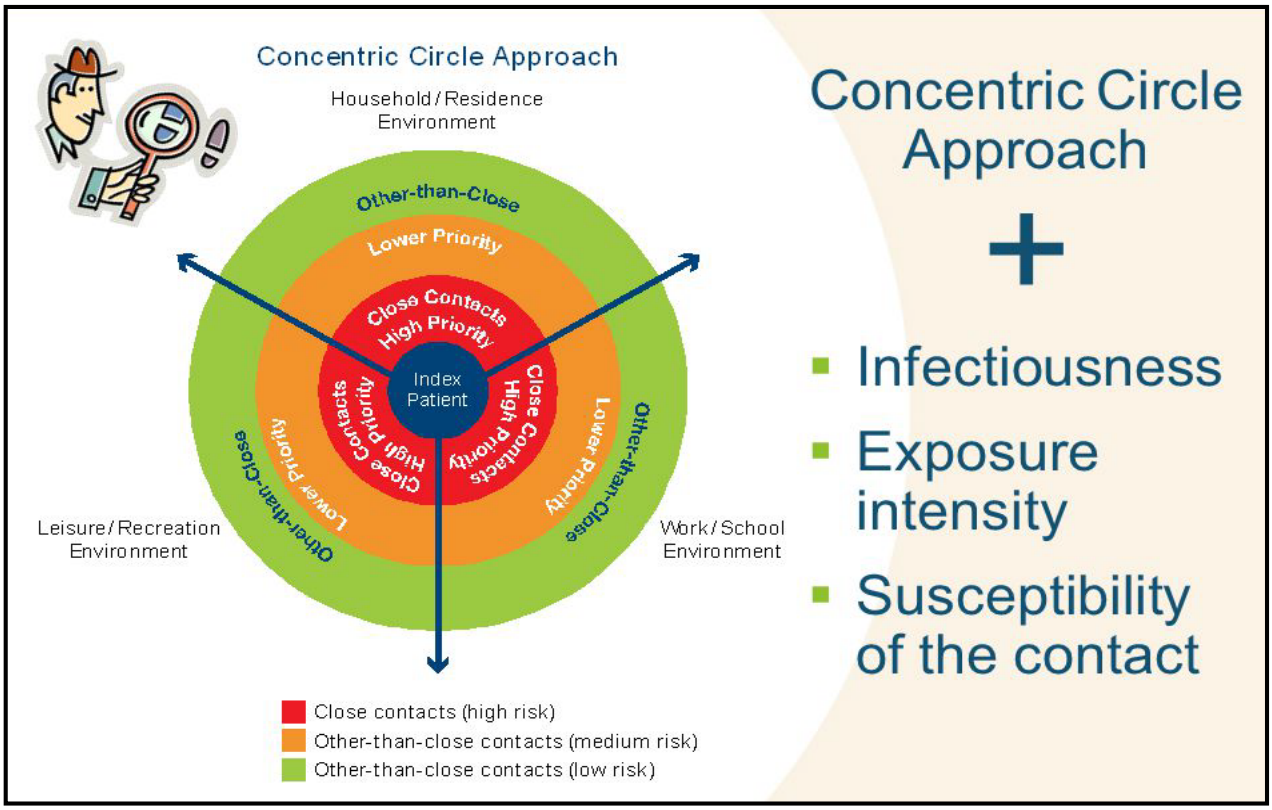


Figure 12.1 concentric circle approaches to contact tracing method
(Source: Caribbean Guideline for Prevention, Treatment, Care and Control of TB/HIV, March 2010.)

Contact investigation should be limited to situations with a clear likelihood of transmission or to those with a higher probability of developing active TB. For instance, young children and immunocompromised persons. A risk assessment based approach is recommended, where the need to screen contacts is prioritized on the basis of the infectiousness of the index case, intensity of exposure and susceptibility of contacts (Erkens et al., 2010)

Table 12.1 Definition of contacts

Concept	Definition	Comments
Index case (index patient). *Further explained in WHO recommendations on defining the index case.*	The initially identified case of new or recurrent TB in a person of any age in a specific household or other comparable setting in which others may have been exposed	An index case is at the "centre" of the contact investigation. Because the investigation generally focuses on a defined group of potentially exposed people in which other (secondary) cases may be found. The index case is generally the case identified initially, although he/she may not be the source case. Contact investigation may centre on secondary cases if the exposed group differs from that exposed to the original index case.
Contact	Any person who has been exposed to an index case (as defined above).	Exposure may be intense or casual, easily identified or obscure. Close exposure, such as sharing a living or working space, is generally easily identified and quantified, whereas casual exposure, such as on public transport or in social situations, may be unidentifiable.
Household contact; *refer Note**	A person who has shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case during the 3-months before commencement of the current treatment episode.	Definitions of 'household' vary considerably and must be adapted to the local context. Within households there is a gradation of exposure, ranging from sharing the same bed as the index case to living in the same compound, but not in the same enclosed space (an individual sharing a bedroom, kitchen, bathroom, or sitting room). Quantification of the amount of exposure, estimated as the time spent with the index case, is likely to be highly subjective. For this reason, the infectious period for the index case is set somewhat arbitrarily at 3 months before initiation of treatment, rather than relying on the index case's recollection of when symptoms began. The 3-month period is a general guideline; the actual period of infectiousness may be longer or shorter. For example, prolonged infectiousness may be associated with non-adherence (if DOT is not being used) or with unrecognized or untreated MDR-TB or XDR-TB.
Close Contact*	A person who is not in the household, but has shared an enclosed space, such as a social gathering place, workplace or facility, for extended periods during the day with the index case during the 3 months before commencement of the current treatment episode.	In many situations, out-of-household exposure is as likely to result in transmission as household exposure. Molecular epidemiological studies showed that transmission was likely to occur in social settings such as informal bars in Mexico and South Africa and in facilities such as correctional institutions and hospitals. Such sites (particularly social settings) are difficult to identify and require knowledge of the culture and behavioural patterns in order to focus contact investigation.

(WHO, 2018c)

Note*: Depending on the setting, a household contact can be:

- Anyone living in the house at the time of the index case's diagnosis
- Anyone living in the household full-time
- Anyone who has lived in the house for a number of weeks or months (3 months)
- Anyone who spends more than a certain number of hours per week in the home (of particular consideration for children who might be in care outside of a home or with a relative who occasionally comes to the home)
- Anyone who has meals in the household on a regular basis (WHO, 2018b)

In a population-based tuberculosis contact investigation study conducted by Baliashvili et al. (2018), household contacts were more likely to have TB Infection (adjusted OR 2.28, 95%CI 1.49–3.49) than close contacts.

12.6. Standard Operating Procedure (SOP)

12.6.1 Flow of information to initiate CI

i. A positive TB patient should be registered by the concerned laboratory personnel in TbISS as soon as possible and **no later than 12 hours following diagnosis**

ii. Once a positive pulmonary TB case is registered in TbISS, the NTCP staffs and relevant district officials in the district will be notified through SMS alert and Email

iii. Following the alert, the M&E Officer, NTCP will call the TB In-charge from where the case is **notified within 12 hours** and will record the information in the defined SMS alert and contact tracing monitoring tool maintained at the NTCP.

iv. Following the call from the NTCP, TB In-charge shall discuss with MS/CMO and **initiate CI at the earliest, no later than 72 hours**

v. NTCP will give a **follow up call after 72 hours of notifying a positive case for follow up and obtain progress within the specified time.**

vi. The TB In-charge is responsible for conducting CI and entering the findings in the TbISS as well as **submit a summary report to NTCP using the defined reporting format within 7 days.**

12.6.2 How to conduct CI?

i. Comprehensive information about the index case should be collected using the Index Case Interview Form.

ii. The index case should be interviewed to elicit the names, contact numbers and address of the household and close contacts. The TB In-charge should contact all the contacts over the phone and inform them for further screening and investigations.

iii. The TB In-charge will call contacts of the index case to health centre if the contacts reside near a health center or visit the place where the contacts are residing for preliminary investigation and to ensure referral of the contacts for further evaluation.

iv. If the notified case is from schools, prisons, institution, office, etc, TB In-charge should carry out targeted screening of contacts of the index case. For example, if a TB case is being reported from a boarding school, targeted screening should focus on screening contacts in the dormitory and classroom.

v. Owing to the risk of exposure to other OPD patients, the contacts will first meet the TB In-charge and then the TB In-charge will direct to the clinicians and facilitate further investigation procedures. For example, all presumptive TB cases or contacts of a confirmed TB case can be fast tracked by the receptionist by providing a "Yellow Sticker" on the OPD prescription form.

12.7. TB Contact Tracing Algorithm

The contact investigation will be conducted following the algorithm as reflected below:

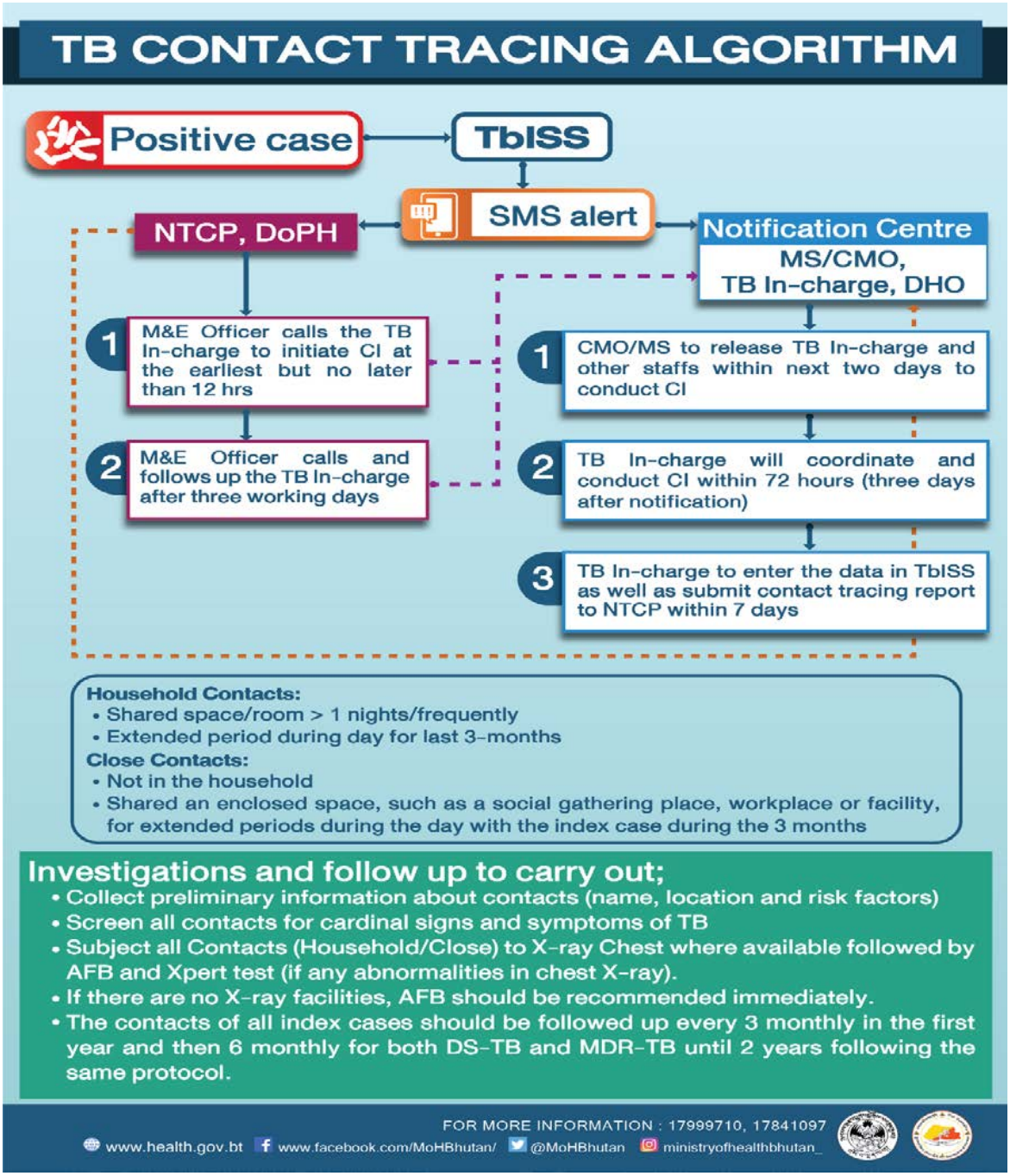


Figure 12.2 TB Contact Tracing Algorithm

12.8 Determining the period of infectiousness

Contact investigation should extend back to the **date of onset of cough** in the index case or for **three months** if the date of onset of cough is unknown or there is no history of cough. The period

of inquiry about contact exposure may also need to be extended if the source case is highly infectious (Woodhouse et al., 2010).

Determining the infectious period focuses the investigation on those contacts most likely to be at risk for infection and sets the timeframe for testing contacts. Cases of pulmonary TB are generally considered to become infectious at the time of onset of cough. If no cough is reported or if the duration is difficult to determine, the time of onset of other symptoms attributable to TB may be used to estimate the onset of infectiousness. In practice, however, it is often difficult to know with certainty when symptoms began. Because the start of the infectious period cannot be determined with precision by available methods, a practical estimation is necessary (Ireland, 2010).

12.9 TB Infection screening and evaluation of CI

12.9.1 Screening tools- Diagnostics

The National Program is incorporating the new Antigen based skin test for TB infection Cy-Tb (formerly known as the C-Tb test, Serum Institute of India). One single test dose of 0.1 mL contains 0.05 µg of rdESAT-6 and 0.05 µg of rCFP-10. The recommended administration using the Mantoux (i.e. intradermal) method. If there is a resultant reaction, the transverse diameter of induration only should be measured and recorded in millimeters after 48–72 hours. It will be used on the groups targeted for TB INFECTION treatment during contact investigation.

12.9.2 Evaluation of contact investigation

The evaluation of outcomes from contact investigation is important for evaluating the TB control programme, determining the appropriateness of decisions made regarding the contact investigation and future planning. At a minimum, the following information should be collected:

- The number of contacts identified (particularly close contacts)
- The number of contacts who underwent a completed medical evaluation and relevant investigations: number, age (especially children <5 years of age), sex and HIV status of the contacts identified
- The number of contacts diagnosed with active TB disease
- The number eligible for TB preventive therapy (TPT) and
- The number who accepted and completed preventive therapy.

