NATIONAL GUIDELINE FOR THE MANAGEMENT OF DRUG RESISTANT TUBERCULOSIS

October 2017 update

National Tuberculosis Control Programme
Department of Public Health
Ministry of Health

Contents

Abbreviations and acronyms

AFB	Acid-Fast Bacilli
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine Aminotransferase
ART	Anti-retroviral Therapy
AST	Aspartate Aminotransferase
BCG	Bacillus Calmette Guérin
BHU	Basic Health Unit
CEM	Cohort Event Monitoring
CPT	Cotrimoxazole Preventive Therapy
CSO	Civil Society Organization
DOT	Directly-Observed Therapy
DOTS	Directly Observed Treatment Short Course (core approach underpinning the strategy for TB control)
DRS	Drug Resistance Surveillance
DST	Drug Susceptibility Testing
EQA	External Quality Assessment
FQ	Fluoroquinolone
FT4	Free Thyroxine
HIV	Human Immunodeficiency Virus
JDWNRH	Jigme Dorji Wangchuk National Referral Hospital
RFT	Renal Function Test
LFT	Liver Function Test
LED	Light Emitting Diode
LPA	Line Probe Assays
MDR-TB	Multi-Drug-Resistant Tuberculosis
M/XDR-TB	Multi- or Extensively Drug-Resistant TB
NGO	Non-Governmental Organization
NTCP	National TB Control Programme
PAS	Para-aminosalicylic Acid
PMDT	Programmatic Management of Drug-resistant Tuberculosis
PPD	Purified Protein Derivative
RCDC	Royal Center for Disease Control
rGLC	Regional Green Light Committee
RR	Rifampicin Resistance
SGPT	Serum Glutamic-pyruvic Transaminase
QA	Quality Assurance
QC	Quality Control
SOP	Standard Operating Procedure
SNRL	Supranational Reference Laboratory

TB	Tuberculosis
TSH	Thyroid Simulating Hormone
UVGI	Ultraviolet Germicidal Irradiation
WHO	World Health Organization
XDR-TB	Extensively Drug-resistant TB

Classification of second line anti-TB drugs

GROUP A Fluoroquinolones		Levofloxacin Moxifloxacin Gatifloxacin
GROUP B Second-line injectable agents		Amikacin Capreomycin Kanamycin (Streptomycin)
GROUP C Other Core Second-line Agents		Ethionamide/Prothionamide Cycloserine/Terizidone Linezolid Clofazimine
GROUP D Add-on agents *(not core MDR-TB regimen components)*	**D1**	Pyrazinamide Ethambutol High-dose isoniazid
	D2	Bedaquiline Delamanid
	D3	*p*-aminosalicylic acid Imipenem-Cilastatin Meropenem Amoxicillin-Clavulanate (Thioacetazone)

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Foreword

The development of resistance to the anti -TB drugs including the development of Multi -Drug Resistant TB (MDR-TB) has emerged as a major public health concern all across the globe. The development of MDR-TB poses a great threat to effective control and prevention of TB. Globally, about half a million MDR-TB cases are being reported every year. Some of the important factors responsible for development of MDR-TB are improper treatment regimen, non-adherence to treatment by patients, poor quality of drugs, and transmission of the disease and existence of co-morbid conditions. The management of MDR-TB is more difficult and is challenged by adverse social and economic factors related to the patients and the community.

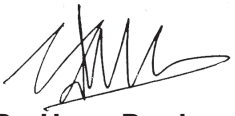
Like many countries in the region and globally, Bhutan, too, is facing public health challenges posed by the emergence of MDR-TB. Although the number of MDR-TB cases in Bhutan is quite small, the number of cases is seen to be increasing every year. In 2014, a total of 61 MDR-TB cases were being diagnosed and enrolled on treatment. The increase in number of MDR-TB cases could be ascribed to improvement in laboratory diagnostic facilities at the Royal Center for Disease Control (RCDC) and placement of GeneXpert machines at referral hospitals and selected hospitals in strategic locations.

Since the development of 1st Edition of MDR-TB guideline in 2011and subsequent edition in 2015;, new developments and updates have taken place across the globe in terms of MDR-TB diagnosis, treatment and management. The need to revise and update the existing MDR-TB guideline was felt necessary to align our treatment and management protocols as per the WHO standards. This guideline has been developed in line with the recent advances and WHO recommendations to guide our health professionals in the effective and better management of MDR-TB.

The guideline describes the components of MDR-TB in the context of country background and global information, laboratory network, case finding,

diagnosis and treatment initiation, management of drug resistant TB in special conditions, management of second line drugs, standards for registering, monitoring, recording and reporting the treatment outcomes of patients with MDR-TB. The document also describes about the MDR-TB expansion plan and GeneXpert deployment plan. While MDR-TB today remains a public health threat, it is important for every one of us to remember that majority of patients with drug-susceptible strains of TB infection can be cured with the standard six-month first-line treatment regimen. Therefore, our focus of care should be to reduce MDR-TB cases to a minimum level by treating and managing the drug susceptible TB cases in a timely and effective manner.

We hope that this guideline will be useful in our day to day's work in the field. We trust that each and every one of you will make the best use of this guideline for the Programmatic Management of Drug Resistant TB. The Ministry of Health looks forward to your commitment in delivering your services to the needs of TB patients with drug resistance in all twenty dzongkhags.



Dr. Ugen Dophu
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Executive Summary

The first edition of the guidelines on programmatic management of drug resistant TB (PMDT) in Bhutan was published in 2011 with subsequent edition in 2015. Since then a lot of global developments have happened in the field of management of drug resistant TB including introduction of new tools for diagnosis. Case definitions and treatment outcome definitions were also updated by WHO in 2013. Management of drug-resistant TB has also seen a recent gain in momentum in Bhutan with improvement in case finding and treatment success rates. It is expected that this momentum will continue and the programme will continue to enroll more and more cases while maintaining a high treatment success rate. In May 2016, WHO issued new guidelines for diagnosis and management of drug-resistant TB which had following major updates:

Case finding and diagnosis

- Expanded case-finding/referral criteria for screening of cases for drug resistance, specifically with the introduction and roll-out of GeneXpert machines.
- Algorithm for the use of GeneXpert has been updated to clarify the role of the tool and how to interpret the results.
- SOPs for case diagnosis with timelines defined to have a better coordination between the laboratory and the programmatic management of cases.

Treatment of DR-TB

- Treatment duration of MDR-TB aligned with WHO guidelines. The intensive phase shall be for 8 months and total duration of treatment will be 20 months in most patients.
- Treatment regimen for XDR-TB, mono and poly-resistant cases described as per the updated WHO guidelines.
- Duration of hospitalization will generally be more than 4 months for administration of injectables, instead of the entire intensive phase.

However, given the special socio-demographic circumstances in Bhutan; there will be exceptional cases which may require longer hospitalisation. This has been explained in relevant chapters.

- Management of adverse effects management is now described in greater details as per the recent WHO guidelines.
- Management of second-line drugs – Drug quantification has been explained with examples in relevant chapter.
- Chapter on ethics in MDR-TB management as well as on the role of community leaders are included.
- Formats for recording and reporting of progress are updated.
- Role of Technical Advisory Committeat national level has now been defined with Terms of Reference.
- With availability of additional diagnostic facilities and equipment for testing drug-resistance using the GeneXpert machine, the programme now aims to move towards universal drug susceptibility testing (DST). This means that all cases starting on treatment will undergo a GeneXpert test in addition to the already recommended use of machines for testing resistance among patients with high risk for drug-resistance.
- All cases starting on second-line treatment shall undergo tests for resistance to second-line drugs using LPA to ensure appropriate regimen from the beginning of the treatment itself.
- The programme will transition towards a shorter MDR-TB treatment regimen for RR-/MDR-TB patients, under several conditions adopting those recommended by WHO.
- The design of conventional MDR-TB regimens will take into consideration a different regrouping of second-line medicines, as and when necessary;
- Options for use of newer drugs where shorter or conventional regimen cannot be used due to several reasons
- Strengthening monitoring of adverse events in patients on second-line treatment with a particular emphasis on those being given shorter regimen.

The Ministry of Health (MoH) is committed to universal access to quality services for all forms of TB. Accordingly, implementation plan has been developed under the National TB Control Programme for the expansion of

services for drug resistant TB. Under the plan, the Programme intends to enroll on treatment 100% of all laboratory confirmed MDR-TB cases. The use of rapid diagnostics like the GeneXpert has already been expanded to 5 centers of the country. The updated PMDT guidelines describe the expanded use of GeneXpert for various categories of patients to ensure universal DST. The programme will transition to use of shorter regimen and keep the options open for treating patients with newer drugs based on individual case needs assessment. In most cases such treatments will be initiated by chest specialists/physicians at national or regional referral hospitals and monitored till sufficient capacity is developed in other health facilities.

Continuing with the 2015 updates, there is a greater emphasis on ambulatory treatment for MDR and XDR-TB patients. However, given the socio-demographic situation of the country and inability to administer injectables in several remote areas, admission for more than 4 months of treatment is still required. With expanding programme, this will necessitate that more and more hospitals have dedicated bed capacity along with necessary infection control facilities to admit and manage MDR-TB patients. This will also mean that staff at hospitals managing MDR-TB cases is trained to perform all the duties related to the PMDT.

An uninterrupted supply of quality assured second-line drugs will be ensured, so that patient treatment can be delivered uninterrupted. Quantification of drugs for MDR and XDR-TB patients is proposed in the expansion plans based on the treatment guidelines and anticipated number of patients to be initiated on treatment.

Implementation of the envisaged activities in this expansion plan requires huge investments. As of now, part of the anticipated funding needs is covered under expected grants from the GF and the RGoB. If at all funding gaps arise, this shall be covered by mobilizing additional domestic and international resources.

Programmatic Management of Drug Resistant Tuberculosis (PMDT)

Chapter 1

Background Information

This chapter provides an overview of Global, Regional and country burden of drug-resistant TB and specifically multidrug-resistant (MDR) and extensively drug-resistant (XDR) Tuberculosis (TB). Possible causes of drug-resistance and its prevention are highlighted. The chapter also provides information on interventions advocated by WHO to control the MDR-TB epidemic. Subsequently the organization of services for control of drug resistance and information on performance of the MDR-TB programme in recent years in terms of case enrolment and treatment success rates has been provided.

Global burden of Drug-Resistant Tuberculosis

Globally in 2015, there were an estimated 580,000 incident cases of MDR and Rifampicin Resistant (RR) TB[1] . An estimated 250,000 people died of MDR-TB in 2015. Among pulmonary TB cases notified in 2015; about 37% (124,990) were detected against the 340,000 MDR-RR TB estimated cases which accounts to 21.5% of the incident cases of MDR-TB.

In SEAR, the estimated incidence of MDR/RR-TB was 200,000. MDR/RR-TB cases estimated among notified pulmonary cases in 2015 were 110,000 out of which 35,953 cases were laboratory (bacteriologically) confirmed and 32,648 were started on treatment. Globally only 52% of MDR-TB patients were successfully treated and 49% in SEAR.