Data from the contact investigation should be collected in a standardized format (Annex 7) and reported to NTCP. NTCP should routinely evaluate the effectiveness of CI and design interventions to improve performance. The yield of CI and the incidence of active TB and LTBI should be evaluated to determine whether the intervention is giving the desired results.

12.10 Monitoring and follow-up of CI

- Monitoring will focus on timeliness and completeness of CI procedures. **Follow up telephonic monitoring will be conducted by the M&E officer to the TB In-charges 3 monthly in the first year and then 6 monthly for both DS-TB and MDR-TB until 2 years following the same protocol.**

- During the follow up of the TB patients after zero month, CXR should be used for screening and should also subject to sputum AFB and Xpert test if symptomatic and abnormal CXR.

- An annual review of the CI will be conducted by the NTCP officials in consultation with the district colleagues.

CHAPTER 13
TB INFECTION PREVENTION AND CONTROL

13.1 Introduction to TB infection prevention and control

A person with pulmonary TB or laryngeal TB can release droplet nuclei with M. tuberculosis bacilli into the air by coughing or sneezing. These droplet nuclei particles are invisible to the naked eye and are approximately 1 to 5 microns in size. Droplet nuclei can remain airborne in a room environment for a long period of time, until they are removed by natural or mechanical ventilation. Anyone who shares air with a person with infectious TB disease of the lungs or larynx is at risk. Fortunately, TB is not usually spread by brief contact. TB is spread when another person inhales these particles and becomes infected with TB.

13.2 Airborne infection control

The selection for which combination of control measures should be implemented will be based on the infection control assessment and by the local epidemiological, climatic and socioeconomic conditions. Generally, the infection control measures are divided into administrative, environmental and personal protection control measures.

13.3 Administrative controls

The first and most important level of a TB infection-control program is the use of administrative measures to reduce the risk of exposure to persons who might have TB disease. Administrative controls consist of the following activities:

- Assign responsibility for TB infection control to TB/IC focal person
- Conduct TB risk assessment
- Develop and institute a written TB infection-control plan (SOP/protocol)
- Implement effective work practices for the management of patients with suspected or confirmed TB disease
- Ensure proper cleaning and sterilization or disinfection of potentially contaminated equipment
- Train and educate health care workers
- Test and evaluate health care workers for TB infection and disease annually
- Apply epidemiologic-based prevention principles
- Use posters and signs demonstrating and advising respiratory hygiene and cough etiquette
- Ensure timely availability of laboratory testing, specimen processing, and reporting with an emphasis on using WHO recommended rapid diagnostic tests.
- Perform active surveillance of healthcare workers for active TB disease.
- Consider routine screening healthcare workers for TB INFECTION and treating them if present.
- Develop an educational program for all healthcare workers
- Use appropriate signage to indicate isolation areas and to promote cough etiquette

- There should be dedicated place for sputum collection with proper ventilation or with UVGI light, if there is dedicated place sputum collection should be carried out in open space

13.3.1 Administrative control strategies for health care facilities

Administrative control measures (policies and work practices) have the greatest impact on preventing TB transmission. They serve as the first line of defence for preventing the spread of TB in health care settings.

a. Outpatient settings:

Out-patient departments are frequently crowded, with poor ventilation, and long waiting times, and now there is the added risk of Covid-19. Therefore, it is important to;

- Triage those with respiratory symptoms (segregating those who are coughing from those who are not). Rapid triaging should be done as early as possible upon the arrival of the patient at the health facility.
- Provide Mask (surgical) should be given to the patient with respiratory symptoms at the reception
- **Triage & Fast-track patients with cough for both clinical and laboratory investigations in all health facilities. For example, a fast-track stamp or token may be provided for respiratory patients during further investigation.**
- Provide patient education on cough hygiene and sputum disposal
- Segregate patients with respiratory symptoms without stigmatizing
- Well ventilated waiting area - preferably through an open corridor/s
- All the OPD patients with flu like symptoms to encourage to visit the Flu Clinics

There is no designated sputum collection place in the hospitals and it is usually promoted in open air space. Therefore, to provide privacy and to assure quality sputum sample, hospitals are encouraged to build a low-cost sputum collection booth with wash basin at a suitable location in the vicinity of the hospital/flu clinic area.

b. Inpatient settings:

- Minimize or no hospitalization of TB patients.
- Maintain gap of 1 meter between beds for admitted patient
- **Establish separate rooms, wards or areas within wards for patients with infectious respiratory diseases, such areas should promote minimum mixing with other patients.**
- Educate inpatients on cough hygiene and sputum disposal
- Establish safe radiology procedures for patients with infectious respiratory disease including smear-positive TB cases or TB suspects
- Teach the attendants and staffs how to wear mask (N95)
- Fit test should be performed while wearing N95 mask

- Provide the sputum cup 1/4th filled with 0.5% bleaching solution
- Tell the patient to spit in the sputum cup only and cover it properly when not in use
- Instruct the patient to stay in the ward and not to roam around and mingle with other patients
- In case the patient has to move around, ask them to wear surgical mask
- If there is no isolation room cohort the patients
- Instruct the patient and attendants to dispose of the face mask in the red bin
- Train the health workers on respiratory protection
- Educate patients on respiratory hygiene and the importance of covering their mouth

Screening of TB amongst health workers

Periodic TB screening should be provided for health care workers and laboratory staffs. It is important to initiate regular screening and monitoring of health care workers using Chest X-ray as per the Health Screening Manual for Healthcare Workers 2020.

13.4 Environmental Controls

The second level of an infection-control program is the use of environmental controls. Environmental controls consist of engineering technologies that are designed to prevent the spread and reduce the concentration of infectious TB droplet nuclei in ambient air. The technologies include

- Ventilation technologies
- Natural ventilation
- Mechanical ventilation
- High efficiency particulate air filtration (HEPA)
- Ultraviolet germicidal irradiation (UVGI)

Ventilation technologies: Is the movement of air in a building and the replacement of air in a building with air from outside. When fresh air enters a room, it dilutes the concentration of particles in room air, such as droplet nuclei containing *M. tuberculosis*.
There are two general types of ventilation:

- Natural Ventilation
- Mechanical Ventilation

i. **Natural ventilation**: relies on open doors and windows to bring in air from the outside.

ii. **Mechanical ventilation:**

Refers to the use of technological equipment to circulate and move air in a building. Mechanical ventilation can consist of two types of technologies, Local exhaust ventilation, and general ventilation.

a) Local exhaust ventilation: is used to control the source of infection by stopping airborne contaminants before they spread into the general environment
b) General Ventilation: General ventilation systems maintain air quality in health care settings by the dilution of contaminated air removal of contaminated air. Air **dilution** occurs when an uncontaminated air supply mixes with contaminated air in a room. The air is then moved from

the room, outside, away from people, air intakes, or windows, by the exhaust system **(removal)**. This process reduces the concentration of TB droplet nuclei in the room.

(A) (B)

(A) Direction of natural ventilation and correct working location.

(B) Direction of natural ventilation and incorrect working condition.

Figure 13.1 Mechanical ventilation

Ventilation:

- Use natural ventilation and fans to provide this air where there is no central ventilation system
- Keep doors, windows, and skylights open as often as possible
- Check that doors, windows, and skylights are easy to open
- Add fans to increase air mixing and directional airflow
- Keep fans running as much as possible when the space is occupied
- Place fans so that air movement can be felt in all occupied parts of the room
- Room fans should be placed in locations where they will add to natural ventilation currents. For example, if a building experiences natural air currents from east to west, fans should be placed so that air is blown out the west windows
- Place fans so that air flows from clean to less clean areas. Place staff near fresh air sources

iii. High Efficiency Particulate Air (HEPA) filters

HEPA filters are special filters that can be used in ventilation systems to help remove droplet nuclei from the air. HEPA filters must be used when releasing air from local exhaust ventilation booths into surrounding areas and when releasing air from an AII room to the general ventilation system.

iv. Ultraviolet Germicidal Irradiation (UVGI)

UVGI, is an air-cleaning technology that consists of special lamps that give off ultraviolet light. The lamps are used to kill the tubercle bacilli contained in droplet nuclei. However, exposure to ultraviolet light can be harmful to the skin and eyes of humans, so the lamps must be installed in the upper part of rooms or corridors or placed in exhaust ducts. HEPA filters and UVGI should be used in conjunction with other infection control measures.

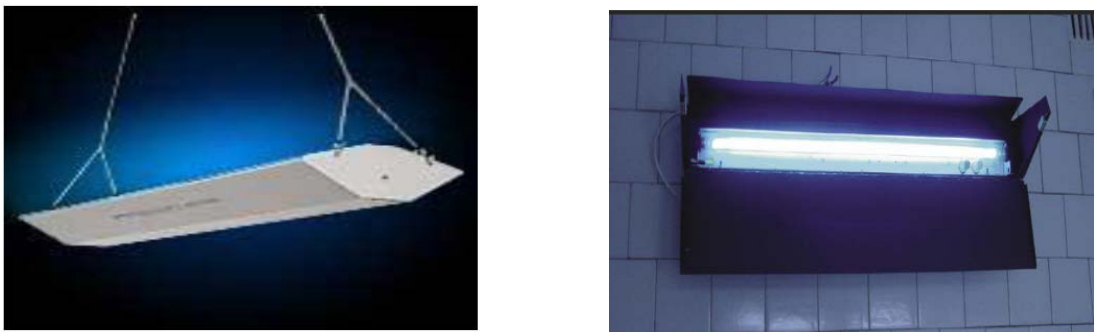


Figure 13.2 Ultra violet germicidal irradiation lamps

13.5 Respiratory-Protection Controls (PPE-Personal protective equipment)

The third level of infection-control is the use of respiratory protection equipment and other PPE. Respiratory-protection controls reduce the risk of TB transmission in settings where administrative and environmental controls may not fully protect persons against droplet nuclei.

13.5.1 Personal Protective Equipment

These include the following:

a. Gloves - should be worn when coming in contact with respiratory secretions or contaminated articles
b. Plastic aprons and gowns - should be worn at the time of contact with the patients and their environment to avoid contamination of clothing
c. Masks- to reduce aerosol spread, give surgical masks to patients. N95 Respirators for healthcare workers in special situations like:
    - During high-risk aerosol generating procedures associated with high risk of TB transmission especially in laboratory where sputum needs to be manipulated during culture.
    - Providing care to infectious or presumptive MDR/XDR-TB patients. TB wound care too requires the wearing of particulate respirators and gloves
    - N95 Masks should be close fitting and filter particles of 1-5 microns. N95 particulate respirators have a filter efficiency of 95% and are usually used.
    - N95 masks can be reused a few times, provided they are not damaged and the elastic bands are working well.
    - Careful labelling is required for a single staff member's use and the masks should be stored without being contaminated (in a Ziplock)
    - Train health worker how to wear, remove, and dispose the mask
    - N95 mask different sizes should be available all the time

13.5.2 Fit check

To be performed every time the respirator is worn.

Negative fit check:

- Cup hands over respirator without excessive pressure. Breathe in sharply

- A light collapse of the respirator should be felt with no air leaking around the face to-face piece seal

Positive fit check:

- Cup hands over respirator. Blow out
- A build-up of air should be felt with no air leaking around the face-to-face piece seal.
- For donning and doffing (refer National guideline on Infection control and medical waste management 2018)

13.6 Infectious waste disposal

- Waste should be segregated at the point of generation in color coded waste bin
- Infectious waste should be treated before disposal (refer National Guideline Infection Control and Medical waste management, 2018)
- Sputum cup should be emptied in the toilet pot once 3/4th filled and flush down with plenty of water and disinfect the toilet pot
- Blood and body fluid should be decontaminated by 0.5% bleaching solution before disposal
- Reusable medical devices should be cleaned and sterilized for reuse (refer National Guideline Infection Control and Medical waste management, 2018)

CHAPTER 14
RECORDING AND REPORTING

An effective and accurate recording and reporting system, whether paper based or electronic, are essential to ensure high quality care of TB patients and accurate sharing of information. A proper and systematic data recording and reporting by the health centers is necessary to monitor the treatment progress of an individual and groups (cohorts) of patients. It will also ensure continuity of care when patients are referred between health care facilities until the treatment outcome of a patient is known (WHO 2012). Moreover, the data collected at the TB Reporting centers is necessary to monitor the trends in the TB epidemic at the district and national level for evidence-based planning and policy development.

Currently, recording and reporting in Bhutan is paper based maintained through district registers and cards. In parallel, there is TbISS (Tuberculosis Information and Surveillance System), an online TB electronic system for data recording and reporting to ensure comprehensive data entry, facilitate communication and to provide a clear flow of data to other levels of the health system. The data recorded in the paper-based system is systematically entered into TbISS at the earliest possible.

14.1 Recording System

14.1.1 District Tuberculosis Laboratory Register for smear microscopy and Xpert MTB/RIF

The Tuberculosis Laboratory Register is maintained at all laboratories and microscopy centers where sputum smear examination or GeneXpert test for TB is carried out. The laboratory technician is responsible for maintaining and timely updating the register. The register includes results from both types of tests – samples for diagnosis and for follow-up.
The register records all symptomatic patients who have had a sputum smear examination, the number of smear-positive cases detected and the number and results of smear examination for treatment follow-up.

It is recommended to maintain two separate district TB lab register; one for PTB and another for EPTB. The content and instruction to fill up the register remains the same.

14.1.2 District TB Register

The district TB register is primarily intended for recording the data needed to monitor performance of TB Reporting center, using information and reports about TB patients. It is also commonly used to summarize test results and treatment decisions in order to determine whether basic diagnostic and treatment guidelines are correctly implemented.

This register is maintained by the district TB in-charge and they are responsible to enter all the information on the TB patients. The register should contain the records of the patient's demographic information, patients diagnosed with TB and eligible for TB treatment and etc. This register should be updated regularly according to the TB Treatment Card of the patient. This will facilitate the TB in-charge in preparing the quarterly TB reports and cohort analysis of treatment outcome.

14.1.3 Tuberculosis Treatment Card

The TB in-charge will fill the Tuberculosis Treatment Card as soon as the patient is diagnosed with TB. The card is kept at the health facility where the patient is treated.

14.1.4 Tuberculosis Patient Card

The TB Incharge will fill up this card as soon as a patient is diagnosed as TB and the card is given to the patient. The patient should be instructed to bring the card when he/she visits the TB unit for anti-TB treatment and during follow up visits. The information and instructions for filling up the card are similar to the TB Treatment Card.

14.1.5 Request form for Bacteriological Examination by Microscopy and Xpert MTB/RIF

This form should be completed by the laboratory technician of the concerned hospital in consultation with physician and district TB incharges. All the required information in the form should be completed for individual patient and the sample collected from the patient need to be shipped to the nearest GeneXpert center for Xpert MTB/RIF test.

This form consists of two parts:

- the upper part of the form should be filled up by the requesting physician for complete information. The reason for subjecting to GeneXpert should be clearly marked in the form along with the OPD slip. The request can also be done on the OPD slip along with request form.
- the laboratory technician of the GeneXpert center should fill the lower part of the form and the report must be sent to the non-GeneXpert (referring) center or the treating physician of the GeneXpert center for necessary action as soon as the results are available.

14.1.6 Contact tracing reporting form for NTCP

This is the reporting form for the contact tracing done for the TB and MDR-TB patients. This form needs to be submitted to the Program after the contact tracing has been carried out.

14.1.7 Sputum Request and Shipment Form for Culture and DST

This form should be completed by the laboratory technician of the referring center with all the required information and two samples collected from the patient need to be shipped to the NTRL/RCDC for culture and DST.

This form consists of two parts:

- the upper part of the form should be filled up by the laboratory technician. The request can also be done on the OPD slip along with request form.
- the laboratory technician/technologist of the NRTL/RCDC should fill the lower part of the form and perform necessary test. The NRTL/ RCDC should send the result of the test to the referring center or the treating physician as soon as the report is ready.

14.1.8 MDR-TB/XDR-TB treatment register

The MDR-TB/XDR-TB treatment register is primarily intended for recording the data needed to monitor performance of TB Reporting center, using information and reports about MDR-TB patients. In contrast to the District TB Register, it is restricted to patients who have actually started on a second-line TB treatment regimen. This register is also commonly used to follow, at a glance, the adequacy of testing and treatment decisions. The register should be updated regularly from the individual MDR-TB/XDR-TB treatment cards and from laboratory registers. Patients are recorded in the register consecutively by date of registration. A patient's date of registration is the day when health staff enter him or her in the register. **Unlike in the past, this register will be maintained by all the TB reporting centres. The TB Incharge will record the patient's information when the patient is transferred to their centre. This will keep track of the patient and their follow up schedules for investigations and review.**

14.1.9 MDR-TB/XDR-TB Treatment Card

The TB in-charge will fill the MDR-TB/XDR-TB Treatment Card as soon as the patient is diagnosed as MDR-TB/XDR-TB. The card is kept at the health facility where the patient is treated. This card will keep track on the schedules for the follow up of the patient while on treatment and until the completion of treatment.

14.1.10 MDR-TB Follow up laboratory register

The MDR-TB follow up laboratory register is intended to record the data using the information and reports about MDR-TB patients from the laboratory registers. **Unlike in the past, this register will be maintained by all the TB reporting centres. The laboratory technician of the TB laboratory unit will record the patient's information when the patient is transferred to their centre. This will keep track of the patient and their follow up schedules for investigations and review.**

14.1.11 MDR-TB/XDR-TB Patient Card

The TB in-charge will fill the MDR-TB/XDR-TB Patient Card as soon as the patient is diagnosed as MDR-TB/XDR-TB. The card is kept with the patient. The patient should be instructed to bring the card whenever he visits the TB unit and Doctor's chamber for review and follow up. This card will keep track on the schedules for the follow up of the patient while on treatment and until the completion of treatment.

14.1.12 TB Infection Treatment Card

This card is introduced for the first time with the revision of the guideline. The TB in-charge will fill the TB Infection Treatment Card as soon as the patient is eligible to receive TB Preventive Treatment (TPT). The card is kept at the health facility where the patient is treated. The card will record the information on the patient who will be put on TPT

14.1.13 TB Infection Patient Card

This card is introduced for the first time with the revision of the guideline. The TB in-charge will fill the TB Infection Patient Card as soon as the patient is eligible to receive TB Preventive Treatment (TPT). The card is kept with the patient and he/she should be instructed to bring the card during his visit to the TB unit.

14.1.14 NTRL Laboratory register for culture, Xpert MTB/RIF and drug susceptibility testing

This register is used for laboratories capable of undertaking more advanced specimen testing (culture, Xpert MTB/RIF, DST), such as reference laboratories. All the laboratory test performed to the patient should be recorded in the register.

14.2 Reporting System

The TB In-charges will prepare the report (paper based) as per the table below by referring the District TB Register and sent it to NTCP on quarterly basis. In parallel, the TB In-charges should also enter the same data in TbISS every day or at the earliest possible. The report will be used by NTCP to monitor laboratory performance, case finding, type of cases by age and gender, cases registered by treatment category, sputum conversion at 2/3 months for the previous quarter and treatment outcomes and quarterly monitoring of Anti-TB Drugs.

The dual reporting is maintained to ensure data accuracy and for verification by the NTCP. The following reporting format (both paper-based and TbISS) will be used for reporting:

14.2.1 Quarterly TB Case reporting

The TB In-charge should fill this report **every three months**. They have to prepare the report at the end of each quarter referring the TB register.
The quarterly report should be submitted manually or electronically to the National TB control Program as per the following schedule.

Time line for the submission of report

Quarter 1(January-March)	Latest by 14th April of the same year
Quarter 2(April-June)	Latest by 14th July of the same year
Quarter 3(July-September)	Latest by 14th October of the same year
Quarter 4(October-December)	Latest by 14th January of the succeeding year

14.2.2 TB & MDR-TB Mortality Reporting Form

All the TB reporting centers in consultation with treating physician should report the death of TB patients who were on treatment. The actual cause of the death should be ruled out and clearly mentioned in the reporting form. The form should be submitted to the Program as and when a death occurs to a TB patient.

14.2.3 TB *Infection* Quarterly Report Form

The TB Infection Quarterly Report will be prepared by the TB Incharge using the information from the TB Infection Treatment cards of the patients. The report should be submitted on a quarterly basis like the quarterly DS TB report. The report can be attached with the Quarterly DS TB Report and submit to the Program.

CHAPTER 15
SUPERVISION, MONITORING AND EVALUATION

This chapter will discuss about the importance and mechanism of supervision, monitoring and evaluation system that need to be rationalized in all districts to ensure quality care. An effort has been made by the NTCP to improve the supervision and monitoring activities by preparing a comprehensive and standardize checklist that could be used during the supervision and monitoring visits. The supervision in particular promotes successful implementation of program activities and M&E ensures that the implementation is moving in the right direction to achieve the desired goals, objectives and targets. Therefore, to ensure that the activities are implemented as planned and the data recorded and reported is accurate and valid which is used ultimately to monitor program indicators, a strong supervision and monitoring with regular communication between the central and peripheral levels of the health system is vital.

15.1 Supervision

Supervision can be defined as a relationship between different levels of the staff which is evaluative, serving to enhance the skills of the staff and to monitor the quality of the services provided by them at various levels of functioning. Supportive supervision of staffs is necessary to improve the management of health service delivery. It will support staffs, improve their knowledge and perfects their skills. It is thus an extension of training. Supportive supervision will also improve their attitudes towards their work and increases their motivation as routine supervision provides a platform to discuss problems with staff and work with them to find solutions (WHO 2008).

15.2 Supervisory visits

Supervisory visits give an opportunity to assess the performance of the health staffs and provide technical advice and guidance to correctly perform activities as stipulated in the programme.

15.3 Objectives of supervision

- build capacity of health staff to implement TB health services as per the National Guideline for the Management of TB
- ensure that the data recorded and reported is accurate and valid and also advice to update the missing information promptly
- provide actionable and timely feedback
- evaluate impact of training on performance of health staff
- assess retraining needs and
- assess stocks and replenishment of supplies.

The frequency and the number of all supervisory visits should be planned carefully and prepared on a schedule based on the priority needs and available performance indicators of each unit. Adequate time should be allocated for each supervisory visit.

15.4 Modality of Supervision and Monitoring

In line with the End TB Strategy 2030, Bhutan will shift to regionally based supervision and monitoring model for TB control activities, which will be done by a trained medical officer or a TB expert in the region. The entire country will be divided into 5 to 6 regions based on the TB burden (Figure 15.1). The TB supervisory and monitoring officer will conduct vigorous supervision and monitoring periodically in his/her area using the check list provided by the NTCP. Reports shall be compiled and submitted to the programme for further necessary action. For TB laboratory focal points, NTRL, RCDC will be responsible to make supervision and monitoring visits periodically so as to ensure laboratory QA. Direct supervision by the central program will be made only if there are major issues in the field which is beyond the scope of the regional TB supervisory officer's capacity or whenever there is a need to intervene by the programme level.

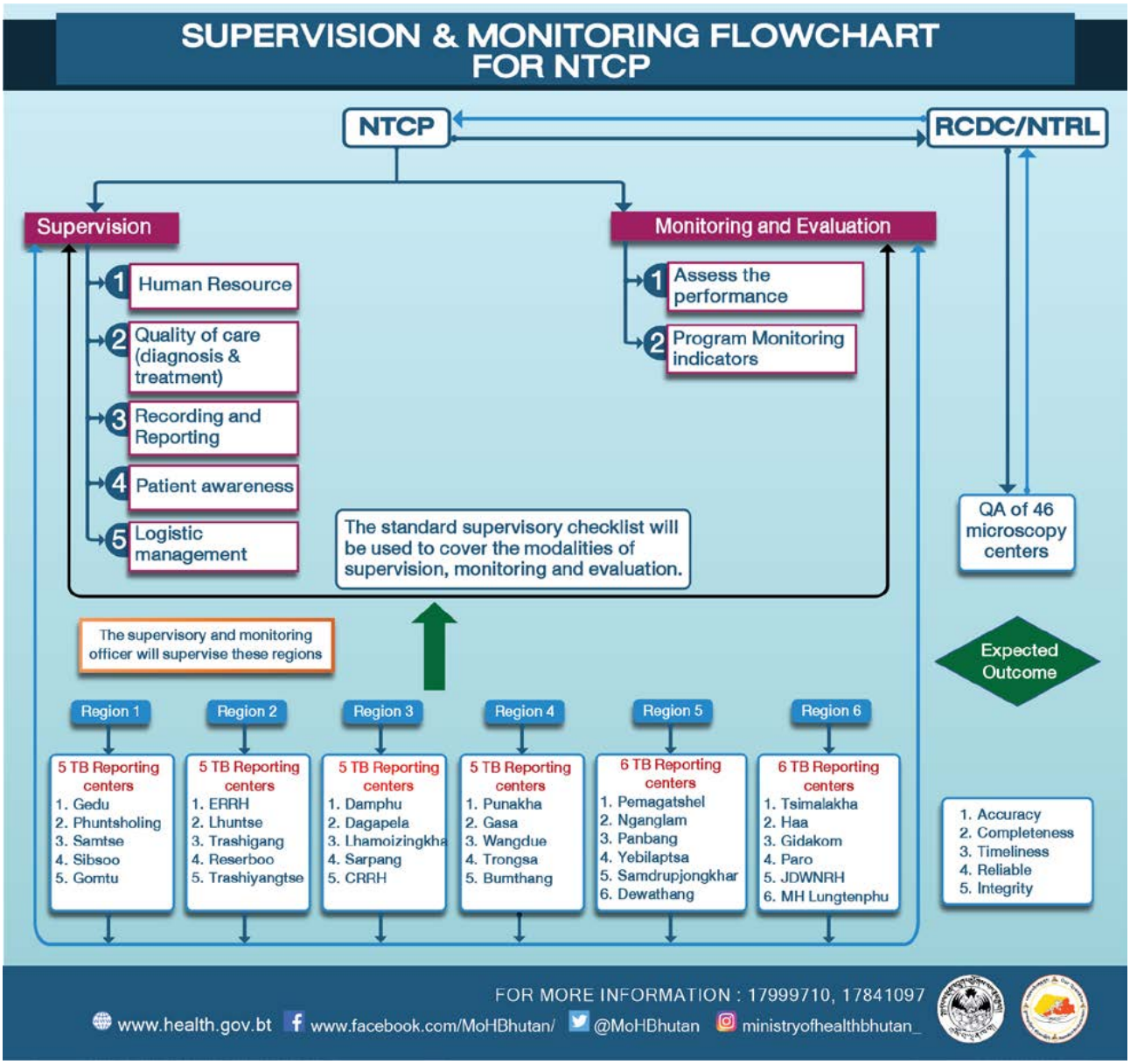


Figure 15.1 Flow chart for field-based Supervision and Monitoring of TB Control Activities in Bhutan.

For the supervisory visit to be productive and effective it should be planned well in advance, preferably at least a quarter earlier. Adequate preparation should be made as well. A supervisory check list should be used. Check list should include activities in relation to

- Quality of care (case finding, microscopy, treatment,)
- Recording and reporting (Use of TB registers, cards and TbISS should be assessed)
- Human resource availability and adequacy for needs including capacity of the staff
- Patient awareness and community-based activities
- Logistics management including drugs and consumables

The concerned staffs should be informed about the visit in advance so that they can be prepared and available at the time of the visit. Occasional surprise visits may also be necessary.