Extensively drug resistant TB had been reported by 117 countries globally and 6 countries in SEAR in 2015. The average proportion of MDR-TB cases with XDR-TB was 9.5% similar to previous year estimates. Globally, 7,234 patients with XDR-TB were enrolled on treatment (more than twice the level in 2014).

[1] *WHO Global TB Report 2016*

Key challenges in the MDR-TB global response include:

- Low DST coverage among TB cases resulting in small proportion of MDR-TB cases detected and notified;

- There are gaps between MDR-TB cases detected and started on treatment, leaving a large number of patients diagnosed with RR/ MDR-TB not started on treatment;

- Poor treatment outcomes due to weak health system and inadequate drug regimens (Only 49% treatment success rate in the South-East Asia Region and high unfavourable outcomes for MDR-TB).

- Insuffcient funding to reach the global targets on MDR-TB response.

The 5 priority actions urgently needed to address the global MDR-TB crisis are:

- Prevent MDR-TB through high quality treatment of drug-susceptible TB;
- Ensure prompt access to appropriate MDR-TB care (including the innovative diagnostics and new drugs and novel regimens), with adequate supplies of quality drugs and scaled-up country capacity to deliver services (including decentralization of MDR-TB care and engagement of all health care providers).
- Prevent transmission of MDR-TB through appropriate infection control;
- Underpin and sustain the MDR-TB response through high level political commitment, strong leadership across multiple governmental sectors, ever-broadening partnerships, and financing for care and research.

Country information

TB situation

Bhutan is considered a relatively low TB burden country as compared to other countries. Tuberculosis (TB) remains a major public health concern and the Royal Government of Bhutan accords high priority to National Tuberculosis

Control Programme (NTCP). It is estimated that in Bhutan, TB prevalence rate is 190/100,000 populations while the TB Incidence rate is 155/100,000 populations. The mortality rate due to TB is 16/100,000 populations.

The prevalence of HIV infection in general population is estimated at less than 0.1%[2]. HIV routine surveillance carried out annually among TB patients shows low level of co-infection.

The National TB Control Program (NTCP) has made substantial progress after implementation of DOTS and subsequent Stop TB Strategy components with major budgetary support from the government, the Global Fund (GF) and technical support from WHO.

The country has now adopted the WHO End TB Strategy from 2016. A consistently sustained case detection and high treatment success rate have resulted in decreasing trends in the TB burden over time. Given the current estimates of incidence and trends noted so far, Bhutan could enter the pre-elimination stage with further intensified efforts to reach the unreached populations.

MDR-TB situation

According to the Drug Resistance Surveillance (DRS) report 2014 conducted by RCDC; the proportion of the MDR-TB cases are as follows:

- New cases – 5%
- Retreatment cases – 35%

A high rate of MDR-TB among new cases is alarming and indicates that MDR-TB is being transmitted as primary infection in the general population. With the introduction of new diagnostic tools (Line Probe Assay) in 2014 and GeneXpert in 2016 it is possible that a greater number of drug resistant cases will get detected.

TB affects men and women equally but mostly affects the younger age group (15-24), which carries 35% of the total burden of TB, and indicates active transmission of TB.

[2] *Health sector response to HIV in the South-East Asia Region, 2013. WHO SEARO*

Causes of drug resistance and prevention

There are two principal pathways leading to the development of drug-resistant TB: (i) primary drug resistance and (ii) acquired (secondary) drug resistance. These pathways are interconnected and have many contributing factors.

i. Primary drug resistance

Primary or initial drug resistance means that a person has been infected with a drug-resistant TB strain. 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. Infection control measures to prevent infection with drug- resistant TB are discussed in Chapter 14.

ii. 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 regimen exclusively based on a single effective TB drug, there is a risk that bacteria with drug-resistant mutations will multiply further during the course of treatment, eventually becoming the dominant strain. If a person infected with a strain, initially resistant to a specific drug is treated with that drug plus only a single new additional drug, then there is a risk of developing resistance to the new drug as well.

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; and patient factors hampering adherence and treatment responses (Table 1.1).

TABLE 1 Factors contributing to poor TB treatment outcomes

HEALTH-CARE PROVIDERS:INAPPROPRIATE TREATMENT	DRUGS: INADEQUATE SUPPLY/QUALITY	PATIENTS: INADEQUATE DRUG INTAKE OR TREATMENT RESPONSE
Absence of guidelines	Poor quality of Medicines	Lack of information (Lack of means to adhere to treatment (transportation, food, etc.))
Inappropriate guidelines		
Non-compliance with guidelines	Poor storage conditions	Adverse effects
Poor training		
No monitoring of treatment	Poor regulation of medicines	HIV, Diabetes mellitus,
Poor patient education		
Poor management of adverse drug reactions	Unavailability of certain medicines (stock-outs or delivery disruptions)	Social barriers
Poor treatment support		
Poorly organized or funded	Incorrect dosing or inaccurate combination	Under-nutrition and Malabsorptions
TB control programmes		Substance abuse/ Dependency/Psychiatric conditions

Interventions to prevent Drug-Resistant TB

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

a. Early detection and high quality treatment of drug-susceptible TB.
b. Early detection and high quality 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.

a. Early detection and high quality treatment of drug-susceptible TB

This key drug-resistant TB prevention measure can be achieved by ensuring that drug-susceptible TB is properly diagnosed, treated and managed. Ensuring early detection of TB involves the introduction or strengthening of interventions to improve access and utilization of high-quality TB services established across the health system. Specific interventions include: suitable diagnostic methods to ensure early detection of TB comprising screening of at risk groups and inclusion of household contacts of infectious TB patients; placing patients on effective treatment with treatment follow-up and minimizing barriers to health care access.

b. Early detection and high quality treatment of drug-resistant TB

Early diagnosis and prompt, effective treatment is among the strongest actions to curb the drug-resistant TB epidemic by interrupting the chain of transmission. The most important element of drug-resistant TB prevention is to ensure proper and complete treatment, through regular intake of drugs with proper monitoring and continuous supply of high quality drugs.

c. Infection control

TB infection control is a combination of measures aimed at minimizing the risk of TB transmission within population. Infection control policies should be well formulated and implemented at every level of health delivery (public and private), in congregate settings, such as prisons, military barracks, homeless shelters, refugee camps, boarding schools and nursing homes,

and at the household level. Community campaigns can focus on how to minimize the exposure of TB in general and how households that have a TB patient within them can help prevent transmission. Community level infection control involves improved general living and working conditions creating environments that are less conducive to TB transmission.

d. Health system strengthening and regulation

Assessing health system barriers and opportunities is an essential part of planning TB control interventions. Such assessments should identify bottlenecks that could be addressed both through TB-specific programmatic interventions and interventions that need to be pursued beyond the purview of the NTPs.

e. Addressing underlying risk factors and social determinants

Optimal diagnosis and treatment of known TB cases are essential, but these are not suffcient to manage or prevent drug-resistant TB. The most critical and immediate social intervention for prevention of drug-resistant TB is to assess social and financial barriers to access and adherence to healthcare services and to address them accordingly. While this includes providing all TB diagnostic and treatment services free of charge to the patients, it must also minimize the cost to patients for other related clinical services (such as managing co-morbidities, notably HIV infection which may have a negative impact on TB treatment outcomes), as well as minimize the indirect costs of care (for example, job security while on MDR-TB treatment).

Organization and management of the DR-TB control programme in Bhutan

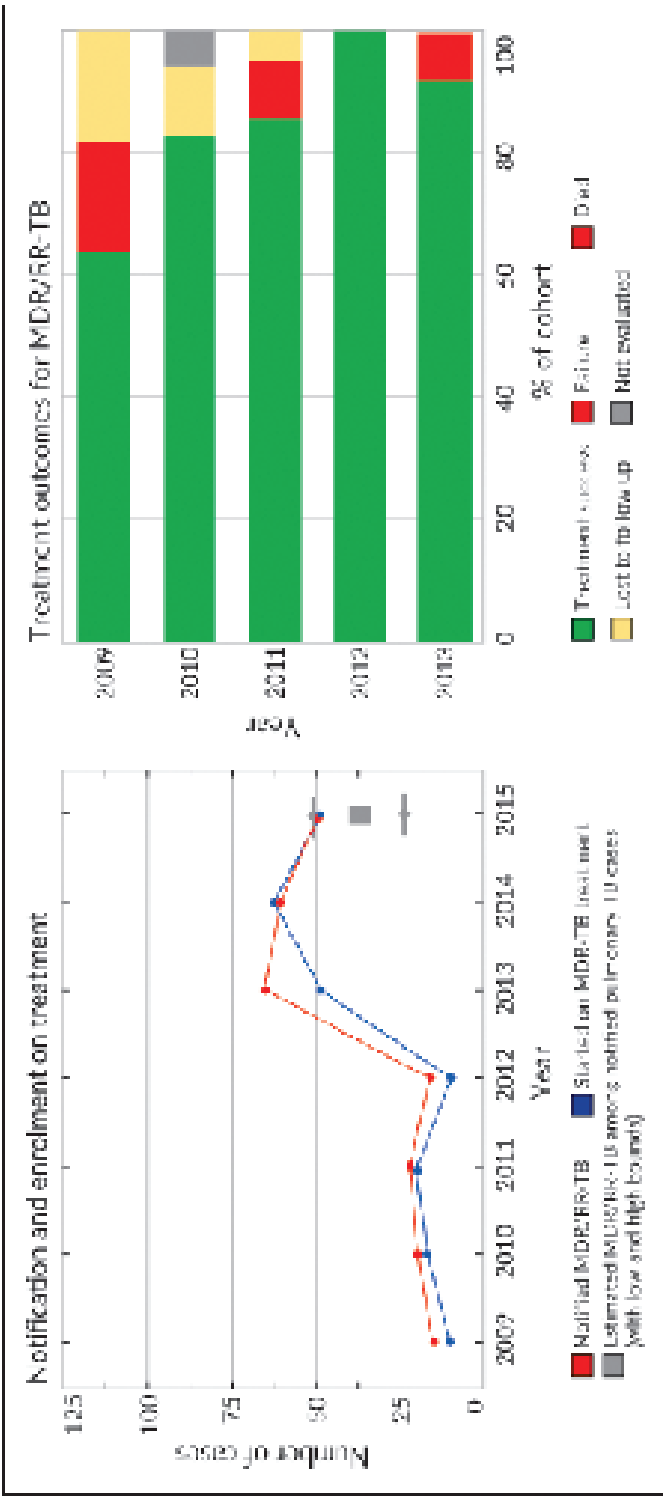
In Bhutan the services for drug-resistant TB are provided by the TB control programme which is itself integrated with general healthcare services. All hospitals including referral hospitals and selected BHU-Is function as microscopy centre for diagnostic and treatment centres for TB. A total of 32 TB reporting centres report on activities related to TB. From BHU Grade II and below, suspected cases are either referred to the district hospital or sputum samples are transported. There are also Out Reach Clinics in rural areas. Village Health Workers (VHWs) are involved in outreach clinic activities.