Some ways to collect information during supervisory visits are:

- Review of documents (Tuberculosis treatment card, Laboratory register, District TB Register, etc.) The information available in treatment card, laboratory register and TB register should be cross-verified, whenever feasible
- Observation of activities of the staff, procedures followed, etc.
- Communication - Talking with the staff, patients and bystanders
- Verification (stock position of drugs and other consumables, equipment)

In reviewing the above documents, emphasis should be given on:

a. **Accuracy:** Also known as validity. Accurate data is considered correct when the data measures what it is intended to measure.
b. **Reliability:** The data generated by a programme's information system are based on protocols and procedures that do not change according to who is using them and when or how often they are used.
c. **Precision:** This means that the data has sufficient detail. For example, an indicator requires the number of TB patients by sex who have received HIV counselling & testing and have received their test results. An information system lacks precision if it is not designed to record the sex of the individual who received counselling and testing.
d. **Completeness:** Completeness means that an information system from which the results are derived is appropriately inclusive.
e. **Timeliness:** The data is considered timely when it is up-to-date (current) and when the information is available on time. Timeliness is affected by: (1) the rate at which the programme's information system is updated; (2) the rate of change of actual program activities; and (3) when the information is actually used or required.
f. **Integrity:** Data has integrity when the system used to generate it is protected from deliberate bias or manipulation for political or personal reasons.
g. **Confidentiality**: Confidentiality means that clients are assured that their data will be maintained according to national and/or international standards. This means that personal data is not disclosed inappropriately, and that data in hard copy and electronic form are treated with appropriate levels of security (e.g. kept in locked cabinets and in password protected files).

Observation of staff and procedures may include:

- Interaction with patients
- Personal safety and infection control
- Quality of care
- Accuracy of procedures
- Measures to minimize wastage

- Waste disposal
- Cleanliness
- Status/condition of buildings and other resources

Communication with staff, patients and bystanders should be done in order to get information on:

- Views and attitudes on services provided
- Patients' satisfaction
- Staff satisfaction
- Records verification - triangulation
- Service improvement needs

Supervising officer should also verify:

- Stocks of drugs
- Drugs balance of each patient provided with DOT
- Stocks of other consumables
- Functionality and maintenance of equipment
- Physical inspection of drugs and consumables

15.5 Monitoring and Evaluation

Monitoring is the process of observing whether an activity or service is occurring as planned. It implies systematic and purposeful observation, aiming to identify any diversion from the planned course of action. It is a routine tracking of programme using input, process, output and outcome data collected on a regular and ongoing basis. This helps identify the need for more formal evaluation of activities and find timely solutions to the problems.

Monitoring in TB programmes is of paramount importance for ongoing programme planning and implementation and monitoring in TB program should move beyond the widely used case detection and treatment outcome indicators and should apply the concept of input, process, output, outcome and impact indicators for measurement of key programme activities.

Monitoring and evaluation can be performed at various levels; from the individual level through the unit level, district level and to the national level. For successful monitoring and evaluation, every aspect of the programme should be covered. This includes:

- Resources: human resources, financial resources and logistics
- Activities: case finding, case holding, treatment, public and private mix (PPM), etc.
- Achievements: meeting intended targets
- Services provided: adequacy, quality of service, sustainability, infection control

TB control measures implemented are one of the most important areas that should be continuously monitored and evaluated at regular intervals. It is carried out by reviewing and analysing the following reports:

- Quarterly Report of Case Finding
- Quarterly Report of Sputum Conversion of smear-positive cases
- Quarterly Report on Treatment Outcome.

Indicators can be used to measure the achievement of activities of a programme. There are certain indicators, which is useful to be examined regularly by the NTCP.

15.6 Programme monitoring indicators

Table 15.1 Programme monitoring indicators

Notification rate of new and relapse TB cases	No. of new and relapse TB cases notified during the year ——————————————— X 100,000 population Mid-year population for the same year If all new and relapse cases were to be notified, this would be an indicator for incidence rates. Notification of new cases is indicator of spread of the disease
Notification rate of new bacteriologically confirmed TB cases	No. of new bacteriologically confirmed cases reported for a specified year ——————————————— X 100,000 population Mid-year population for the same year This indicator as well as the indicator above is important for observing trends in case notification over several years. This is usually calculated annually. This should be analysed by age and sex at national level (age group/ sex specific rates per 100,000 populations). It provides information on the trend of TB.
Proportion of bacteriologically confirmed TB cases	Total number of bacteriologically confirmed cases reported for a specified year ——————————————— X 100 Total number of TB cases reported for the same year This indicator is particularly helpful in determining the use of lab diagnostics in diagnosing TB cases. As the use of newer, sensitive diagnostics increases, this proportion should increase.
Proportion of bacteriologically confirmed cases among TB symptomatic tested	No. of bacteriologically confirmed cases detected ——————————————— X 100 Total number of TB symptomatic examined When the prevalence of TB decreases in the community this rate also decreases. However in certain instances, the rate may increase initially if there are intensified case finding activities and with introduction and greater use of highly sensitive molecular tests like Xpert MTB/RIF
Re treatment TB cases	No. of retreatment TB registered during specified time period ——————————————— X 100 Total number of TB cases registered in the same period

	Generally, retreatment cases are a small proportion of TB cases. A high proportion of retreatment cases could be due to cases not being given appropriate treatment in the first course of treatment, adherence problems or poor quality of drugs. This should decline with time with proper implementation of quality assured services. However, a very low proportion of retreatment cases may also point to the fact that history of previous treatment is not being properly taken.
New extrapulmonary TB cases	No. of new extra pulmonary TB cases registered during a specified time period ———————————————— X 100 Total No of new TB cases registered in the same period High proportions of EP-TB cases may indicate an improved access to diagnostics specifically WHO approved rapid diagnostics (like Xpert MTB/RIF), imaging diagnostics detecting occult TB or a higher proportion of HIV co-infection. The data needs to be analysed taking into account local epidemiology
Diagnosis of childhood TB	No of childhood TB cases registered during a specified time period ———————————————— X 100 Total No of all TB cases registered in the same period The proportion is targeted to be **at least 10% by 2020**
Detection rate of RR/MDR-TB cases	No of laboratory confirmed RR/MDR-TB cases registered during a specified time period ———————————————— X 100 Estimated MDR-TB cases among notified TB cases in the same period The proportion is targeted to be at **least 85% of the estimated cases by 2020**
Proportion of HIV TB co-infected cases started on ART	No of HIV-TB co-infected cases started on ART ———————————————— X 100 Number of TB cases found HIV positive in the same period The proportion is targeted to be **100% by 2020**
Sputum conversion rate at the end of the intensive phase of treatment for new TB cases	No of new bacteriologically confirmed pulmonary TB cases registered in a specified time period that are smear negative at the end of initial phase of treatment ———————————————— X 100 Total No of new bacteriologically confirmed pulmonary TB cases registered for the treatment in the same period The proportion of new cases showing negative sputum smear at the end of 2 months is at least 80%

Cure rate of new bacteriologically confirmed TB cases	No of new bacteriologically confirmed TB cases registered in a specified time period that were declared cured ——————————————— X 100 Total number of new bacteriologically confirmed TB cases registered in the same period
Treatment completion rate for new bacteriologically confirmed TB cases	No of new bacteriologically confirmed TB cases registered in a specified time period that completed treatment and did not meet the criteria for cure or failure ——————————————— X 100 Total No of new bacteriologically confirmed TB cases registered in the same period
Treatment completion rate for all TB cases	No of TB cases registered in a specified time period that completed treatment and did not meet the criteria for cure or failure ——————————————— X 100 Total No of TB cases registered in the same period
Cure rate of patients started on second line treatment	No of RR/MDR- TB cases registered in a specified time period that were declared cured ——————————————— X 100 Total number of RR/MDR- TB cases registered in the same period
Treatment completion rate of RR/MDR-TB cases	No of RR/MDR-TB cases registered in a specified time period that completed treatment and did not meet the criteria for cure or failure ——————————————— X 100 Total No of RR/MDR-TB cases registered in the same period
Treatment Failure Rate	No of new bacteriologically confirmed pulmonary TB cases registered in a specified time period that are sputum positive at five months or later after initiating treatment ——————————————— X 100 Total No of new bacteriologically confirmed pulmonary TB cases registered in the same period **Ideally this should be less than 5%**
Loss to follow-up Rate	No of all TB cases registered in a specified time period that interrupted treatment for more than two consecutive months ——————————————— X 100 Total No of TB cases registered in the same period
Death rate	No of all TB cases registered in a specified time period that interrupted treatment for more than two consecutive months ——————————————— X 100 Total No of TB cases registered in the same period

	This is usually between 3-5%. All deaths among TB patients that occurred due to any cause are accounted here.
Treatment Success Rate*	Treatment Success Rate = Cure rate + Treatment Completion rate The target for treatment success rate is at least 90% for all TB cases. * Can be used to measure treatment success rate of RR/MDR-TB cases as well. The country target of success rate among RR/MDR-TB cases is 75%

Cohort analysis of re-treatment cases, clinically diagnosed cases and extra pulmonary cases also should be done in the same way as of the analysis carried out for bacteriologically confirmed TB cases. The supervision and monitoring visit from the central level is carried out using the a predefined checklist.

CHAPTER 16
MEDICINES AND CONSUMABLES MANAGEMENT

It should be ensured that a regular, uninterrupted supply of quality assured drugs, laboratory consumables and documentation materials are available for all facilities where patients are diagnosed and treated. Diagnosis through smear microscopy and treatment of all registered TB patients should be provided free of charge. The Department of Medical Products (DMP) and NTCP are responsible for the planning, procurement and supply of Anti-TB drugs, laboratory consumables and documentation on materials to dzongkhags and PHCs. Managing drugs and supplies involves ensuring that sufficient quantities are available. It also involves maintaining good storage conditions for the drugs so that they will be available and effective when they are needed. Minimizing losses through expiration, deterioration, etc is also important. Therefore, keeping accurate inventory records and providing stock movement information is also a key component. Taking into account of unforeseen delays/disruptions in supply as well as increases in the number of patients, a buffer stock should be managed at all levels. The process of drug management has several components, which are interlinked and have to be carried out in a specific order. The components of this management cycle are given below.

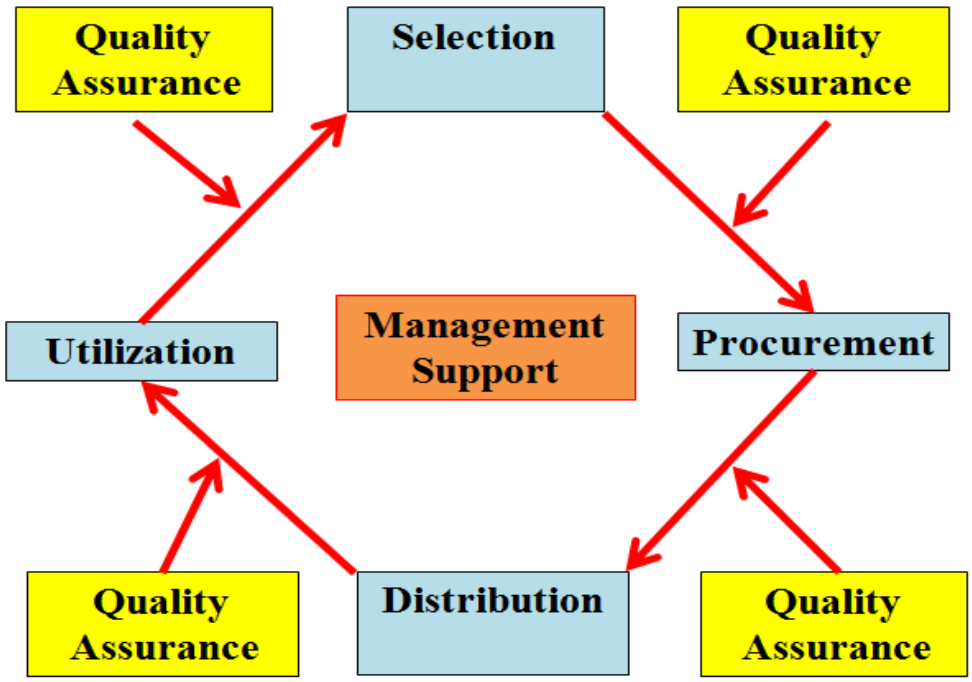


Figure 16.1 Drug management cycle

16.1 Selection of Medicines and Consumables

Usually the selection of medicines and consumables are carried out using a tender procedure and should be based on the quality, efficacy, safety and cost of the items. Anti TB medicines are procured through the Global Drug Facility using the support of Stop TB Partnership and shall be WHO prequalified.

16.2 Quantification

Quantification of Anti TB medicines is usually done according to the number of patients diagnosed during the previous year and the expected cases in the coming years per the program forecast. The quantification of medicines shall be done using the QuanTB tool by the program in collaboration withDMP. The DMP shall be responsible for supplying the medicines to the health facilities upon directives from the program. A buffer of 10% to 15% shall be calculated during the quantification.

This estimation of the quantity of medicines required is adjusted annually and based on the number of TB cases treated during the previous year; treatment regimen adopted, buffer stock (including quantity of drugs required during lead time to supply) and stock-in-hand at the time of the drug order. The medical store incharges/TB incharges are required to submit the stock details quarterly and whenever required.

16.3 Procurement and Distribution

After quantification, DMP will initiate the procurement of medicines in close collaboration with the program.

Once the goods are received, the DMP will complete all the required formalities and intimate the program for distribution order. Upon receiving the distribution order, the medicines will be distributed accordingly. Accordingly, for the additional requirement of the medicine, the respective TB incharges should send the requisition to the program.

16.4 Laboratory Consumables

All Hospitals require an adequate supply of sputum containers to collect and transport sputum specimens. TB laboratories need a high-quality binocular microscope and a regular supply of slides and reagents. With the expansion of GeneXpert machines and culture facilities to certain laboratories, these laboratories will now also calculate the number of reagents required for these tests, based on expected number of tests to be performed and about 20% buffer stock. The requirement of laboratory consumables and supplies should be calculated by using the existing formula of the DMP.

16.5 Inspection and Storage of Medicines and Supplies

Upon receipt, all drugs and supplies shall be inspected by the QI team. The committee will physically inspect the supplies with the ‘Invoice’ and the specifications as per the purchase order awarded. The committee will then report any discrepancies or damages, if any.

Medicines and supplies should be stored in optimal conditions in a secured room. The medicines and laboratory reagents should be monitored regularly for the expiry date. The supplies with shorter expiry dates should be placed in the front and those with later expiration dates should be placed behind (first expiry-first out or FEFO). A stock ledger must be maintained and updated whenever medicines and other materials are received or dispensed at all levels.
The medical store In-charge will ensure the inspection of supplies, its optimum storage and its proper recording as detailed in the “Good Store Management for Managing Drugs and Supplies”.

16.6 Documentation of materials

In general, forms will be provided once a year for the entire year. Estimates are based on the number of forms and registers expected to be used in the year plus 20% to allow for an increase in detection of new TB patients and loss through errors and damage.

TB Treatment Cards
On average, 2 TB Treatment Cards are needed for each expected patient (all categories) plus 20% for reserve minus stock in hand.

Bacteriological examination Requisition Forms
Estimate about 10 requests for Bacteriological Examination forms per new TB case.

TB Register
Generally, one TB register is sufficient for a small or medium-sized health facility for a year.

16.7 Monitoring and Supervision of Stores

The monitoring and supervision of medicines/supplies management must be done at all levels. The medical store in charge/TB in charge shall monitor the stocks of medicines and report quarterly. These in charges should act promptly in the case of stock outs by internal mobilization and report to DMP and the Program for necessary action. They should also report the stock status to the program whenever asked. The DMP and Program shall also make supervisory visits to the stores and health facilities randomly to monitor and give feedbacks wherever necessary.

16.8 Testing of anti-TB medicines

Anti-TB medicines shall be tested randomly by the National Drug Testing Lab at their own lab or other labs if deemed necessary.

CHAPTER 17
ADVOCACY, COMMUNICATION AND SOCIAL MOBILIZATION

Strengthening health system to provide quality TB care and prevention is always accorded as a priority. Besides this, advocacy, communication and social mobilization (ACSM) is acknowledged as an essential component for effective TB control, particularly in the context of achieving equitable access to quality services for all population groups (WHO 2010). Advocacy and awareness generally aim to disseminate messages, practices and ideas (information) to individual or target groups by utilizing appropriate media of dissemination (communication) to bring about change in knowledge, belief, attitude and behaviour. The objectives specific to each component are as follows:

i. Advocacy: To mobilize commitment and resources for sustained quality TB care and control, in collaboration with all sectors and stakeholders.

ii. Communication: To strengthen advocacy, generate awareness on TB and TB control services for better use of services, and to mobilize all stakeholders to support and promote services for TB control.

iii. Social Mobilization: To mobilize civil society and generate support for all those in need of TB services, through sustainable community ownership and participation.

ACSM is indispensable for TB control at various level and therefore but not limited to, the following are provided as broad interventions for implementation:

17.1 National Level (Programme level)

At the National Level, the NTCP shall focus on all three types of advocacy as identified in WHO capacity building training module 2019 as stated below:

a. **Policy advocacy:** Policy advocacy informs senior politicians and administrators how an issue will affect the country, and outlines actions to take to improve laws and policies.
b. **Programme advocacy:** Programme advocacy targets opinion leaders at the community level on the need for local action.
c. **Media advocacy:** Media advocacy validates the relevance of a subject, puts issues on the public agenda and encourages the media to cover TB-related topics regularly and in a responsible manner so as to raise awareness of possible solutions and problems.

Further, NTCP should consider to implement following activities as a part of ACSM at national level:

- Showing TV spot or video clips
- World TB Day Observation
- Display of banners and posters on TB at strategic locations
- Quiz/Essay competition on prevention and control of TB
- Sensitization and mass distribution of IEC materials to Schools, Monastic Bodies and during mass gathering.
- Sensitization during annual Dzongdag and Gup Conferences

- Use Social Media (Facebook page-End TB Bhutan)
- Panel discussion on BBS-TV
- Q&A Session on BBS TV, BBS radio and other radio studios in Thimphu

17.2 Dzongkhag/District Hospital level

- Dzongkhag level advocacy and awareness programmes
- Appraisal by DHOs/ CMOs/MOs /TB-Charges on TB during Dzongkhag Tshodue (DT) meetings
- Showing TV spot or video clips on TB through local TV cable operators and OPD/patient waiting area in the hospitals
- World TB Day Observation at Dzongkhag level
- Awareness programmes in schools, institutions and other during public gatherings like Tshechus and National Day celebrations
- Quiz/ Essay competition on TB in schools and institutions
- Display of banners and posters on TB at strategic locations
- Awareness program during mass gathering and encourage public to come forward for screening

17.3 Hospital (10 Bedded) level

- Appraisal by HA during *Gewog Tshodue*
- Distribution of IEC materials like pamphlets, leaflets, etc
- Wall writings, posters and diagnostic cards, at different levels of district
- Skit /drama on TB during local public gatherings
- World TB Day Observation at *Gewog* level
- Showing TV spot or video clips on TB through local TV cable operators and at OPD/patient waiting areas/in patient observation rooms.
- Awareness programmes in schools during public gatherings like Tshechus and Zomdu

17.4 Community level/Village level

Awareness programs at community level are crucial to increase utilization of TB services and reduce misconceptions, stigma and discrimination against those with TB. There are studies pointing out how community empowerment through meaningful participation in the TB response can lead to identifying missing cases, reducing loss of time in diagnosis as well as demanding quality TB care and treatment as a right (WHO 2019). Therefore, NTCP considers communities as key partner to ensure early diagnosis and treatment as well as encourage communities to come forward in accessing TB services. There are no non-governmental organizations (NGOs) and civil society organizations (CSOs) in Bhutan that are directly providing TB related services. Hence, the programme will still strive to involve cured patients, Multi-Sectorial Task Force (MSTF), Community Based Support Systems (CBSS), Village Health Workers (VHW) and Community Action Group (used for Malaria programme) in supporting TB patients. The program will focus on capacity building of local leaders and representatives of above-mentioned groups in high TB burden districts to support patients in treatment adherence and provide necessary psychological support during as well as after the treatment for integration back into their communities.

Following are the key activities:

- Awareness and screening by HAs/VHWs during annual household visits
- Individual & family counselling
- Distribution of leaflets/pamphlets and video spots on TB during local public gatherings
- Identify DOT providers and advise them on the importance of timely completion of treatment
- Encourage the close contacts and TB presumptive for screening
- Arrange reintegration activities at Chiwog and Gewog level to reduce stigma and discrimination by visiting TB patient's family

The broad structural composition and its role and responsibilities of NTCP in overall TB control is in Annex 8.

Annex 1
Dosage for Weight Band for Medicines used in DS-TB Regimens for Adult

Drug	Weight Based Daily Dose	Formulation	30-35 kg	36-45 kg	46-55 kg	56-70 kg	>70 kg
Ethambutol	15-25 mg/kg	400mg tab	800mg	800mg	1200mg	1200mg	1200mg
Pyrizinamide	20-30 mg/kg	400mg tab	1200mg	1600mg	1600mg	1600mg	2000mg
Isoniazid	4-6 mg/kg	300mgtab	150/200mg	300mg	300mg	300mg	300mg
Rifampicin	8-12 mg/kg	300mgtab	300mg	450mg	450mg	600mg	600mg

Annex 2

Dosage by Weight Band for Medicines used in MDR-TB Regimens for adults and children

Dosing of medicines used in second-line MDR-TB regimens by weight band in patients older than 14 years										
Group	**Medicine**	**Weight-base daily dose**	**Formulation**	**Weight bands for patients older than 14 years[a]**					**Usual upper daily dose[b]**	**Comments**
				30-35kg	**36-45kg**	**46-55kg**	**56-70kg**	**>70kg**		
A	Fluoroquinolones Levofloxacin	-[c]	250mg tab	3	3	4	4	4	1.5g	
			500mg tab	1.5	1.5	2	2	2		
			750mg tab	1	1	1.5	1.5	1.5		
	Moxifloxacin	Standard dose [c,d]	400mg tab	1	1	1	1	1	400mg	
		high dose[c,d]	400mg tab	1 or 1.5	1.5	1.5 or 2	2	2	800mg	as used in the standardized shorter MR-TB regimen
	Bedaquiline	-[c]	100mg tab	4 tabs of for first 2 weeks, then2 tabs od M/W/F for 22 weeks					400mg	
	Linezolid	-[c]	600mg tab	(<15 y)	(<15y)	1	1	1	1.2g	
B	Clofazimine	-[c]	50mg cap or tab	2	2	2	2	2	100mg	
			100mg cap or tab	1	1	1	1	1	100mg	
	Cycloserine or terizidone	10-15mg/kg	250mg cap	2	2	3	3	3	1g	
C	Ethambutol	15-25mg/kg	400mg tab	2	2	3	3	3	-	
	Delamanid	-[c]	50mg tab	2bd	2bd	2bd	2bd	2bd	200mg	
	Pyrazinamide	20-30mg/kg	400mg tab	3	4	4	4	5	-	
			500mg tab	2	3	3	3	4	-	
	Imipenem-cilastatin	-[c]	0.5g+0.5g vial	2 vials(1g+1g)bd					-	To be used with clavulanic acid
	Meropenem	-[c]	1g vial(20ml)	1 vial 3 times per day or 2 vials bd					-	To be used with clavulanic acid
	Amikacin	15-20mg/kg	500mg/2ml vial [e]	2.5ml	3ml	3 to 4 ml	4ml	4ml	1g	
	Streptomycin	12-18mg/kg	1g vial [e]	Calculate according to the dilution used					1g	

	Ethionamide or prothionamide	15-20mg/kg	250mg tablet	2	2	3	3	4	1g	Once daily dose advised but can start with 2 divided doses until tolerance improves
	p-aminosalicylic acid	8-12g/day in 2-3 divided doses	PAS sodium salt(4g)sachet	1bd	1bd	1bd	1bd	1 to 1.5bd	12g	
			PAS acid(4g)sachet	1bd	1bd	1bd	1bd	1 to 1.5bd		
Other medicines [f]	Isoniazid	4-6mg/kg(standard dose)[d]	300mg tab	2/3	1	1	1	1	-	100mg isoniazid tablet can facilitate the administration of certain dosages
		10-15mg/kg(high dose)[d]	300mg tablet	1.5	1.5	2	2	2		Pyridoxine given with isoniazid in patients at risk (such as those with HIV, malnutrition)
	Clavulanic acid [g]	-[c]	125mg tabg[g]	1bd	1bd	1bd	1bd	1bd	-	Only to be used with carbapenems
	Kanamycin	15-20mg/kg	500mg/2ml vial [e]	2 to 2.5ml	2.5 to 3ml	3 to 4 ml	4ml	4ml	1g	M/W/F dosing of aminoglycosides at 25mg/kg/day may limit toxicity and inconvenience when the injectable agents are used in longer MDR-TB regimens
	Capreomycin	15-20mg/kg	500mg/2ml vial [e]	2.5ml	3ml	3to4ml	4ml	4ml	1g	
	Gatifloxacin	-[c]	400mg tab	2	2	2	2	2	800mg	Not used in <18year olds(no quality assured product currently available)
	Thioacetazone	-[c]	150mgtab	1	1	1	1	1	-	Not used in <18year olds(no quality assured product currently available)

(<15 y) = follow the separate dose schedule for patients younger than 15 years of age;

bd = two times a day; cap = capsule; g = gram; im = intramuscular; iv = intravenous; kg = kilogram; ml = millilitre; mg = milligram; M/W/F = Monday, Wednesday, Friday; soln = solution; susp = suspension; tab = tablet

[a] *Dosages were established by the Guideline Development Group for the WHO treatment guidelines for rifampicin- and multidrug-resistant tuberculosis, 2018 update and the WHO Global task force on the pharmacokinetics and pharmacodynamics (PK/PD) of TB medicines and other experts. They are based on the most recent reviews and best practices in the treatment of MDR/RR-TB. For certain agent's the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling (Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol 2008; 48:303–32). Due to the pharmacokinetic properties of certain medicines the doses to achieve blood concentrations similar to target levels in an average adult patient. In patients <30 kg follow the schedule for <15 year olds unless otherwise indicated. If multiple dose options are given for one weight band select the lower or higher option depending on whether the patient is at the lower or higher limit of the body weight range. Dosing more closely to the target mg/kg/day should be aimed for, and is more feasible with oral or parenteral fluids and when solid forms of different dosages are available. Fractioning of tablets into halves or less should be avoided, if possible. Therapeutic drug monitoring is advised when the dose is at the upper and lower ends of the range to minimize the adverse therapeutic Consequences of over- and under-exposure, respectively (especially for injectable agents, linezolid and fluoroquinolones).*

[b] *Clinicians may decide to exceed these values in particular cases to improve therapeutic effect.*

[c] *No weight-based dosing is proposed.*

[d] *Unless there is risk of toxicity, the high dose may be used if antimicrobial levels may be lowered because of pharmacokinetic interactions, malabsorption or other metabolic reasons or if the strain has low-level drug resistance.*

[e] *Weight-based daily dose is for 6 or 7 days/week administration (M/W/F scheduling may permit higher dosing). Volumes shown may differ by preparation. Streptomycin may be diluted in three different ways. For iv use, the volume may be increased.*

[f] *In the 2018 WHO treatment guidelines, these agents are either no longer recommended (kanamycin, capreomycin),only recommended as a companion agent (amoxicillin/clavulanic acid) or not included because of lack of data from the latest analysis on longer MDR-TB regimens in adults (gatifloxacin, isoniazid and thioacetazone).*

[g] *Only available in combination with amoxicillin as co-amoxyclav (e.g. 500 mg amoxicillin/125 mg clavulanic acid fixed dose combination).It is given with each dose of carbapenem, either as 125 mg bd or 125 mg 3 times daily.*