The Royal Center for Disease Control functions as the National TB Reference laboratory. The RCDC is linked to the Regional Supra-National Reference Laboratory (SNRL) in Bangkok, Thailand, and is accredited for culture and first-line DST (Drug Susceptibility Testing). Solid and Liquid culture plus Line Probe Assay (LPA) are available in RCDC. Sputum samples from the districts are being shipped to the RCDC for culture and DST.

The programme has identified three hospitals as the MDR-TB treatment sites. Currently, Gidakom hospital serves as the MDR-TB in-patient centre for JDWNRH and houses the most of MDR-TB cases in the country. MDR-TB treatment initiated in these hospitals is based on Laboratory confirmed results. The Gidakom hospital, Gelephu RR Hospital and Monggar RR Hospital will serve as MDR-TB treatment sites and the services will be expanded to include other hospitals as treatment initiation sites for MDR-TB.

Programme Performance in Recent Years

The status of MDR-TB case notification and treatment success rate is shown in figures 1 and 2.


Treatment outcomes for MDR/RR-TB
2009
2010
2011
2012
2013
0
20
40
60
80
100
% of cohort
Treatment success
Failure
Died
Lost to follow up
Not evaluated
Notification and enrolment on treatment
Number of cases
125
100
75
50
25
0
2009
2010
2011
2012
2013
2014
2015
Year
Notified MDR/RR-TB
Started MDR-TB treatment
Laboratory-confirmed pulmonary TB cases
(with low and high burden)

Chapter 2

Case Finding

This chapter provides details about the screening criteria to be used for drug resistance, both among symptomatics i.e. those in whom there are symptoms suggestive of TB but no diagnostic test has been undertaken, and screening of those already diagnosed with TB but history or clinical progress suggests possibility of resistance. Flow chart for use of Gene-Xpert, being relatively new test being rolled out in the country at the time of formulation of these guidelines, has been provided in the chapter along with other relevant details to interpret the results. The chapter also defines registration categories for various drug resistant cases. Finally SoPs are provided at the end to streamline the diagnosis of patients likely to have drug resistance so as to quickly enroll such patients on appropriate treatment regimen.

Cases to be screened for drug resistance by using Xpert MTB/RIF test

As per the existing programme policy, all sputum smear positive patients are screened for drug resistance using conventional methods in addition to those at risk of drug resistance or those where there is a possibility of an unfavourable outcome because of co-morbidities and hence at high risk of mortality due to drug resistance. Henceforth, all tuberculosis cases both pulmonary and extra-pulmonary whether new or re-treatment cases will be subjected to screening for drug resistance TB with GeneXpert. However, priority will be given to the following groups:

1. All TB cases starting on treatment will be screened with GeneXpert, if not already done at the time of diagnosis. However, in clinically diagnosed and extra-pulmonary (EP) TB cases, the testing will depend on availability of adequate specimen.

2. **High Risk groups –** Certain categories of patients are considered at high risk for drug resistance TB and this group also includes vulnerable populations in whom, because of their immunity and co-morbidity, mortality could be higher if they have associated drug resistance.

Therefore, the following groups will be subjected to Xpert test without undergoing sputum microscopy:

- All re-treatment TB cases - both smear-positive and negative cases (Relapse, Failure and treatment after loss to follow-up cases)
- Symptomatic close contacts of MDR-TB cases including health care workers or those contacts who have suspicion of TB on physical examination by a physician. Non-symptomatic close contacts will be screened using chest X-ray. Patients with anomalies on Chest X-ray suggestive of TB will be screened using GeneXpert irrespective of symptoms;
- Non-converters at 2/3 months of TB treatment;
- Treatment failure cases at 5, 6 and 8 months of TB treatment;
- TB-HIV co-infected cases
- Diabetes, chronic kidney disease, drug users and immuno-compromised patients.

3. **Others:** Apart from the high risk groups identified above, the following should also be screened with GeneXpert for drug-resistance TB:
    - Prisoners
    - Children
    - Elderly
    - Migrant workers specifically those in mining industry, hydro-power project sites, cement industry and quarries
    - Bridge population
    - Other congregate settings like hostels/dormitories/nunneries/ monasteries/military barracks.

Diagnosis

All TB cases and symptomatics belonging to various screening categories, as indicated above, will undergo Xpert MTB/RIF test.

All high and other risk cases found rifampicin resistant (RR) will be started on Second-line treatment while waiting for other primary drug susceptibility test (DST) results.

A low risk cases found RR will undergo another rapid DST using Xpert MTB/RIF or LPA on a fresh sample and decision should be taken according to the algorithm shown in figure 3.

Contact screening will promptly be initiated among all household contacts and specifically children as well as all other close contacts at workplace, prisons and other congregate settings. District health authorities and TB-In-charge will oversee contact screening by BHU staffs, health assistants in institutional setting or other focal point in congregate settings. Programme will disseminate these guidelines to all relevant staff. Contact screening will be completed within 15 days of diagnosing a case of DR-TB and a report filed along with treatment records of the patient.

Diagnosis and Interpretation of results from GeneXpert MTB/RIF

As far as possible, the laboratory personnel who are trained on how to use GeneXpert machines should be able to interpret and provide accurate and appropriate results of the tests performed. Accurate and appropriate results will enable the clinicians to make correct decisions about the interventions needed in patient management and registration, and to any additional laboratory work-up that may be required. All patients identified as having TB or rifampicin resistance by Xpert MTB/RIF should be initiated on treatment regimen as per the TB and MDR-TB guidelines at the earliest possible. The prompt initiation of treatment will have a positive effect on patient`s outcomes, and a treatment regimen can be modified later if additional results become available. A diagnostic algorithm as shown in Figure No 3 to help detect the MTB/RIF among various identified groups of patients will guide the clinicians for appropriate diagnosis and treatment initiation. A small proportion of tests may result in an error or invalid results, a repeat test need to be performed.

When 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.

When 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. Sample will be sent for drug susceptibility testing to first line drugs. The patients will be continued on drug-susceptible TB treatment until the results for other first line drugs resistance becomes available.

When Xpert MTB/RIF detects M.tuberculosis with rifampicin resistance, decisions about next steps depend on the patients risk group.

In patients from a group considered to be **at high risk of MDR-TB,** a standardized treatment regimen for MDR-TB as per guideline should be initiated. Sample from such patient should be subjected to LPA for Isoniazid resistance and the results are expected within three days.

In all cases diagnosed as RR-TB by rapid DST (GeneXpert), isoniazid (H) will be added to the regimen and samples will be sent for LPA and conventional culture and DST.

Confirmatory testing of rifampicin resistance using another testing technology is not necessary in such cases (given the high PPV for rifampicin resistance in this group). 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 stopping isoniazid, changing the quinolone and/or second-line injectable, or, in the case of XDR-TB, placing the patient on an appropriately designed regimen that includes group V drugs. The patient's registration should be modified to reflect any new information, and the case should be notified according to national guidelines.

In patients considered to be **at low risk of MDR-TB,** rifampicin resistance may be unexpected and clinicians may be hesitant to enroll patients on MDR-TB treatment due to lengthy treatment duration and concerns about toxicity of the drugs. An unexpected geneXpert MTB/RIF result may be attributed to the Positive Predictive Value (PPV) for rifampicin resistance in a group that has

a low underlying prevalence, or may result from non-systematic or random errors at the pre-analytical or post-analytical stages of testing (these errors are relatively frequent even in quality-assured laboratories). These include clerical errors made when information about specimens or test results is recorded or administrative errors that result in specimens being mixed up. A repeated Xpert MTB/RIF test on a fresh specimen can be useful to decide on clinician's confidence when deciding on treatment. In rare cases, when a patient is strongly suspected of having MDR-TB even after a negative result from Xpert MTB/RIF, a follow up test be done using phenotypic culture-based DST to detect rifampicin resistance.

When the result of a second Xpert MTB/RIF test identifies TB but not rifampicin resistance (an expected result in an individual at low risk of MDR-TB), a standardized first-line treatment regimen should be started, and the patient should be registered as having susceptible, bacteriologically confirmed TB.
When the result of a second Xpert MTB/RIF test on a fresh specimen again shows rifampicin resistance, a standardized treatment regimen for MDR-TB with the addition of isoniazid 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 LPA and phenotypic DST to re-confirm resistance to rifampicin and also 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.

In cases where discordant results are obtained from Xpert MTB/RIF and phenotypic DST or LPA, the available culture isolate should be referred to a reference laboratory for DNA sequencing; while awaiting the results, a clinical decision should be made whether to continue the MDR-TB regimen or not.
The Xpert MTB/RIF test is not suitable for monitoring a patient's response to treatment. Conventional microscopy and culture are required for monitoring MDR-TB patients during treatment.

Diagnosing Paediatric TB and drug resistance among TB cases

The presence of three or more of the following should strongly suggest a diagnosis of TB among paediatric cases:

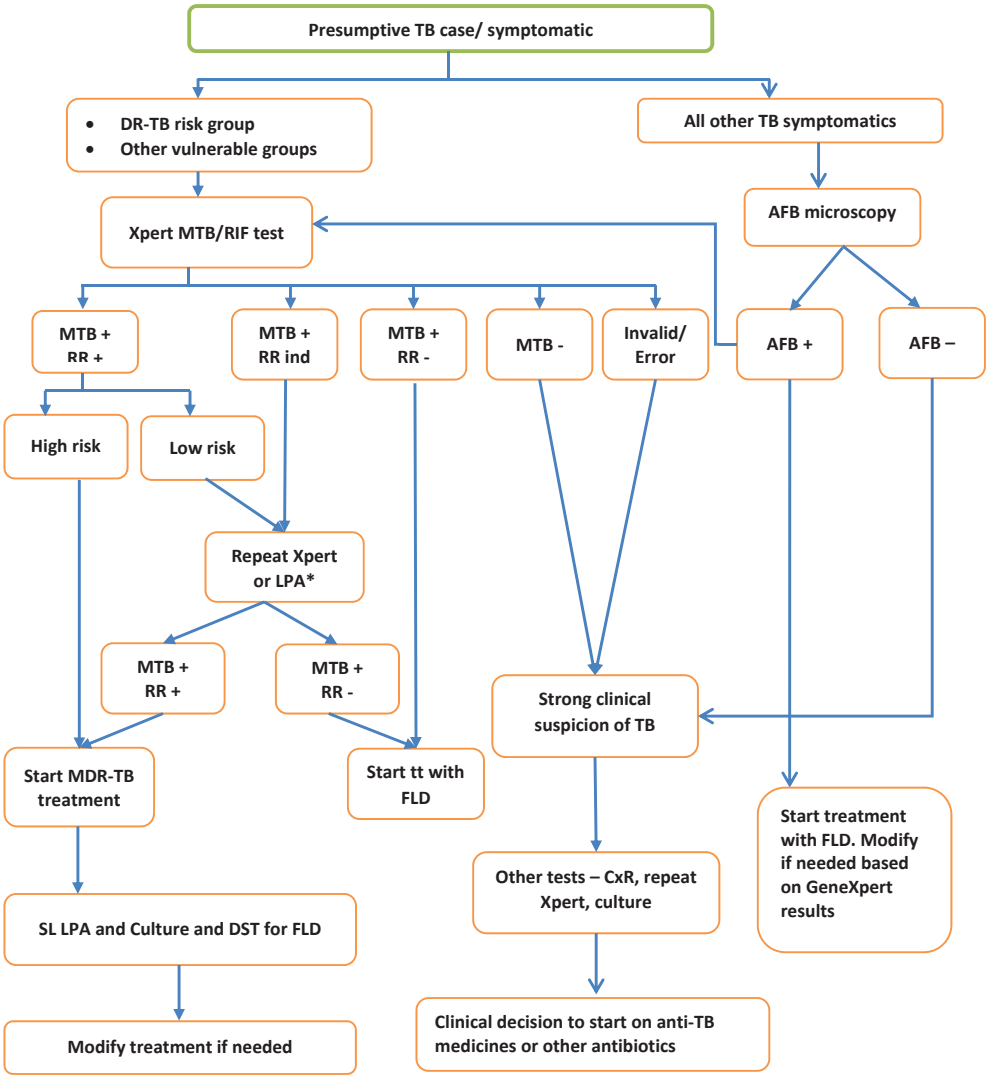
- Chronic symptoms suggestive of TB;
- Physical signs highly suggestive of TB;
- Chest radiograph suggestive of TB;
- A positive tuberculin skin test;

Specifically in cases of a close family member diagnosed with drug resistance, an evaluation by a physician, including history and physical examination will be undertaken. Sputum investigations (ideally a rapid diagnostic method such as X-pert MTB/RIF, culture and DST) and HIV testing will be undertaken. Gastric aspirate may be used since young children may not be able to expectorate sputum. Bronchoscopic alveolar lavage (BAL) and various extra-pulmonary TB site specimens should be sent for GeneXpert. The management of paediatric drug resistant TB is described later in this guideline.

All health facility workers will be sensitized on various screening criteria by the TB-In-charge and Medical Officer. In case there are private health facilities or industries, the managers there will also be sensitized by the TB in-charges on need for early diagnosis and treatment of drug resistant TB among workers.

The TB Unit will liaise with HIV- VCT unit and diabetes clinic for cross-referral. The referral for diagnosis would be ensured within 7 days after appropriate counseling.

Figure 1: Flow chart for diagnosis of drug resistance TB using GeneXpert MTB/RIF test



MTB – Mycobacterium tuberculosis; RR – Rifampicin resistance; FLD – First line drugs; DST – Drug susceptibility testing; MDR – Multi drug resistance; FQ – fluoroquinolones;

Diagnosing drug resistance among extra-pulmonary TB cases

For diagnosing drug-resistance in extra-pulmonary TB cases, geneXpert MTB/RIF would be used in preference to conventional microscopy and culture as the initial diagnostic test for cerebrospinal fluid (CSF) specimens from patients suspected of having TB meningitis and for testing specific non-respiratory specimens (lymph nodes and other tissues except for pleural fluid) from patients suspected of having extra-pulmonary TB with drug-resistance.

Classification of drug resistance (not mutually exclusive)

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

RR/MDR-TB patient registration groups

Patients are assigned to a registration group based on the most recent treatment history at the time of collecting the biological specimen that was used to confirm MDR-TB or RR-TB.

- **New -** no or less than one month of anti -TB treatment;
- **Relapse -** previously treated for TB and whose most recent treatment outcome was cured or treatment completed, and subsequently diagnosed with a recurrent episode of TB;
- **Treatment after loss to follow-up -** Previously treated for TB and was declared Lost to follow-up at the end of the most recent course of treatment;

- **Treatment after failure of first treatment** with first-line drugs-A patient who has received first-line drug treatment for TB and in whom treatment has failed.
- **Treatment after failure of retreatment regimen** with first-line drugs-A previously treated TB patient who has received a retreatment regimen with first-line drugs and in whom the retreatment has failed.
- **Other previously treated patients-** A previously treated TB patient whose outcome after the most recent course of treatment is unknown or undocumented.

Resistance category of patients on second line treatment

Patients enrolled on second line treatment will be reported for resistance as below:

- **Confirmed RR-TB or MDR-TB.**
- **Presumptive RR-TB or MDR-TB-**Patients may be registered and started on SLD on the basis of significant risk for drug resistance before laboratory confirmation of resistance. This decision shall be undertaken by the Medical Specialist/Chest physician.
- **Poly-/mono-resistant TB without rifampicin resistance-**Some of these cases may have second-line anti-TB drugs added to their treatment.
- **XDR-TB (confirmed or presumptive)-**Patients may be started on XDR-TB treatment on the basis of a laboratory diagnosis or, in its absence, because of significant risk.

Chapter 3

Organization of the Laboratory network

Definitive diagnosis of drug-resistant TB requires that Mycobacterium tuberculosis bacteria be detected and resistance to anti-TB drugs determined. This can be done by performing a WHO- endorsed rapid molecular test to detect the TB bacillus as well as resistance or by isolating the bacteria by culture and conducting drug susceptibility testing (DST) using solid or liquid media.

Early detection of drug resistance allows the use of appropriate treatment regimens for patients, which has an important impact on improved TB control. The development of rapid methods for DST is crucial due to increasing rates of multidrug-resistant TB (MDR-TB) and the emergence of extensively drug-resistant TB (XDR-TB), with very high reported HIV-associated mortality.

This chapter describes the available laboratory services in Bhutan and the standards for laboratory services needed to diagnose and treat drug-resistant TB. It is built on existing laboratory standards outlined in guidelines by WHO adapted in context of the country.

Diagnostic facilities available in the country

The laboratory network in the country to support the diagnosis of TB and drug resistant TB is as follows:

- District level/ BHU I – microscopy and transport of sputum for rapid DST at Referral hospitals and designated hospitals; and transport of sputum for culture and DST to the Reference Laboratory;
- Regional level – Microscopy, Xpert MTB/RIF testing and transport of sputum to Reference Laboratory for culture and DST;
- National level – Microscopy and Xpert MTB/RIF testing at the Jigme Dorji Wangchuk National Referral Hospital (JDWNRH), Eastern Regional Referral, Monggar and Central Regional Referral, Gelephu, Phuntsholing and Samdrupjongkhar hospitals and transport of sputum for culture and DST to the Reference Laboratory;
- Reference Laboratory - LPA and Culture & DST of FLDs and SL LPA at the National TB Reference Laboratory and SLDs at SNRL, Bangkok.

To have an effective network of laboratories and provide prompt diagnostic services it is essential that sputum transportation works efficiently.

Sputum from all screening categories will be collected and transported by the Lab technician or a person designated by the hospital In-charge to the nearest sites for undertaking the X-pert MTB/RIF testing. The sample transportation can be done by using the ambulance service and Bhutan postal services. In case of delay in transportation, the sample will be kept in cold conditions using cold-box or refrigerator. Standard biohazard triple packaging will be used to pack the samples. The shipment of the samples must be done within 5 days from the date of sample collection.

Lab technician at the GeneXpert testing site and the TB In-charge will be responsible for ensuring availability of GeneXpert MTB/RIF results within 2 days from the receipt of samples.

After getting results of the first specimen, sputum for RR cases will be collected and transported in similar manner for further culture and DST. The turnaround time for DST results is expected to be not more than 6 weeks if using liquid culture and twelve weeks for solid culture. All cases started on second line TB treatment will be offered second line DST in collaboration with SNRL, Bangkok. TB In-charges will coordinate with treating physicians and lab personnel to ensure timely shipment and receipt of the results.

Laboratory quality assurance

Quality Assurance (QA) is a system designed to continuously improve the reliability and efficiency of laboratory services under the supervision of a reference laboratory.

Key activities for ensuring the quality of lab service include:

- **Training and competence assessment of the staff -** All training conducted should include a competency assessment of participants. Competency is defined as a demonstrated ability to apply knowledge and skills, and clear criteria for competency should be set in advance. Staff competency should be monitored on a regular basis, and refresher training must be provided.
- **Instrument verification -** Instruments should be evaluated as being

"fit for purpose" through verification with known positive and/or negative material prior to commencing testing of clinical specimens, and after calibration or repair of instruments. Verification testing should be repeated in case of any deviation from expected results, and suppliers should be contacted in case of repeated errors for troubleshooting.

- **Method validation -** All tests used in the laboratory must be validated for their intended use.
- **Quality Control-** Quality Control (QC) or Internal Quality Control (IQC) is the systematic internal monitoring of working practices, technical procedures, equipment and materials. Following are some of the IQC activities:
- **Sputum microscopy-**The purpose of QC in sputum microscopy is to ensure that staining solutions work well and that they are not contaminated with AFB. Good quality solutions and staining technique make reading and reporting easier and more reliable. Accurate record keeping of preparation and testing provides confidence in results.
- **Solid culture and DST-**Every new batch of Lowenstein-Jensen (LJ) media prepared should be tested for contamination and susceptibility with the standard H37Rv strain. Similarly control strain; M. tuberculosis SM & RFP resistance, M. tuberculosis INH & EBM resistance were used to check quality of every new batch of drug LJ media prepared for DST. In case of any discrepancies results with control strains on drug free media; the whole batch of DST samples were considered as invalid and test should be repeated.
- **MGIT 960 Liquid culture and Drug Sensitivity testing-** The new lot of MGIT medium and enrichment should be tested for quality control using H37RV and M. fortuitum strains and DST using H37RV, RF and SM resistant strain, INH and EMB resistant strain. Each set of DST should have H37RV strain along with the test samples as a control strain.
- **Line Probe Assay (LPA)-** To validate the correct performance of the test and the proper functioning of kit constituents, each strip includes 5 control zones; a Conjugate Control zone [CC] to check the binding

of the conjugate on the strip and a correct chromogenic reaction. An Amplification Control [AC] to check for a successful amplification reaction. Three Locus Control zone (rpoB, katG and inhA) checking the optimal sensitivity of the reaction for each of the tested gene loci. Line probe assay should have a negative strip run for every 11 samples hybridized after amplification of the bacterial DNA.

- **Gene Xpert MTB/RIF-** Each test includes a Sample Processing Control (SPC) and probe check control (PCC).Sample Processing Control (SPC)—Ensures the sample was correctly processed. Probe Check Control (PCC) — measures the fluorescence signal from the probes to monitor bead rehydration, reaction-tube filling, probe integrity and dye stability. Probe Check passes if it meets the assigned acceptance criteria.