Dosing of medicines used in second-line MDR-TB regimens by weight band in patients under 15 years [a]												
Group	**Medicine**	**Weight-base daily dose [b]**	**Formulation**	**weight bands among patients not yet 15 years old [a]**							**Usual upper daily dose [b]**	Comments
				5-6kg	**7-9kg**	**10-15kg**	**16-23kg**	**24-30kg**	**31-34kg**	**>34kg**		
A	Fluoroquinolones: Levofloxacin	15-20mg/kg	100mg db	1	1.5	2 or 3	3 or 4	(>14y)	(>14y)	(>14y)	1.5g	
			250mg tab	0.5	0.5	1 or 1.5	1.5 or 2	2	3	(>14y)	1.5g	
	Moxifloxacin	10-15mg/kg	100mgdb [c]	0.8	1.5	2	3	4	(>14y)	(>14y)	400mg	
			400mg tab [c]	2 ml [c]	3 ml [c]	5 ml [c]	0.5 or 0.75	1	(>14y)	(>14y)	400mg	use 10mg/kg in <6 months
	Bedaquiline	-	100mg tab	-	-	-	2 tabs od for two weeks; then 1 tab od M/W/F for 22 weeks		4 tabs od for 2 weeks; then 2 tabs od M/W/F for 22 weeks		-	Only in patients>5 years old(lower dose from 15-29kg;higher dose from >29kg)
	Linezolid	15mg/kg od in <16kg	20 mg /ml susp	4ml	6ml	8ml	11ml	14ml	15ml	20 ml [d]	600 mg	
		10–12 mg/kg od in >15 kg	600 mg tab[c]	0.25	0.25	0.25	0.25	0.25	0.25	0.75[d]		
B	Clofazimine	2–5 mg/kg	50 mg cap or tab	1 alt days	1 alt days	1 alt days	1	2	2	(>14 y)	100 mg	Give on alternate days if dose in mg/ kg/day is too high
			100 mg cap or tab	M/W/F	M/W/F	1 alt days	1 alt days	1	(>14 y)	(>14 y)	100 mg	
	Cycloserine or terizidone	15–20 mg/kg	125 mg mini capsule (cycloserine)[c]	1	1	2	3	4	(>14 y)	(>14 y)	1 g	
			250 mg cap [c]	4–5 ml c	5–6 ml c	7–10 ml c	2	2	2	(>14 y)	1 g	

C	Ethambutol	15–25 mg/kg	100 mg dt	1	2	3	4	-	-	(>14 y)		
			400 mg tab[c]	3 ml[c]	4 ml[c]	6 ml[c]	1	1 or 1.5	2	(>14 y)		
	Delamanid	–	50 mg tab	–	–[e]	–[e]	–[e]	1 bd	1 bd	2 bd	200 mg	Only in patients >2 years old (25 mg bd in 3–5 years; 50 mg bd in 6–11 years; 100 mg bd in 12–17 years)
	Pyrazinamide	30–40 mg/kg	150 mg dt	1	2	3	4or5	-	-	(>14 y)	-	
			400 mg tab	0.5	0.75	1	1.5 or 2	2.5	3	(>14 y)		
			500 mg tab	0.5	0.5	0.75 or 1	1.5	2	2.5	(>14 y)		
	Imipenem-cilastatin	-	0.5 g + 0.5 g vial	-	-	-	-	-	-	-	-	Not used in patients <15 years (use meropenem)
	Meropenem	20–40 mg/kg iv every 8 hours	1 g vial (20 ml)	2ml	4ml	6ml	8-9ml	11ml	(>14 y)	(>14 y)	-	To be used with clavulanic acid
	Amikacin	15–20 mg/kg	500 mg/2 ml vial[f]	0.4 ml	0.6 ml	0.8 - 1.0 ml	1.2 - 1.5 ml	2.0 ml	(>14 y)	(>14 y)	1 g	
	Streptomycin	20–40 mg/kg	1 g vial[f]	Calculate according to the dilution used	(>14 y)	(>14 y)	1 g					
	Ethionamide or prothionamide	15–20 mg/kg	125 mg dt (ethionamide)	1	1	2	3	4	4	(>14 y)	1g	
			250 mg tab	0.5	0.5	1	2	2	2	(>14 y)	1g	
	p-aminosalicylic acid	200–300 mg/kg in 2	PAS acid (4 g) sachet	0.5–0.75 g bd	0.75–1 g bd	1–2 g bd	2–3 g bd	3–3.5 g bd	(>14 y)	(>14 y)	-	Full dose can be given once daily if tolerated

		divided doses	PAS sodium salt (4 g) sachet	0.5–0.75 g bd	0.75–1 g bd	1–2 g bd	2–3 g bd	3–3.5 g bd	(>14 y)	(>14 y)		
			PAS sodium salt 60% (9.2 g) sachet	1.5 g bd	2–3 g bd	3–4 g bd	4 or 6 g bd	6 or 8 g bd	8–12 g bd	8–12 g bd	-	
Other medicines	Isoniazid	15–20 mg/kg (high dose)	50 mg/5 ml soln	8–10 ml	15 ml	20 ml	-	-	-	-		300 mg isoniazid tablet can be used in patients >20 kg Pyridoxine is always given with high dose isoniazid in children (12.5 mg od in <5 y olds and 25 mg od in >4 y olds)
			100 mg tab	1	1.5ml	2	3	4	4	(>14 y)		
	Clavulanic acid [h]	-	250mg amoxicillin/62.5 mg clavulanic acid/5ml susp[h]	2mldbd [h]	3mlbd[h]	5mlbd[h]	8mlbd[h]	10mlbd [h]	(>14y)	(>14y)		
	Kanamycin	15–20 mg/kg	500 mg/2 ml vial[f]	0.4 ml	0.6 ml	0.8–1.0 ml	1.2–1.5 ml	2.0 ml	(>14 y)	(>14 y)	1 g	1 g vials (3 ml) also available
	Capreomycin	15–20 mg/kg	500 mg/2 ml vialf	0.4 ml	0.6 ml	0.8–1.0 ml	1.2–1.5 ml	2.0 ml	(>14 y)	(>14 y)	1 g	1 g vials (2 ml) also available
	Gatifloxacin	-	400 mg tab	-	-	-	-	-	-	-	-	Not used in <18 y olds (no quality assured product currently available)
	Thioacetazone	-	-	-	-	-	-	-	-	-	-	Not used in <18 y olds (no quality assured product currently available)

(<15 y) = follow the separate dose schedule for patients younger than 15 years of age;
bd = two times a day; cap = capsule; g = gram; im = intramuscular; iv = intravenous; kg = kilogram; ml = millilitre; mg=milligram; M/W/F = Monday, Wednesday, Friday; soln = solution; susp = suspension; tab = tablet

[a] Dosages were established by the Guideline Development Group for the *WHO treatment guidelines for rifampicin- and multidrug-resistant tuberculosis, 2018 update* and the WHO Global task force on the pharmacokinetics and pharmacodynamics (PK/PD) of TB medicines and other experts. They are based on the most recent reviews and best practices in the treatment of MDR/RR-TB. For certain agent's the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling (Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. Annu Rev Pharmacol Toxicol 2008; 48:303–32). Due to the pharmacokinetic properties of certain medicines the doses to achieve blood concentrations similar to target levels in an average adult patient. In patients <30 kg follow the schedule for <15 year olds unless otherwise indicated. If multiple dose options are given for one weight band select the lower or higher option depending on whether the patient is at the lower or higher limit of the body weight range. Dosing more closely to the target mg/kg/day should be aimed for, and is more feasible with oral orparenteral fluids and when solid forms of different dosages are available. Fractioning of tablets into halves or less should be avoided, if possible. Therapeutic drug monitoring is advised when the dose is at the upper and lower ends of the range to minimize the adverse therapeutic Consequences of over- and under-exposure, respectively (especially for injectable agents, linezolid and fluoroquinolones).

[b] Clinicians may decide to exceed these values in particular cases to improve therapeutic effect.

[c] No weight-based dosing is proposed.

[d] Unless there is risk of toxicity, the high dose may be used if antimicrobial levels may be lowered because of pharmacokinetic interactions, malabsorption or other metabolic reasons or if the strain has low-leveldrug resistance.

[e] Weight-based daily dose is for 6 or 7 days/week administration (M/W/F scheduling may permit higher dosing). Volumes shown may differ by preparation. Streptomycin may be diluted in three different ways.For iv use, the volume may be increased.

[f] In the 2018 WHO treatment guidelines, these agents are either no longer recommended (kanamycin, capreomycin),only recommended as a companion agent (amoxicillin/ clavulanic acid) or not includedbecause of lack of data from the latest analysis on longer MDR-TB regimens in adults (gatifloxacin, isoniazid and thioacetazone).

[g] Only available in combination with amoxicillin as co-amoxyclav (e.g. 500 mg amoxicillin/125 mg clavulanic acid fixed dose combination).It is given with each dose of carbapenem, either as 125 mg bd or 125 mg 3 times daily.

Annex 3
Managing adverse effects of second line drugs

ADVERSE EFFECT	SUSPECTED AGENT/S	MANAGEMENT STRATEGIES
Rash, allergic reaction and anaphylaxis	Any drug	1. For serious allergic reactions, stop all therapy pending resolution of reaction. In the case of anaphylaxis manage with standard emergency protocols.
		2. Eliminate other potential causes of allergic skin
		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 if other measures are not helpful • Phototoxicity may respond to sunscreens, but these can also cause rash • 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.
		4. Once the rash resolves, reintroduce remaining drugs, one at a time with the one most likely to cause the reaction last. Consider not reintroducing even as a challenge any drug that is highly likely to be the cause.
		5. Suspend permanently any drug identified to be the cause of a serious reaction.
Nausea and vomiting	Eto, Pto, PAS, Bdq H, E, Z, Amx/Clv, Cfz	1. Assess for danger signs including dehydration, electrolyte disturbances and hepatitis. Initiate rehydration therapy if indicated and correct any electrolyte disturbances. If there is blood in the vomit, check haemoglobin and treat for possible bleeding ulcers.
		2. Initiate a stepwise approach to manage nausea and vomiting.
		•**Phase 1:** Adjust medications and conditions without lowering the overall dose: -Give Eto/Pto at night -Give Eto or PAS twice or thrice daily -Give a light snack (biscuits, bread, rice, tea) before the medications -Give PAS two hours after other anti-TB drugs.
		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. (If ondansetron is not available, promethazine can be used.) For refractory nausea give 24 mg, 30 minutes before the dose can be tried.

		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.
Gastritis and abdominal pain	PAS, Eto, Pto, Cfz, FQs, H, E, and Z	1. Abdominal pain can also be associated with serious adverse effects, such as pancreatitis, lactic acidosis and hepatitis. If any of these are suspected, obtain appropriate laboratory tests to confirm and suspend the suspected agent.
		2. If symptoms are associated consistent with gastritis (epigastric burning or discomfort, a sour taste in mouth associated with reflux) initiate medical therapy with the use of H2-blockers (ranitidine 150 mg twice daily or 300 mg once daily) or proton-pump inhibitors (omeprazole 20 mg once daily). Avoid the use of antacids as they decrease absorption of fluoroquinolones.
		3. For severe abdominal pain stop suspected agent(s) for short periods of time (one to seven days).
		4. 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.
Diarrhoea and/ or fl atulence	PAS, Eto/Pto	1. Encourage patients to tolerate some degree of loose stools and flatulence.
		2. Encourage fluid intake.
		3. Treat uncomplicated diarrhoea (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 24 hours.
		4. Check serum electrolytes (especially potassium) and dehydration status if diarrhoea is severe.
		5. Fever and diarrhoea and/or blood in the stools indicate that diarrhoea may be secondary to something other than the simple adverse effect of anti-TB drugs.
Hepatitis	Z, H, R, Pto / Eto, and PAS	1. If enzymes are more than five times the upper limit of normal, stop all hepatotoxic drugs and continue with at least three non-hepatotoxic medications (for example, the injectable agent, fluoroquinolone and cycloserine). If hepatitis worsens or does not resolve with the three-drug regimen, then stop all drugs.
		2. Eliminate other potential causes of hepatitis (viral hepatitis and alcohol induced hepatitis being the two most common causes) and treat any that is identified.
		3. Consider suspending the most likely agent permanently. Reintroduce remaining drugs, one at a time with the least hepatotoxic agents first, while monitoring liver function by testing the enzymes every three days, and if the most likely agent is not essential consider not reintroducing it.
Hypo-thyroidism	Eto/Pto, PAS	1. Most adults will require 100–150 mcg of levothyroxine daily. Start levothyroxine in the following manner: •Young healthy adults can be started on 75–100 mcg daily •Older patients should begin treatment with 50 mcg daily •Patients with significant cardiovascular disease should start at 25 mcg daily.
		2. Monitor TSH every one to two months and increase the dose by 12.5–25 mcg until TSH normalizes. Adjust the dose more slowly in the elderly and in patients with cardiac conditions.
Arthralgia	Z, Bdq, Fluoroquinolones	1. Initiate therapy with nonsteroidal anti-inflammatory drugs (indomethacin 50 mg twice daily or ibuprofen 400 to 800 mg three times a day).

		2. Lower the dose of the suspected agent (most commonly pyrazinamide) if this can be done without compromising the regimen.
		3. Discontinue the suspected agent if this can be done without compromising the regimen.
Tendonitis and tendon rupture	Fluoroquinolones	1. If significant inflammation of tendons or tendon sheaths occur:
		•Consider stopping fluoroquinolones
		•Give a non-steroidal anti-inflammatory drug (ibuprofen 400 mg four times daily)
		•Rest the joint.
		2. If treatment failure is likely without the fluoroquinolone
		•Reduce dose if possible
		•Ensure joint is strictly rested
		•Inform patient of the possible risk of tendon rupture and discuss the risks and benefits of ongoing use of the fluoroquinolone.
Electrolyte disturbances (hypokalaemia and hypomagne saemia)	Cm, Km, Am, S	1. Check potassium.
		2. If potassium is low, also check for magnesium and calcium (if unable to check for magnesium, consider empiric treatment with magnesium in all cases of hypokalaemia). Replace electrolytes as needed. Dose oral electrolytes apart from fluoroquinolone as they can interfere with fluoroquinolone absorption
Nephrotoxicity (renal toxicity)	S, Km, Am, Cm	1. Discontinue the suspected agent.
		2. Consider using capreomycin if an aminoglycoside had been the prior injectable drug in the regimen.
		3. Consider other contributing aetiologies (non-steroidal anti-inflammatory drugs, diabetes, other medications, dehydration, congestive heart failure, urinary obstruction, etc.) and address as indicated.
		4. Follow creatinine (and electrolyte) levels closely, every one to two weeks.
		5. Consider dosing the injectable agent two to three times a week if the drug is essential to the regimen and the patient can tolerate (close monitoring of creatinine). If the creatinine continues to rise despite twice/thrice a week dosing, suspend the injectable agent.
		6. Adjust all TB medications according to the creatinine clearance
Vestibular toxicity (tinnitus and dizziness)	S, Km, Am, Cm, Cs, FQs, H Eto, Lzd	1. If early symptoms of vestibular toxicity appear, change the dosing of the injectable agent to twice/thrice a week.
		2. Consider using capreomycin if an aminoglycoside had been the prior injectable in the regimen.
		3. If tinnitus and unsteadiness worsen with the above adjustment, stop the injectable agent. This is one of the few adverse reactions that cause permanent intolerable toxicity and can necessitate discontinuation of a class of agents.
Hearing loss	S, Km, Am, Cm, Clr	1. Document hearing loss and compare with baseline audiogram if available. (Some degree of hearing loss occurs with most patients starting with high frequency loss.)
		2. If early symptoms of hearing loss are documented, change the dosing of the injectable agent to twice/thrice a week. Also, consider using capreomycin if an aminoglycoside had been the prior injectable in the regimen.

		3. Discontinue the injectable agent if hearing loss continues despite dose adjustment and add additional drugs to reinforce the regimen. Even when additional drugs are not available, stopping the injectable agent can be considered based on the patient's desire to maintain hearing.
Peripheral neuropathy	Cs, Lzd, H, S, Km, Amk, Cm, H, Fluoroquinolones, rarely Pto/Eto, E	1. Correct any vitamin or nutritional deficiencies. Increase pyridoxine to the maximum daily dose (200 mg per day).
		2. Consider whether the dose of cycloserine can be reduced without compromising the regimen. If isoniazid is being used (especially high dose isoniazid), consider stopping it. If possible, switching the aminoglycoside to capreomycin may also be helpful.
		3. Initiate medical therapy:
		•Nonsteroidal anti-inflammatory drugs or acetaminophen may help alleviate symptoms.
		•Therapy with tricyclic antidepressants such as amitriptyline (start with 25 mg at bedtime, the dose may be increased to a maximum of 150 mg) can be tried. Do not use tricyclic antidepressants with selective serotonin reuptake inhibitors and antidepressant drugs.
		•Carbamazepine, an anticonvulsant, at 100 to 400 mg twice daily can be tried.
		•Gabapentin (used off-label) at 300 mg thrice a day; it can be used at a maximum dose of 3600 mg/day in three or four divided doses. Rarely, medication may be discontinued, but only if an alternative drug is available and the regimen is not compromised
Headache	Cs, Bdq,	Rule out more serious causes of headache including meningitis, and other infections of the central nervous system. (HIV coinfected patients should receive a head computed tomography scan and cerebrospinal fluid analysis.) Start analgesics like ibuprofen or paracetamol. Also encourage good hydration. Consider low dose tricyclic antidepressants for refractory headaches
Depression	Socioeconomic circumstances, chronic disease, Cs, fluoroquinolones, H, Eto/Pto	1. Assess and address underlying socioeconomic issues.
		2. Assess patients for coexisting substance abuse and refer to treatment if appropriate.
		3. Initiate individual counselling (or group counselling if the patient is sputum smear and culture negative).
		4. When depression is more significant, initiate antidepressant therapy (amitryptiline, fluoxetine or similar). Tricyclic antidepressants and selective serotonin reuptake inhibitors should be given together and should not be given to patients on linezolid.
		5. 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 to see if the depression is lessened is a common strategy).
		6. Discontinue the suspected agent if this can be done without compromising the regimen
Psychotic symptoms	Cs, H, fluoroquinolones	1. Stop the suspected agent for a short period of time (1–4 weeks) while psychotic symptoms are brought under control. The most likely drug is cycloserine followed by high dose isoniazid.
		2. If moderate to severe symptoms persist, initiate antipsychotic therapy (haloperidol).

		3. Hospitalize in a ward with psychiatric expertise if patient is at risk to himself/herself or others.
		4. Increase pyridoxine to the maximum daily dose (200 mg per day).
		5. Lower the dose of the suspected agent (most commonly cycloserine to 500 mg a day) if this can be done without compromising the regimen.
		6. Discontinue the suspected agent if this can be done without compromising the regimen. 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 trained in the adverse effects of second-line anti-TB drugs
Seizures	Cs, H, fluoroquinolones	1. Hold cycloserine, fl uoroquinolones 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. When seizures have resolved, restart medications one at a time. Cycloserine should not be restarted unless it is absolutely essential to the regimen. If cycloserine is reinitiated, start a dose one weight band lower.

Peripheral neuropathy

Prevalence (DR TB patients)	up to 30% of patients More common with comorbidities such as HIV, DM, alcohol use
How to detect?	Symptomatic Subjective neuropathy scale: ACTG Brief Peripheral Neuropathy Testing
Common causes	Lzd, HD-INH, Cs, Pto/Eto, alcohol S, Km, Cm, FQ, E, d4T, ddI
How to manage?	Consider discontinuation of Lzd, INH, Cs. Physical therapy; sturdy shoes; SSRIs; avoid TCA in persons on Bdq/Dlm
Additional tests/precautions	Prevention: pyridoxine for all patients on INH, Lzd, Cs. Additional testing: alcohol screening, examine extremities for lesions, sores, loss of function.

Managing peripheral neuropathy

ACTG Brief Peripheral Neuropathy Screen (BPNS):

Step 1. Grade Subjective Symptoms

Ask the subject to rate the severity of each symptom on a scale from 01 (mild) to 10 (most severe) for right and left feet and legs. Enter the score for each symptom in the columns marked R (right lower limb) and L (left lower limb).

Normal	Mild ---------- Severe									
00	01	02	03	04	05	06	07	08	09	10

Symptoms	R	L
a. Pain, aching, or burning in feet, legs		
b. "Pins and needles" in feet, legs		
c. Numbness (lack of feeling) in feet, legs		

Use the single highest severity score above to obtain a subjective sensory neuropathy score.

Subjective Sensory Neuropathy Score	Severity grade
00	0
01 – 03	1
04 – 06	2
07 – 10	3

Severity grade*	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Paresthesia	Mild discomfort; no treatment required	Moderate discomfort; non-narcotic analgesia required	Severe discomfort; or narcotic analgesia required with symptomatic improvement	Incapacitating; or not responsive to narcotic analgesia
Action	Stop Cs and Lzd. If symptoms improve, consider restarting these drugs. Consider restarting Lzd at a lower dose.	Stop Cs and Lzd. If symptoms improve, consider restarting cycloserine. Do not reintroduce Lzd. Provide symptomatic relief as described below.	Same as Grade 2.	Same as Grade 2.

*Reference: NIAID Division of Microbiology and Infectious Diseases, severity scale, Nov-2007.

Myelosuppression

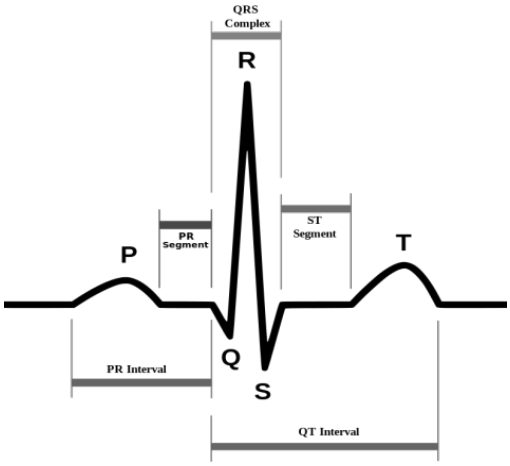
Prevalence (DR TB patients)	18% of patients in a trial with Lzd More common in patients with comorbidity, including HIV, alcohol use
How to detect?	Complete blood count, hemoglobin, platelets, white blood cells
Common causes	TB, Lzd, HIV, ART (AZT), alcohol (low platelets)
How to manage?	Iron supplementation, decrease dose of Lzd, transfusion or EPO if indicated, discontinue other medications.
Additional tests/precautions	Prevention: vitamin B6 Additional tests: Pregnancy testing, other co-morbidities, alcohol screening, investigation for possible hemorrhage.

Managing Myelosuppression

Severity grade*	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Anemia	10.5 - 9.5 g/dL	9.4 - 8.0 g/dL	7.9 - 6.5 g/dL	< 6.5 g/dL
Platelets decreased	75,000 – 99,999 /mm^3	50,000 – 74,999 /mm^3	20,000 – 49,999 /mm^3	< 20,000 /mm^3
Absolute neutrophil count low	1500 - 1000/mm3	999 - 750/mm3	749 - 500/mm3	<500/mm3
Action	Monitor carefully, and consider reduction of dose of Lzd.	Monitor carefully, and consider reduction of dose of Lzd to 300mg daily; in case of Grade 2 neutropenia, stop Lzd immediately. In case of Grade 2 anemia, consider EPO. Restart at reduced dose once toxicity has decreased to Grade 1.	Stop Lzd immediately. In case of Grade 3 anemia, consider EPO. Restart at reduced dose once toxicity has decreased to Grade 1.	Stop Lzd immediately. Consider hemotransfusion or EPO. Restart at reduced dose once toxicity has decreased to Grade 1.

QT Prolongation

Prevalence (DR TB patients)	Can occur in up to 10% of patients
How to detect?	ECG
Common causes	Mfx, Bdq, Cfz, Dlm, Lfx Many other drugs: • *e.g. erythromycin, clarithromycin, quinidine, ketoconazole, fluconazole,* • *Antipsychotics (all have some risk including haloperidol, chlorpromazine and risperidone),* • *Many anti-nausea drugs (ondansetron / granisetron, domperidone),* • *Methadone,* • *Some antiretrovirals.* Genetic causes such as long QT syndrome; hypothyroidism.
How to manage?	Assess for symptoms, repeat to confirm, review all medications; if >500 msec and does not correct, d/c BDQ
Additional tests/precautions	Potassium, TSH



The QTc Fridericia's formula corrects for the heart rate :

$$QTcF = \frac{QT}{\sqrt[3]{RR}}$$

Where:

QTcF = corrected QT interval
QT = time between start of QRS complex and end of T wave
RR = time between start of one QRS complex and start of the next QRS complex

Severity grade*	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Prolongation of QTcF	QTcF 450 – 480 ms	QTcF interval 481 – 500 ms	QTcF ≥ 501 ms on at least two separate ECGs.	QTcF ≥ 501 or >60 ms change from baseline and Torsade de pointes or polymorphic ventricular tachycardia or signs/symptoms of serious arrhythmia
Action	Monitor more closely; at least weekly ECG until QTcF has returned to grade 1 or less.	Monitor more closely; at least weekly ECG until QTcF has returned to grade 1 or less.	Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.	Stop the suspected causative drug(s). Hospitalize and replete electrolytes as necessary.

Checking and repleting serum electrolytes:

- Serum potassium (K+), ionized calcium (ionized Ca++), and magnesium (Mg++) should be obtained in case of prolonged QT.
- Abnormal electrolytes are most commonly due to the injectable and should be corrected.
- If low K+ is detected, urgent management needed with replacement and frequent repeat K+ test (daily or multiple times a day) to document K+ is improving.
- If K+ is low, always check Mg++ and Ca++, and compensate as needed.
- If unable to check, consider oral empiric replacement doses of Mg++ and Ca++.

Hearing loss

Prevalence (DR TB patients)	30% of patients *Patients with previous exposure to aminoglycosides may have already sustained a degree of hearing loss.*
How to detect?	Monthly audiometry while on injectables
Common causes	Injectable agents
How to manage?	Early identification is key, this is a **major cause of permanent disability! → Discontinue injectable**
Additional tests/precautions	Consider examination of tympanic membranes. *Concomitant use of furosemide, particularly in the setting of renal insufficiency, may exacerbate ototoxic effects of the injectables.*

Visual loss

Prevalence (DR TB patients)	Lzd is by far the most common cause of optic neuritis - 18% of patients in trials, mostly after 4 months of treatment.
How to detect?	Visual acuity, color testing (red-green Ishihara chart)
Common causes	Age, cataract, E, Lzd, Eto/Pto, Cfz, rifabutin, H, S, ddI
How to manage?	Rule out other causes, discontinue or lower dose of E and/or Lzd
Additional tests/precautions	Examination of optic nerve. Rule out diabetes

Severity grade*	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Optic nerve disorder	Asymptomatic; clinical or diagnostic observations only	Limiting vision of the affected eye (20/40 or better)	Limiting vision in the affected eye (worse than 20/40 but better than 20/200)	Blindness (20/200 or worse) in the affected eye
Action	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.	Stop Lzd immediately if there are any suspicions of optic neuritis. Do not restart it.

*NCI Common Terminology Criteria for Adverse Event, v.4.03 14-Jun-2010.

Hepatitis

Prevalence (DR TB patients)	Up to 25%
How to detect?	Symptomatic, screening (transaminases) *Baseline: screen for hepatitis B and C*
Common causes	Viral hepatitis, alcohol, NVP, any of the TB medications Can be very difficult to decide causative agent in multidrug regimen. C*otrimoxazole in HIV patients*
How to manage?	Discontinue medications and serially reintroduce
Additional tests/precautions	Consider serum bilirubin, alcohol screening, hepatitis B and C serology, liver ultrasonography

Severity grade*	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
ALT (SGPT)	1.1 – <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
AST (SGOT)	1.1 – <2.0 x ULN	2.0 – <3.0 x ULN	3.0 – 8.0 x ULN	> 8 x ULN
Action	Continue treatment regimen. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.	Continue treatment regimen. Patients should be followed until resolution (return to baseline) or stabilization of AST/ALT elevation.	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.

*Reference: NIAID Division of Microbiology and Infectious Diseases, severity scale, Nov-2007.

Acute kidney injury

Prevalence (DR TB patients)	up to 10% *More common in persons with HIV, Diabetes*
How to detect?	Urea, creatinine
Common causes	Injectables (TDF rarely)
How to manage?	Discontinue injectables
Additional tests/precautions	Consider HIV, diabetes investigations, prerenal, intrinsic renal, and postrenal alternative etiologies. Consider strict weight-based dosing of the injectable if the patient's weight <50 kg

Severity grade*	**Grade 1 Mild**	**Grade 2 Moderate**	**Grade 3 Severe**	**Grade 4 Life-threatening**
Hypokalemia	3.4 - 3.0 mEq/L	2.9 - 2.5 mEq/L	2.4 - 2.0 mEq/L or intensive replacement therapy or hospitalization required	< 2.0 mEq/L or abnormal potassium *with* paresis, ileus or life-threatening arrhythmia
Action	Continue injectable. Start oral potassium replacement therapy. Check serum magnesium and replace if necessary.	Continue injectable. Start aggressive oral potassium replacement therapy. Replace magnesium empirically if unable to check serum magnesium.	Stop injectable temporarily.Start IV potassium replacement therapy in addition to oral. Replace magnesium and other electrolytes as necessary.	Stop injectable temporarily. Start IV potassium replacement therapy in addition to oral. Replace magnesium and other electrolytes as necessary.