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

National External Quality Assurance Scheme (NEQAS)- a program whereby the national reference laboratory (NTRL) monitors quality and results of AFB sputum microscopy centres in the district hospitals. NEQAS methods comprises of;

- ✓ Panel testing
- ✓ Blinded Rechecking
- ✓ On-site evaluation
- ✓ Annual Maintenance and calibration of X-pert MTB/RIF machine.

International External Quality Assurance Scheme (IEQAS)- a program where Supra National Reference Laboratory (SNRL) and SAARC TB Reference Laboratory (STRL) monitors quality and result of Culture, DST and AFB microscopy in NTRL. IEQAS method comprises of:Proficiency testing of Sputum smear microscopy by SAARC TB Reference Laboratory (STRL), Nepal;

- ✓ Annual assessment visit by SNRL, Bangkok
- ✓ Panel sample testing for culture and first line DST received from SNRL, Bangkok
- ✓ Reconfirmation of DR and MDR isolates from SNRL, Bangkok.
- ✓ Annual Maintenance and calibration of X-pert MTB/RIF machine.

Quality Improvement- Data collection (identification of non-conformities), data analysis and creative problem solving are key components of the QI process, which involves not only continual monitoring but also identifying and analyzing actual and potential defects.

Quality indicator monitoring- provided in the table 2.

Performance indicators-Culture positivity rates, Contamination rates, Smear status rates, Turn-around time (TAT), Drug resistance rates and Proficiency test performance are some of the general areas to monitor under performance indicator.

Quality indicators monitoring

Table 2: 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
	LPA- >200 test run/year
	Gene Xpert MTB/RIF- >2400 test run per year
Service interruptions	No interruptions
a) Stock outs	No stock outs leading to service interruption
b) Equipment down time	No equipment down time leading to service interruption
Turn-around time	90% of results meet test-specific TAT
Test statistics (quality indicator) report	100% reports completed by defined due date
EQA results	>90% EQA panels are passed
QC results	>90% QC results meet expected criteria
Specimen rejection	<1% specimens rejected
Technician productivity	Report average number of tests performed per month per technician

Turn-around- time for laboratory tests

Table 3: Target for turn-around- time for each of the laboratory tests

Test	Description	Target
Smear microscopy	Time between receipt of specimens for smear at the laboratory and result reporting	24-48 hrs
Solid culture	Time between receipt of specimens for culture at the laboratory and result reporting	2-8 weeks average for smear-positive samples and 4–8weeks average for smear-negative samples.
Liquid culture		8-10 days for smear-positive samples and 2–6 weeks for smear-negative samples
Solid media DST	Time between inoculation of DST and result reporting (mean, range and 90th centile). For total DST TAT, add this value to culture TAT.	4-6 weeks
Liquid media DST		After inoculation, 2 weeks
LPA	Time between receipt of specimens for LPA at the laboratory and result reporting (mean, range and 90th centile).	1-2 days (longer if batching of Tests). For indirect LPA, add the culture TAT for total TAT
Xpert MTB/ RIF	Time between receipt of specimen for Xpert MTB/RIF at the laboratory and result reporting.	2-24hrs

Laboratory bio-safety

Essential measures to be in place and enforced for lab bio-safety include:

1. Appropriate layout of the laboratory in line with the techniques implemented:
    - o containment rooms;
    - o bio-safety cabinets;
    - o aerosol-containment centrifuges;
    - o ventilation systems providing unidirectional airflow;
2. Effective and specific administrative controls
    - o Standard operating procedures;
    - o Waste management procedures;
    - o Accident management plans;
    - o Health monitoring of the staffs;
3. Proper practices and procedures for general laboratory safety;
4. Personal protective equipment appropriate for the techniques being performed.

Second line LPA and DST

It is expected that at least 60 MDR-TB cases will be enrolled each year. The programme aims to offer SL LPA to all cases initiated on second line treatment from 2018 onwards and complete DST as and when the capacity in country is developed. RCDC has already developed the capacity for SL LPA and would strive to develop in-country capacity for SL DST facilities in future. However till such capacity is in place, samples will be sent to SNRL Bangkok for SL DST.

In case of resource constraints SL LPA will be prioritized for:

- All patients starting on shorter regimen;
- Patients having history of prior use of SLD specifically fluoroquinolones or injectibles irrespective of regimen being chosen;
- History of contact with known or suspected XDR-TB cases;
- Migrant workers and bridge population (Bhutanese who have possibly contracted MDR-TB outside the country during a recent visit to neighboring countries).

Chapter 4

Treatment initiation

It is necessary that all patients diagnosed with drug resistance are promptly enrolled on appropriate treatment in alignment with globally recommended standards. This chapter details the process of enrolment, assigning responsibilities and the baseline investigations that need to be performed at the time of enrolment. Thereafter, treatment regimen is described for various forms of drug resistant TB including MDR-TB, XDR-TB, mono and poly-resistant TB in alignment with WHO guidelines. The chapter also describes various treatment strategies that can be used while initiating the patients on treatment with second-line drugs.

Process of enrolment

In case rapid DST results show a person to be RR/ MDR-TB, such person will be initiated on second-line treatment immediately at the National Referral Hospital or any of the regional referral hospitals by chest specialist/ physician trained in the management of DR-TB. In all such cases, MDR-TB registration numbers will be provided at any of the treatment initiation sites by TB In-charge. The patient will initially be admitted to the hospital for treatment observation and completion of baseline tests.

When the treatment is initiated at the regional referral hospital, the TB In-charge will coordinate with the National Referral Hospital for pending baseline investigations and severe adverse drug reactions or complications that are not manageable at the regional hospital.

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 co-morbid conditions and pre-existing drug allergies. These include:

- ✓ Mycobacterial cultures, DST to FLDs and SLDs.

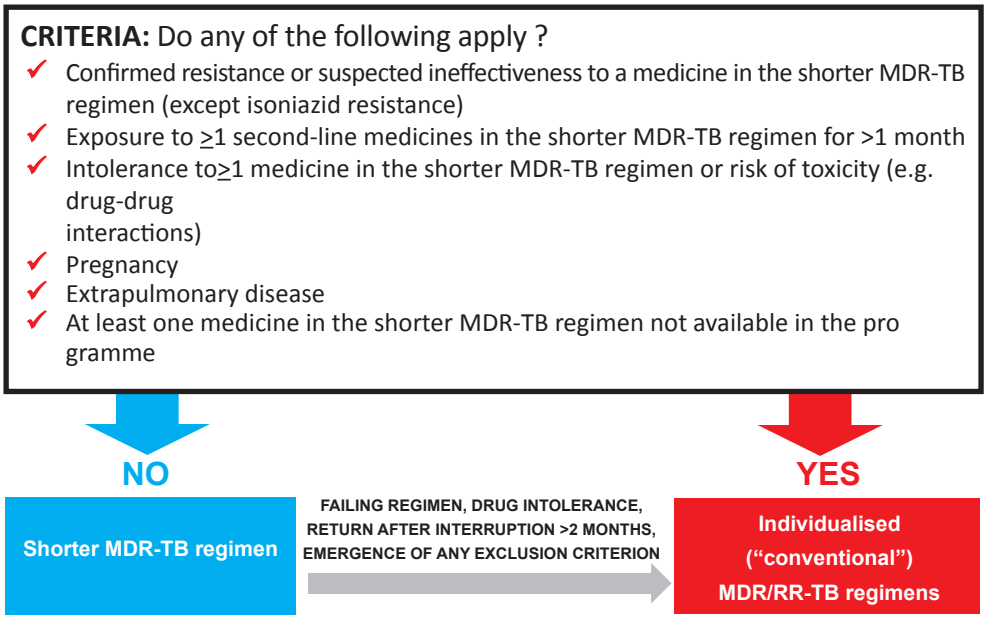
- ✓ Baseline serum potassium, serum creatinine, serum glucose and serum glutamic-pyruvic transaminase (SGPT)/alanine transaminase (ALT)
- ✓ If HIV positive, the case will be referred for CD4 (CD4% in children and viral load testing)
- ✓ HbsAg, anti-HCV.
- ✓ Baseline full blood count
- ✓ Pregnancy test for women of child bearing age
- ✓ Routine baseline FT4 and TSH test can be done on all patients.
- ✓ Audiometry
- ✓ Chest radiograph.
- ✓ ECG.
- ✓ Baseline psychosocial assessment

Table 4: Conditions to be screened at initial medical evaluation

HIV infection	Mental illness	Seizures
Acute or chronic liver disease	Breast feeding	
Pregnancy	Hypertension	Renal in-sufficiency
Diabetes mellitus	Drug or alcohol dependency	Malnutrition

Treatment regimen for MDR-TB

Taking into account the WHO recommendations on shorter regimen, the programme plans to have a phased introduction of this regimen in the country. Criteria for deciding treatment regimen will be as follows:



The shorter regimen that will be used is as recommended by WHO:
Intensive phase 4-6 Km-Mfx-Pto-Cfz-Z-H$_{HIGH-DOSE}$-E
Continuation phase 5 Mfx-Cfz-Z-E

The regimen can be used in all adult, children and PLHIV patients if they do not fall in any exclusion criteria as above.
In the initial phases of implementation, the shorter regimen will be used only in new RR/MDR-TB cases after checking for exclusion criteria as above. It is possible that around ~15-30 cases will be initiated on treatment in the first year of implementation. Based on developing evidence and further guidance of WHO, the regimen may be considered for all eligible cases in the coming years.
For other cases, longer MDR-TB regimen will continue to be used:
Intensive phase 8 Z+Ka+Lfx+Eto+Cs
Continuation phase 12 Z+Lfx+Eto+Cs

Z–Pyrazinamide; Ka–Kanamycin; Lfx– Levofloxacin; Eto– Ethionamide; Cs- Cycloserine

Note: The regimen can be individualized after receiving reports of the SL-LPA.

In all cases diagnosed as RR-TB by rapid DST, Isoniazid (H) will be added to the longer regimen and samples will be sent for LPA and conventional culture and DST. After receiving results of DST to H, decision to continue H will be taken based on whether the mycobacterium is found susceptible to H or not. The injectable (Ka) will be administered 6 times a week during the intensive phase while oral drugs will be administered daily under observation for the entire duration.

An intensive phase of eight months will be used for most patients and the duration may be modified according to the patient's response to therapy. Intermittent therapy with the injectable agent (three times a week) can also be considered in patients who have been on the injectable for a prolonged period of time and when toxicity becomes a greater risk to the patient. However, this will be done only in consultation with the chest specialist/medical specialist/ Technical Advisory Committee (TAC).

The total treatment duration will not be less than 20 months for most cases. A decision to prolong treatment will also be undertaken in consultation with the chest specialist/medical specialist/TAC.

Cm and PAS will be made available as reserve drugs for about 2% of cases that may have significant adverse effects to any of the drugs in standardized treatment or in special conditions.

The dosages of the drugs according to weight are given in the annexure 1 and 2 for adults and children (Annexure 1 and Annexure 2).

Treatment regimen for XDR-TB

It is expected that 6-7 XDR cases will be reported in Bhutan if SL DST is offered to all MDR-TB patients (as per global estimates of 9-10% among MDR-TB cases). Standardized regimen to be used for such cases would be:

Intensive phase 12Z+Cm+Mfx+Cfz+Lzd+PAS+Amx/Clv

Continuation phase 12Z+Mfx+Cfz+Lzd+Amx/Clv

Z-Pyrazinamide; Cm-Capreomycin; Mfx-Moxifloxacin; Cfz- Clofazimine; Lzd-Linezolid; PAS-Para-amino-Salicylicacid ; Amx/Clv-Amoxicillin/Clavulanate

As in case of MDR-TB, the injectable will be administered for 6 days a week for the intensive phase while the oral drugs will be administered for all 7 days of a week throughout the treatment. The intensive phase will last for 12 months and the total duration of at least 24 months in most cases.

In case the country considers using Bdq (Bedaquiline) or Dlm (Delamanid) in future, the regimen will include the new drugs replacing drugs for which resistance is found on SL DST or where higher rates of side effects are reported.

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

Table 5: Pattern of resistance and recommended regimen

PATTERN OF DRUG	REGIMEN	MINIMUM DURATION OF TREATMENT	COMMENTS
H (± S)	R, Z, E and FQ	6–9	Use geneXpert MTB/RIF at month, 0,2, and 3 and if rifampicin resistance is found; switch to full MDR-TB treatment.
H and E (+/-S)	R, Z and FQ	9–12	Use Xpert MTB/RIF at month 0, 2, and 3 and if rifampicin resistance is found; switch to full MDR-TB treatment. Some experts recommend using a second-line injectible agent for the first three months.
H, E, Z, (± S)	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 the regimen for patients with extensive disease. Z should be added if resistance is uncertain. Use GeneXpert MTB/RIF at month 0, 2, and 3 and 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	Add H if resistance to H is not established.

The use of Xpert MTB/RIF at month 0, 2 and 3 is not intended for monitoring response to therapy as the test may be positive for Mycobacterium tuberculosis for patients with a positive response and even after cure. Rather, it is intended only to detect rifampicin amplification during therapy.
H=isoniazid; S=streptomycin; R=rifampicin;Z=pyrazinamide;E=ethambutol;FQ=fluoroquinolone.

Chapter 5

Case management system

Treatment of drug resistant TB in its current form is long and challenging because of the toxicity of the regimen. Even with introduction of shorter regimen, the need for appropriate management of patients is no less. It is imperative that all patients initiated on treatment take the complete course regularly so as to prevent risk of amplification of resistance and cut the chain of transmission.

Health-care providers have an obligation to support patients' ability to complete therapy. There are several ethically sound strategies to support patients to adhere to treatment, including directly observed therapy with a patient centered approach. It is crucial for patients to be engaged as partners in the treatment process, respecting their autonomy and privacy. Use of all reasonable and ethical means to persuade and to enable patient's adherence to treatment in order to protect public health should always be tried first.

Patient Centered Care and DOT

The patient-centered approach as advocated in the WHO TB strategy consists of enabling patients to exercise their rights and fulfill their responsibilities with transparency, respect and dignity, by giving due consideration to their values and needs. A patient-centered approach may increase the chances of successful treatment outcomes, and improve well-being and financial risk protection by improving adherence to treatment, benefiting patients and society as a whole.

Given that MDR-TB and XDR-TB treatment are often the last therapeutic option for many patients and that there are serious public health consequences if treatment fails, it is advisable that all patients receive medicines under DOT as a way to ensure full adherence to treatment, with a strict patient-centered approach based on sound ethics and with due respect for human rights.

DOT can be performed either at facility-based or community-based levels. It should be emphasized to all health care workers that treatment observation is:

- To support patient take medicines and not just observe;
- To identify and address side effects early;
- To ensure proper follow-up of treatment;
- To ensure regular and complete treatment

Transition to ambulatory care

Most patients will need admission to a hospital for 4 months of intensive phase of treatment. They can be discharged earlier if two consecutive negative cultures are obtained. The decision to decentralize treatment after 4 months/culture conversion will be taken based on:

- Clinical assessment and improvement in 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).
- 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.
- Feasibility of administering injectables and undertake follow-up examinations near patient's home. If a patient is coming from a remote area with no health facility nearby to administer the injectable and the clinician and TB in-charge are convinced that ambulatory treatment will not be possible, the patient will be explained the need to stay in hospital at least till the intensive phase is over or a workable alternative is found.

A quick training of health staff at the facility managing a decentralized treatment of MDR-TB case will be conducted before the patient is transferred. Medical Officer and TB In-charge will be responsible for coordinating decentralization of treatment. In case of community based DOT, a suitable DOT provider will be identified in consultation with the patient.

Reasons for ambulatory care:

The reasons for moving to an ambulatory care are:

1. Published studies[2] show that MDR-TB patients become rapidly non-infectious after start of effective therapy.
2. The country will need to invest lots of resources in infection control in hospitals if longer stay for such patients is maintained.
3. It may not be convenient for all patients to stay long time away from families and some of them may risk losing their jobs.

Education and counseling

Education and counseling 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 patient take complete course of the treatment. The process of counseling 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 counseling process. Counseling 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 counseling 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.

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2 *A.S. Dharmadhikari et al. Rapid impact of effective treatment on transmission of multi drug-resistant tuberculosis. INT J TUBERC LUNG DIS 18(9):1019–102*

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

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 labor or other similar strenuous duties.

Nutrition

All patients will undergo a nutrition status assessment at the beginning of treatment and any time during the treatment, as considered appropriate. All in-patients will receive a high protein diet and any additional support measures considered appropriate during evaluation. Additional nutritional support to MDR-TB patients while in the hospital will need to be adjusted from the regular budget of the concerned hospital against the patients' diet.

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 sufferings 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 dyspnoea**-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 metre-dosed inhaler with a spacer or mask. Depression and anxiety, if present, should be addressed.
- **Hospitalization, hospice care or nursing home care-** Home-based care should 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 counseling 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.

Chapter 6

Monitoring treatment response

This chapter 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 at least in the intensive phase 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 X-pert MTB/RIF and line probe assays should not be used to monitor response to treatment in all cases. However X-pert 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. The chapter lists common side effects while management is included in the annexure (Annexure 3).The chapter defines various treatment outcomes as well as the process of assigning the treatment outcomes.

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 – cough, sputum production, fever and weight loss – generally improve 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 6: Monitoring schedule of MDR-TB patients on treatment

MONITORING EVALUATION	RECOMMENDED FREQUENCY
Evaluation by clinician	*During the intensive phase:* Every day during the first weeks if hospitalized and at least every week if treated as outpatient, until the treatment is well tolerated. Once stable the patient is seen twice a month or once a month. During the continuation phase: Monthly assessments unless there is a medical necessity to see the patient more often. The DOT provider sees the patient daily between consultations and signals any concerns to the clinician.
Treatment adherence and tolerance	Daily by the DOT provider.
Sputum smears and culture	Monitoring smears and culture throughout treatment –sputum smear monthly throughout the treatment and sputum culture monthly until culture conversion followed by three monthly until end of treatment.
Weight	At baseline, then every two weeks for first three months and then monthly thereafter.
Height	At start of treatment for all (to be able to assess BMI throughout treatment); monthly for children (to assess growth).
Drug testing susceptibility	At baseline for first- and second-line anti-TB drugs. Repeat DST for patients who remain culture-positive or revert after fourth month of treatment.
Chest radiograph	At baseline, and then every six months.

Table 7: Schedule of follow-up for MDR-TB/XDR-TB patients without complications

<table>
<tr><th>MONTH</th><th>CLINICAL consultation</th><th>WEIGHT</th><th>SMEAR</th><th>CULTURE</th><th>DST</th><th>CXR</th><th>LFT</th><th>Cr, K</th><th>TSH</th><th>ECG</th><th>AUDIOMETRY</th><th>HIV Testing</th></tr>
<tr><td>0 (baseline)</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td></tr>
<tr><td>1</td><td rowspan="3">Every two weeks</td><td rowspan="3">Every two weeks</td><td>✓</td><td>✓</td><td></td><td></td><td>✓</td><td>✓</td><td></td><td rowspan="12">Monthly if on XDR-TB Rx and every 6 monthly if on MDR-TB Rx</td><td>✓</td><td rowspan="12">Repeat if indicated</td></tr>
<tr><td>2</td><td>✓</td><td>✓</td><td></td><td></td><td>✓</td><td>✓</td><td></td><td>✓</td></tr>
<tr><td>3</td><td>✓</td><td>✓</td><td></td><td></td><td>✓</td><td>✓</td><td>✓</td><td>✓</td></tr>
<tr><td>4</td><td>✓</td><td>✓</td><td>✓</td><td rowspan="9">If culture positive</td><td></td><td>✓</td><td>✓</td><td></td><td>✓</td></tr>
<tr><td>5</td><td>✓</td><td>✓</td><td>✓</td><td></td><td>✓</td><td>✓</td><td></td><td>✓</td></tr>
<tr><td>6</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td></tr>
<tr><td>7</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td></td><td rowspan="6">Every three months</td><td>✓</td><td></td><td>✓</td></tr>
<tr><td>8</td><td>✓</td><td>✓</td><td>✓</td><td>✓</td><td></td><td>✓</td><td></td><td>✓</td></tr>
<tr><td>9</td><td>✓</td><td>✓</td><td>✓</td><td rowspan="4">Every three months</td><td></td><td rowspan="4">If on injectable and 3 monthly if not on injectables</td><td>✓</td><td rowspan="4">If on injectables</td></tr>
<tr><td>10</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td><td></td></tr>
<tr><td>11</td><td>✓</td><td>✓</td><td>✓</td><td></td><td></td><td></td></tr>
<tr><td>12</td><td>✓</td><td>✓</td><td>✓</td><td>♦</td><td>✓</td></tr>
<tr><td>until completion</td><td>✓</td><td>monthly</td><td>monthly</td><td>Every six months</td><td>Every three monthly</td></tr>
</table>

Adverse effects monitoring

As per experience from within Bhutan as well as other implementing countries, adverse effects to second line drugs is one of the common causes for patients discontinuing the treatment. Steps will be taken for early detection of adverse events and its proper management. For this, active monitoring of adverse effects will be advocated. A checklist has been developed and is given in Annexure 4 of this guideline. Time lag between onset of symptoms and action taken will be monitored by TB In-charge. All cases with serious side effects or needing expert intervention should be referred within 7 days of onset of symptoms. The BHU staff and the TB In-charge will coordinate this referral.