*Reference: NIAID Division of Microbiology and Infectious Diseases, severity scale, Nov-2007.

Hypothoiridism

Prevalence (DR-TB patients)	up to 10% *More common in HIV infected*
How to detect?	TFT (High TSH = hypothyroidism)
Common causes	Pto/Eto, PAS, d4T
How to manage?	Thyroid replacement therapy
Additional tests/precautions	QTc interval

Severity grade*	Grade 1 Mild	Grade 2 Moderate	Grade 3 Severe	Grade 4 Life-threatening
Hypothyroidism	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; thyroid replacement indicated; limiting iADL	Severe symptoms; limiting self care ADL hospitalization indicated	Life-threatening consequences; urgent intervention indicated
Action	Continue anti-TB drugs.	Continue anti-TB drugs. Start thyroxine.	Continue anti-TB drugs. Start thyroxine.	Stop all anti-TB drugs. Start thyroxine.

*NCI Common Terminology Criteria for Adverse Event, v.4.03 14-Jun-2010.

Annex 4

Suspected Adverse Drug Reaction (ADR) Reporting Form

SUSPECTED ADVERSE DRUG REACTION (ADR) REPORTING FORM
CONFIDENTIAL
If you are suspicious that an adverse reaction may be related to a drug or a combination of drugs, PLEASE COMPLETE THIS FORM and send it to the nearest Pharmacovigilance Centre/Drug Regulatory Authority.

A. PATIENT INFORMATION

1. Patient Details*

Patient name or initials: _____ **Age**/Sex: _____
Weight (if known): _____ Ward/Dept/Unit: _____

2. Relevant Tests/Laboratory Data (if any):
3. Other relevant information (including pre-existing medical conditions viz. allergies, pregnancy, alcohol use, renal dysfunction, diabetes etc.):

B. SUSPECTED DRUG(S)*

Drug name	Prescribed for/indication	Manufactured by:	Batch no/Exp.date	Route	Dose/strength	Date started	Date stopped

C. SUSPECTED DRUG REACTION(S)*

1. Please describe the reaction and any treatment given/action taken.
   Date reactions started: _____
   Date reaction stopped: _____
   Outcome: (Tick all that is appropriate)
   Recovered ☐ Recovering ☐
   Continuing ☐
   Others (SPECIFY) _____
2. Do you consider the reaction to be serious?
   Yes ☐ No ☐
   If yes, please indicate why the reaction is considered to be serious (Tick all that is appropriate)
   I. Patient died due to reaction _____
   II. Prolonged hospitalization_____
   III. Life threatening_____
   IV. Significant disability_____
   V. Medically significant (including congenital anomaly), Five details:_____

D. Other medications (including self-medication, (herbal and traditional medicines)

Did the patient take any other medicines prior to this reaction?
Yes_____ **No**_____

Drug name (both generic and brand)	Dosage	Route	Date started	Date stopped

E. Reporter details*

Name: _____

Designation: _____

Address: _____

_____

Contact No._____ Date: _____

Signature: _____

Please send this form to National Pharmacovigilance Centre (DRA), telephone: 337075 fax: 335803, email: ndem@dra.gov.bt or to the nearest Regional Pharmacovigilance Centre. Thank you for taking the time to fill in this report!

For official use by DRA:

Date of receipt of the report: _____

Received by: _____

Report ID no._____ Product MAH:

Action taken:

Annex 5

Routine Checklist for follow up and monitoring for MDR-TB/XDR-TB patients including aDSM

Month		0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Bacteriological Examination results																						
Sputum smear result																						
Sputum culture result																						
Investigations Report																						
CBC	**Hb**																					
	TLC																					
LFT	**AST**																					
	ALT																					
	TB/DB																					
RFT/ SE	**urea**																					
	Crt																					
	Ca																					
	Mg																					
	K																					
Uric acid																						
RBS																						
TFT (3 monthly)																						
Weight (monthly																						
ECG (2weekly for 6 months)																						
PTA (monthly if on injectables)																						
Visual acuity (sos)																						
CXR (6 monthly)																						
aDSM monitoring date and month																						
Brief summary of Adverse drug reactions (ADR) with date and month: ……																						

Annex 6
Dose adjustments for Second-line drugs in patients with renal insufficiency

Drug	Recommended dose and frequency for patients with creatinine clearance <30 ML/MIN or for patients receiving haemodialysis (unless otherwise indicated dose after dialysis)
Isoniazid	No adjustment necessary
Rifampicin	No adjustment necessary
Pyrazinamide	25-35 mg/kg per dose three times per week (not daily)
Ethambutol	15-25 mg/kg per dose three times per week (not daily)
Rifabutin	Normal dose can be used. If possible, monitor drug concentrations
Rifapentine	No adjustment necessary
Streptomycin	12-15 mg/kg per dose two or three times per week (not daily) [b]
Capreomycin	12-15 mg/kg per dose two or three times per week (not daily) [b]
Kanamycin	12-15 mg/kg per dose two or three times per week (not daily)[b]
Amikacin	12-15 mg/kg per dose two or three times per week (not daily)[b]
Ofloxacin	600-800 mg per dose three times per week (not daily)
Levofloxacin	750-1000 mg per dose three times per week (not daily)
Moxifloxacin	No adjustment necessary
Gatifloxacin	400mg three times a week
Cycloserine	250mg once daily or 500mg/dose three times per week
Terizidone	Recommendations not available
Prothionamide	No adjustment necessary
Ethionamide	No adjustment necessary
Para-aminosalicylic acid	4g/dose, twice daily maximum dose
Bedaquiline	No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution).
Linezolid	No adjustment necessary
Clofazimine	No adjustment necessary
Amoxicillin/clavulanate	For creatinine clearance 10-30ml/min dose 1000mg as amoxicillin component twice daily; for creatinine clearance <10ml/min dose 1000mg as amoxicillin component once daily.
Imipenem/Cilastin	For creatinine clearance 20-40 ml/min dose 500mg every 8 hours; for creatinine clearance <20ml/min dose 500mg every 12 hours.
Meropenem	For creatinine clearance 20-40 ml/min dose 750 mg every 12 hours; for creatinine clearance <20ml/min dose 500mg every 12 hours.

Annex 7
Contact Tracing Summary Reporting Form

Reporting Format for DS/MDR-TB Contact Tracing

Name of TB Reporting Centre: ……

Name of the District: ……

Details of Index Case:

Name: ……..…… Sex: …… Age: ……

CID…… TB Registration No.: ……

Current Address/Village: …… Mobile No.: ……

Contact Tracing Summary Report:

Date CI conducted: …/…../ …… CI follow-up (specify month as 0/3/6/9/12): ……..

Place (House/Work Place/Others): ……

Report Prepared by:

Name……

Designation ……..…..…

Mobile No……..……...…

Email ID……..…. (Dated Signature)

Provide the details of the contacts investigated below:

Sl. No.	Name of the contact	Age	Sex	Type of Contact (HH / Close)	Investigation carried out (mention the test date and result below)					Remarks
					Symptomatic (If yes, *Specify*)	Chest X-Ray	AFB/GeneXpert	Culture	TST/TBST	

Note: Please use one sheet for each index case and submit the report to NTCP after completing contact investigation.

No. of active TB diagnosed among contacts: ……..…… **No. of contacts put on TPT:** ……..……

Report Verified by:

Name……

Designation ……..……..……

Mobile No……..

Email ID…… (Dated signature)

Annex 8
Roles and Responsibilities

The following task shall be carried out as applicable to the relevant partners:

i. Hospitals and Health Services

Hospital Administration

- Facilitate fast tracking of patients with symptoms suggestive of TB from reception till diagnosis and providing of surgical masks to these patients during their presence in hospital
- Ensure availability of PPEs for staff
- Ensure proper infection control strategies in OPDs, TB treatment units and Isolation wards
- Propose and secure budget for samples shipment and facilitate transportation of TB related samples
- Update relevant staff on the TB treatment guidelines and protocols including any changes
- Ensure providing diet as recommended by treating physicians
- Facilitate TB contact investigation
- CMOs to assist TB In-charge and ensure that the diagnosed patient and completes treatment as per guidelines
- Use hospital data on TB for planning and monitoring of TB related activities in the Dzongkhag or hospital
- Annual indenting of N95 masks and TST reagents

Physicians

- Patient management as per national guidelines

Laboratories

- Ensure conducting required investigations advised by physicians
- Proper storage of samples and provide packaging for transportation of sputum to the RCDC and GeneXpert centres whenever required
- Coordinate with laboratory staff at the referred laboratory to verify
- receipt of samples as well as timely collection of results and dissemination to physicians
- Follow up reports and communicate reports to physicians and referring laboratories
- Quality assurance and participate in quality proficiency survey as per Laboratory services guidelines

Outdoor TB treatment unit /TB incharges

- Follow up patients recorded by physicians in the Presumptive TB register
- Appropriate classification and registration of cases based on case definition
- Counselling of patients and families
- Provide/ arrange directly observed treatment (DOT) to patients
- Identification of DOT providers and monitor DOT

- Send samples for GeneXpert and DST
- Update TbISS and follow-up reports
- Ensure availability of ATTs
- Include TB related activities in the IWP
- Conduct contact investigation of household and close contacts of all TB cases
- Initiate Isoniazid preventive treatment (IPT) / TB Infection treatment or other drugs as per national guidelines
- Decentralization of patients to respective BHUs for completion of treatment under direct observation if requested by patient's party
- Ensure that follow up sputum samples are collected and examined as per NTCP guidelines
- Ensure early follow-up action for patients who interrupt treatment and resume their treatment as per NTCP guidelines
- Follow up, receive, and provide feedback on transferred/referred patients

Recording and Reporting

- Appropriate registration of all TB cases
- Maintain TB register and treatment cards/patient cards
- Prepare and submit monthly and quarterly NTCP reports
- Maintain separate records of IPT implementation and contact tracing
- Liaise between Dzongkhag/district hospital and BHU's in terms of logistic support and TB control related activities
- Ensure reports/feedback to the NTCP and BHUs

Indoor TB treatment Units

- Ensure DOT by patient in administering anti- TB medicines.
- Monitor for patient complaints due to ATT and inform treating physicians
- Ensure PPEs are available for staff
- Ensure availability of sputum collection cups for patients and proper disposal of sputum
- Provide health education to patients and attendants
- Avoid mixing of respiratory disease patients with general patients unless sputum AFB negative

Infection control focal person

- Strengthen facility infection control committees to incorporate airborne and TB infection control as a core responsibility.
- Develop a facility plan for implementation of airborne (including TB) infection control.
- Ensure proper implementation of all recommended controls, complement and align activities with the national guidelines.
- Advise hospital administration on updated infection control practices for implementation support
- Fit test

ii. Basic Health Units /HAs of Hospital CHUs

Case Finding

- Identify people with signs and symptoms of TB, advise patients to collect sputum, and transfer specimen to the nearest district hospital for appropriate laboratory examination
- If the patient is willing to go themselves to the district hospital, option should be provided
- Follow up patients as per the diagnostic algorithm wherever possible.
- Responsible for continuation of treatment both initial and continuation phase under direct observation for the patients till completion of treatment.

Follow up

- Supervise and monitor treatment of all patients
- Ensure DOT
- BHUs/Hospitals to Identify and train suitable community DOT providers for those patients who are not within the easy reach of BHUs or Hospitals
- Trace any patients who interrupt treatment and manage their further treatment as per NTCP guidelines
- Contact tracing to be done as per guideline
- Provide feedback on the transferred/referred cases
- Provide health education and counselling to all TB patients and their family members at the beginning and on a regular basis
- Raise awareness about TB among general public in their catchment areas as regular activity

Recording and reporting

- Maintain records of patients transferred from the dzongkhag hospitals
- Provide feedback to the dzongkhag hospitals
- Prepare monthly TB reports and submit them to the Dzongkhag.

iii. Microscopy Centre

- Collect requisite number of sputum specimen from the patient with proper guidance
- Examine sputum specimens of all TB symptomatic referred for the same
- Examine follow up sputum samples of TB patients referred to the centre
- Report test results to referring clinician or medical Officer

iv. District Health Offices

- Facilitate regular awareness programs about TB for the general public
- Impart training and refresher courses to all health workers
- Support health centers for implementing TB related activities
- Propose and secure budget for conducting TB related activities in the district

- Include TB related agenda in VHW programs
- Support budget proposals for shipment of samples to higher centers
- Facilitate contact investigations

v. Individual Institutions

- Facilitate logistics and resource for creating awareness sessions on TB to their residents, employees or students
- Protect people with TB from discrimination such as expulsion from workplaces, educational institutions, health institutions, transport systems, housing or deportation
- Promote human rights including addressing stigma with special attention to gender, ethnicity and protection of vulnerable groups.

vi. Community Based Support Systems of Dzongkhags

- Conduct awareness sessions on TB while conducting community level activities

vii. NTCP and MoH

- Formulate Policies
- Coordinate with partners including funding agencies
- Planning and budgeting for program activities
- Provide support for sanction of budget proposed from Districts for samples shipment cost
- Facilitate sustainable transfer of samples to higher centres in collaboration with relevant agencies.
- Develop and strengthen human resources for TB treatment and control
- Coordinate with national and international agencies for improving the technical capacity in the country to undertake TB related laboratory services, including quality assurance
- Coordinate with DMP for procurement of TB drugs and other supplies
- Coordination with other programs and Dzongkhags
- Develop research agenda and Coordinate with academic institutes for undertaking operational research on TB
- Monitoring and supervision of NTCP activities at all levels, providing
- Feedback and reporting to the Ministry of Health and related agencies.

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