Adverse effect management

Table 8: Common side effects and ancillary medicines used

INDICATION	DRUG/S
Nausea, vomiting, upset stomach	Metoclopramide, dimenhydrinate, prochlor-perazine, promethazine, odansetron (and other serotonin 5-HT3 receptor antagonist)
Heartburn, acid indigestion sour stomach, ulcer	H2-blockers (ranitidine, cimetidine, famotidine, etc.), proton pump inhibitors (omeprazole, lansoprazole, etc.). Avoid antacids because they can decrease absorption of fluoroquinolone.
Oral candidiasis	Fluconazole, clotrimazole lozenges, nystatin suspension
Diarrhoea	Loperamide
Depression	Selective serotonin reuptake inhibitors (fluoxetine, sertraline), tricyclic an depressants (amitriptyline)
Severe anxiety	Lorazepam, diazepam
Insomnia	Dimenhydrinate
Psychosis	Haloperidol, thorazine, risperidone (Also include stocks of benzotropine or biperiden to preventextrapyramidal effects.)
Seizures	Phenytoin, carbamazepine, valproic acid, Phenobarbital
Prophylaxis of neurological complications of cycloserine and isoniazid	Pyridoxine (vitamin B6)
Peripheral neuropathy	Amitriptyline, gabapentin
Vestibular symptoms	Meclizine, dimenhydrinate, prochlorperazine, Promethazine

INDICATION	DRUG/S
Musculoskeletal pain,arthralgia, headaches	Ibuprofen, paracetamol, codeine
Cutaneous reactions, itching	Hydrocortisone cream, calamine, caladryl lotions
Systemic hypersensitivity r eactions	An histamines (diphenhydramine, chlorpheniramine, dimenhydrinate), corticosteroids(prednisolone, dexamethasone)
Bronchospasm	Inhaled beta-agonists (albuterol, salbutamol etc.), inhaled corticosteroids (beclomethasone, etc.),oral steroids (prednisolone), injectable steroids(dexamethasone, methylprednisolone)
Hypothyroidism	Levothyroxine
Electrolyte wasting	Potassium, magnesium and calcium replacement therapy (oral and intravenous formulations)

Note: Adverse effects with commonly implicated drug and management approach is provided in Annexure 3.Further management of AEs is detailed in Annexure

Pharmacovigilance and active Drug Safety Monitoring and Management (aDSM)

Active TB drug safety monitoring and management (aDSM) is a means to safeguard patient health and contributes to global knowledge about the safety of individual medicines and drug combinations, especially in novel regimens

Some important terminologies

Pharmacovigilance: the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.

Active TB drug-safety monitoring and management (aDSM): active and systematic clinical and laboratory assessment of patients on treatment with new TB drugs, novel MDR-TB regimens or XDR-TB regimens to detect, manage and report suspected or confirmed drug toxicities.

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.

Adverse drug reactions (ADR): a response to a medicine which is noxious and unintended, and which occurs at doses normally used in humans.

Serious adverse event (SAE): an AE which either leads to death or a life-threatening experience; to hospitalization or prolongation of hospitalization; to 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.

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”.

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.

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.

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 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 counseled early and often about AEs.

The pharmacist/pharmacy unit at district hospitals will be responsible for reporting adverse effects as reported by the clinicians or other health workers and DOT providers, make records, and send to Drug Regulatory Authority (DRA) in the country.

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

Assigning treatment outcomes

An outcome of cure and treatment success will be assigned by treating facility if all the criteria as laid in the guidelines are met in consultation with the respective TB In-charge. Such outcomes will be informed to the regional/ national referral centres within 7 days of assigning the outcome.

In cases of a suspected treatment failure, TB In-charge will promptly inform the regional/ national referral centres and future course of action will be decided by TAC as may be possible. Cases of death among MDR-TB diagnosed patient whether before starting treatment or after the start of treatment will be discussed by TAC. Lost to follow-up will be minimized by active retrieval and support to patients.

Recording treatment outcomes

Table 9: Definitions of treatment outcomes for drug-resistant patients

TREATMENT OUTCOME	DEFINITION
Cured	Treatment completed as recommended by the national guideline 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
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.
Treatment failed[a]	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: • Lack of conversiona by the end of the intensive phase;or • Bacteriological reversionb 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.
Died	A patient who dies for any reason during the course of treatment.
Lost to follow-up	A patient whose treatment was interrupted for two consecutive months or more.
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).
Treatment success	The sum of Cured and Treatment completed.

[a]For treatment failed, lack of conversion by the end of the intensive phase implies that the patient does not convert within the maximum duration of the intensive phase of eight months (conventional regimen) and 6 months (shorter regimen) treatment applied by the programme.

[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.

Reducing lost to follow-up cases

As the number of cases initiated on second line treatment increase and the programme is going to have a shift towards greater ambulatory care, it is important to have a system in place to reduce loss to follow-up. In case the patient is not able to adhere to treatment, all efforts should be made to address problems of the patient through psycho-social support. The need for support will vary from case-to-case basis. At least one initial home visit will be made to patient's home by the TB-In-charge and the BHU staff/VHW when providing decentralized treatment to verify address as well as counsel friends and relatives.

In case a dose of medicines is missed, the VHW/DOT provider/BHU 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 counseling is not successful over phone. If the VHW/DOT provider/BHU staffs are not able to convince patient, local community members/leaders may be involved along with the TB-In-charge.

Indications for suspending treatment

If the patient continues to deteriorate despite the relevant measures being taken, treatment failure could be considered in consultation with the TAC. 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 7
Management of drug-resistant TB in special populations and situations

This chapter 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. In all such cases the TAC at the national level should be consulted before making any changes to the regimen. Specific cases may also need consultation with respective specialists.

HIV co-infection

Drug-resistant TB is often associated with higher mortality rates in people living with HIV (PLHIV), meaning that be after integration of HIV and drug-resistant TB services is necessary, both in high HIV prevalence settings, but also in any setting where HIV co-infection is common among TB patients. 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 counseling in all patients with presumed or diagnosed drug-resistant TB will be performed. GeneXpert MTB/RIF test will be used in HIV-positive TB symptomatics. Mycobacterial cultures will also be used in HIV-positive TB symptomatics 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 tolerated. Generally this should be within the first two weeks of initiating MDR-TB treatment. Efforts will be made to provide integrated care specifically when

managing co-morbidities. A joint monitoring of patients by both programmes on progress and any side-effects need to be undertaken. Adverse effects and drug-drug interactions are much more common in people living with HIV/AIDS. 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).Monitoring needs to be more intense for both response to therapy and adverse effects.Co-trimoxazole preventive therapy will be provided for patients with active TB and HIV. Also, nutritional and socio-economic supports are recommended in these patients.Effective TB infection control and other airborne infection control will be practiced in such cases.

Paediatric cases

Anti-TB drugs should be dosed according to weight and adjusted regularlyas weight increases during treatment. The weight based chart for drug administration in children is given in Annexure 2.

Most second-line TB drugs do not have paediatric liquid or tablet formulations, so it may be necessary to split the pills in order to approximate the correct doses. To split a tablet into 3/4th, it is suggested to split the tablet in half and then split a half tablet into another half. Discard the smaller quarter tablet and give the child a half tablet plus the remaining quarter tablet. Doses of most anti-TB drugs have not been established for children below 5 kg, but often the potential benefit outweighs the risks. In such cases, the child should be dosed as close to the middle of the mg/kg range as possible.

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 minimise teratogenic effects of second line drugs. The general principle to follow in treatment of pregnant women is to treat with three or four second-line anti-TB

drugs plus pyrazinamide. Fluoroquinolones, cycloserine, para-aminosalicylic acid (PAS) and amoxicillin/clavulanate along with pyrazinamide are considered the drug of choice for MDR-TB treatment during pregnancy.

There is a need to avoid injectable drugs during pregnancy. Aminoglycosides can be particularly toxic to the developing foetal ear. Capreomycin is the injectable drug of choice if an injectable drug cannot be avoided. Injectable drugs can be added back postpartum to make a more complete regimen.

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.

In certain cases, termination of pregnancy can be considered if the mother's life is at risk. The risk and benefit of termination should be clearly explained to the mother and father and a mutually acceptable decision taken

Lactating mothers

It is preferable to provide infant formula options as an alternative to breast feeding. The infant formula should be available free of charge for the patient, especially in resource-poor settings. Since the formula milk is already available through the HIV programme, however concerned hospital administration should provide formula milk from the regular patient diet budget. In Bhutan, the number of such mothers is expected to be few and hence there appears to be no problem in following this recommendation.

Clinicians and parents may agree to breast feeding when the formula milk is not a feasible option. A woman who is breast feeding and has active drug-resistant TB should receive a full course of anti-TB treatment. 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.

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 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.

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 diffcult 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 thereafter in view of the renal toxicity of aminoglycosides.

Renal Insufficiency

Renal insuffciency 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 insuffciency, and the dose and/or the interval between dosing should be adjusted. The dosing is based on the patient's creatinine clearance.

Table 10: Dose adjustments for second-line drugs in patients with renal insuficiency

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 to avoid toxicity.
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	400 mg three times a week
Cycloserine	250 mg once daily, or 500 mg/dose three times per week[c]
Terizidone	Recommendations not available
Prothionamide	No adjustment necessary
Ethionamide	No adjustment necessary
Para-aminosalicylic acid[e]	4 g/dose, twice daily maximum dose[d]
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 10–30 ml/min dose 1000 mg as amoxicillin component twice daily; for creatinine clearance <10 ml/min dose 1000 mg as amoxicillin component once daily
Imipenem/cilastin	For creatinine clearance 20–40 ml/min dose 500 mg every 8 hours; for creatinine clearance <20 ml/min dose 500 mg every 12 hours
Meropenem	For creatinine clearance 20–40 ml/min dose 750 mg every 12 hours; for creatinine clearance <20 ml/min dose 500 mg every 12 hours

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 present 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.

Substance Dependence

Patients with substance dependence 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

Management of contacts of MDR-TB patients

Close contacts of multi-drug resistant TB (MDR-TB) patients are defined as people living in the same household as the index patient, or spending many hours a day together with the patient in the same indoor space. For drug-susceptible TB, contact investigation includes the treatment of active or latent TB. However for MDR-TB, the programmatic priority is to find and treat contacts who have active TB. Contact tracing is crucial in the prevention of transmission of multi-drug resistant TB.

Managing Contacts

Diagnostic work-up of contacts starts with an evaluation by a physician, including history and physical examination. The contacts then need to undergo a chest radiograph and sputum investigations. GeneXpert MTB/RIF would be used along with sputum smear microscopy, culture and drug susceptibility testing (DST). Interpretation of results and treatment regimen for contacts remain similar to those for other MDR-TB patients.

Prophylaxis of Contacts

The goal of preventive therapy is to prevent people with latent TB infection from developing active TB. Given the poor outcomes under the best available treatment for active MDR-TB, an effective preventive therapy for people likely to be infected with latent MDR-TB such as household contacts would be an important intervention. Due to lack of evidence, there is no consensus about whether close contacts of MDR-TB patients should be given preventive therapy, and if so, which drugs should be given. On the basis of the currently available evidence, the universal use of second-line anti-TB drugs for the treatment of latent TB in MDR-TB contacts is not recommended. It is however recommended to perform an initial detailed evaluation of all close contacts and a clinical evaluation whenever they develop symptoms suggestive of TB. In addition, children under five and people of all ages living with HIV should

receive a clinical evaluation every six months for two years after their last MDR-TB exposure, whether or not they are symptomatic. If active disease develops, prompt initiation of treatment with a regimen designed to treat MDR-TB is recommended.

After discharge of MDR-TB patients from in-patient facility to their homes, it is necessary to educate patient and family members to practice infection control measures. The patient should be taught cough etiquette, sputum disposal and to sleep in separate room as far as possible. He or she should be encouraged to spend more time outdoors and to avoid spending time in crowded places like public transport, public gatherings etc.

Chapter 9

Infection Control

Infection control policies and strategies for drug-resistant TB are similar to those for drug-susceptible TB as the transmission of both forms of mycobacterium is similar. However, infection control for drug-resistant TB has assumed greater importance because of the nature of the disease and associated threats.

National TB Control Programme, gives due importance to infection control at all health facilities managing TB and drug resistant forms of TB. Although interventions at places administering patients will defer from those at places just managing drug resistant cases on outpatient basis, basic principles remain the same. All staffs need to be aware of the potential risk and would need to follow appropriate guidelines to mitigate the associated risk. Similarly, infection control policy needs to be followed at the household level and in congregate settings (military barracks, prisons, student hostels, nursing homes, monastic institutions) to interrupt the chain of transmission. Infection control measures should be prioritized in setting where capacity for early detection and immediate enrollment on effective treatment is not yet readily available.

Infection Control

To prevent further spread of MDR-TB, an important activity is Infection control. Infection control will be emphasized through all platforms and monitored during supervisory visits and monitoring meetings

The NTCP will conduct annual monitoring of TB disease among health workers. Awareness activities for airborne infection control through health education messages will be undertaken at health facilities as well as through mass media.

While all general principles of airborne infection control are important, the major activities are grouped under three main heads – Administrative control, Environmental control and Personal protection. These are further explained as under:

Administrative Control

- Identify an isolation facility for patients admitted with TB.
- Promptly identify people with TB symptoms (triage), separate infectious patients from other patients at the OPD, control the spread of pathogens by encouraging cough etiquette and respiratory hygiene and try to minimize time spent in health-care facilities.
- Provide a package of prevention and care interventions for health workers, including HIV prevention, antiretroviral therapy and isoniazid preventive therapy for HIV-positive health workers.

Environmental Control

- Use ventilation systems. Cross ventilation should be encouraged.
- Mixed mode ventilation would be suitable for Bhutan (natural plus artificial). Exhaust fans with directional control of air flow at all indoor and outdoor health care facilities should be used.
- Use ultraviolet germicidal irradiation fixtures, exhaust fans when adequate ventilation cannot be achieved.

Personal Protective Equipment (PPE)

- Use of particulate respirators (N95 or equivalent) for health care workers.
- Surgical mask to be used by coughing patients and cough etiquette to be followed.

Hospitals with in-patient facilities for MDR-TB patients will have ward refurbishment for proper infection control measures including mixed mode ventilation. Since the country faces extreme winters, natural ventilation cannot be the only means of infection prevention and mechanical ventilation has to be added. For staff working at these facilities, adequate supply of PPE needs to be ensured by the concerned hospital administration. This includes N95 or equivalent respirators for the staff and surgical masks for the patients. There will also be display of posters at these facilities educating patients about cough etiquettes

Chapter 10

Management of Second Line Anti-TB Drugs

Uninterrupted supply of quality assured drugs has always been an important element in control of all forms of TB. Second-line drugs to treat drug-resistant TB must be managed appropriately in order to ensure that the correct medicines are selected, procured in the right quantities, distributed to treatment centers in a timely manner, handled and stored to maintain quality and availability of sufficient stocks, and used rationally by the health worker and patients.

While drug management remains the primary role of pharmacists, it is important that all health staff play their respective roles so as to support adequate supply of all second-line drugs for the patients already on treatment, for patients starting on treatment and also for those whose treatment is being decentralized. This would mean that proper information about drug stocks is available at all levels. This chapter describes second-line drug management along with tools that may be required at treating facilities to quantify needs.

Management of SLDs

The procurement sec on under Department of Medical Supplies and Health Infrastructures (DoMSHI) will be responsible for procurement of MDR-TB drugs on annual basis. The overall drug quantification and forecasting including distribution will be worked out by the NTCP in close coordination with DoMSHI at the national level. The requisition of the second line drugs by the MDR-TB treatment sites needs to be submitted to the DoMSHI with a copy endorsed to the Health Care and Diagnostic Division under the Department of Medical Services. The quantification have to be worked out based on the number of MDR-TB patients detected and enrolled/initiated on treatment in the previous year.

When required an additional stock of the SLDs, the existing system of inter-hospital mobilization has to be followed. For the patient transferred out from the referral hospital to district hospital one month medicine will be provided to

the centre. The respective district hospital should submit timely indent of the SLDs for the subsequent month and ensure that the DOT is followed strictly and monitored.

Ordering SLD needs and stock maintenance

Sufficient stocks of second-line drugs will be held at each level to prevent disruption in treatment due to unforeseen reasons. The need for buffer stocks is because of:

1. The programme is in expansion phase and the number of patients on treatment increase each year
2. With introduction of X-pert MTB/RIF testing, the number may go up further
3. At the national level, it is observed that there is at least 6 months lead time between the drug order and receipt from international suppliers because of small order size.
4. The country has several difficult areas where access becomes an issue especially in extreme winter. Such areas need continuous supply of SLDs.

Therefore the levels of stocks to be maintained at each level shall be:

- At national level - One year need + 20% buffer stock.
- At regional level – One quarter need + One month buffer stock.
- At decentralized levels – One month need + One week buffer stock.

For patients in difficult and hard to reach areas the buffer stock level may be increased to two weeks, especially in winter when the area may get cut-off.

Quantification of drug needs at regional and district levels

A step-by-step approach is placed below to quantify the needs. As a first step, daily needs of each drug are calculated for patients on treatment. The table below exemplifies two of the drugs that could be in use at the health facility. Similar steps are to be followed for each of the drugs. However, weight band variations also need to be considered in quantification of SLDs.

Table 11: Calculation of daily needs for second line drugs at a treatment facility

Patients	Drugs used to treat RR/ MDR-TB patients					
	Z 500 mg	Km 1 gm	Lfx 250 mg	Eto 250 mg	Cs 250 mg	B6
1		1		3		
2		1		3		
3		1		3		
4		0		3		
		0		2		
5		**3**		**14**		

Name or registration number of the patients on treatment.

Example of drugs that are being used in each patient. Fill all columns as necessary.

Step 2 – Calculate monthly needs

Monthly need – Multiply the daily consumption of injections by 26 (for 6 days a week administration) and that of oral drugs by 30. In the example above, total for Kanamycin,

(3) will be multiplied by 26 while the total for Ethionamide (14) will be multiplied by 30.

Step 3 –Quarterly need (for hospitals)

Multiply the quantity arrived in step 2 above by a factor of '3'.

Step 4 – Quantities to order

- Take into account number of additional patients expected and add to the needs column.
- Add the buffer needed e.g. for hospital add one month supply.
- Subtract the available quantities (Stock in hand)

The quantities are then reflected in the drug requisition form. An example of drug requisition form is given on the next page (Table 12).

Table 12: TB Medicine Requisition Form

Requesting Facility: _____ Date Requested: _____

For the month/s of: _____

#	Description	Unit	Quarterly Use	Buffer	Quantity Needed	On-hand	Quantity Requested	Units per Container	# Containers sent
			(a)	(b)	(c=a+b)	(d)	(e=c-d)		
1	Pyrazinamide 500mg	Tab	4095	1365	5460	1210	**4250**		
2	Syringer 500		290	130	520	110	**410**		
3	Kynamycin 1g	Vial	390	130	520	110	**410**		
4	Levofloxacin 250mg	Tab							
5	Ethionamide 250mg	Tab	3444	1148	4592	950	**3642**		
6	Cycloserine 250mg	Cap							
7									

The buffer is 1 month's supply.

Requested by: _____

Signature: Date:

Quantification tools

Since the number of cases in Bhutan is small, NTCP will continue to use excel based calculations at national level along with QuanTB that has been found helpful. This will also help programme during transitioning from longer to shorter regimen.

Calculation for First Line Drugs

FLDs	No.of patients	No.of dose/pt	Days	Quantity	Buffer interest of 10%	Grand Total	PACK SIZE	unit price(in USD)	Estimated Cost(in USD)
HRZE	1200	3	60	216000	21600	237888	672	40.71	14411.34
HRE	100	3	150	45000	4500	49728	672	19.67	1455.58
HR	1200	3	120	432000	43200	475776	672	19.67	13926.36
Streptomycin	100	1	60	6000	600	6600	100	64	4224
HRZ(P)	80	4	60	19200	1920	21168	84	2.95	743.4
HR (P)	80	4	120	38400	3840	42240	84	2.41	1212.23
H 300mg for Adult	360	1	240	86400	8640	95000	672	12.76	1425
E 400mg Adults	60	4	240	57600	5760	63840	672	20.21	1919.95
Z 400 mg Adult	60	3	240	43200	4320	47712	672	15.8	1121.8
H 100mg Pediatrics	88	1	180	15840	1584	17500	100	1.13	197.75
E 100mg Adults	60	3	180	32400	3240	35700	100	3.6	630
R 150mg	60	1	180	10800	1080	11900	100	3.6	630
R 300mg	60	2	180	21600	2160	23800	100	3.6	630
Total									**42527.41**

Calculation for Second Line Drugs

SLDs	No.of patients	No.of dose/pt	days	Quantity	Buffer interest of 10%	Grand Total	PACK SIZE	unit price(in USD)	Estimated Cost(in USD)
Kanamycin	60	1	240	14400	1440	15800	100	83.58	13205.64
Ethionamide 250mg	60	3	600	108000	10800	118800	100	7.93	9420.84
Cycloserine 250mg	60	3	600	108000	10800	118800	100	21.57	2545.26
Pyrazinamide 400mg	60	4	600	144000	14400	158592	672	15.8	3728.8
Levofloxacin 250mg	60	3	600	108000	10800	118800	100	3.96	4704.48
PAS sodium	2	12 gram	600	14400	1440	15840	25sac	33.75	21384
Total									**54989.02**

QuanTB Tool XDR-Drugs

Pre-XDR drugs	No.of estmated patients to be enrolled on treatment	No.of dose/pt	Days/Duration of the treatment	Quantity	Buffer of 5%	Grand Total	Pack size	Unit price(in USD)	Estimated Cost(in USD)
Amikacin 500mg/2ml inj 100 amp	3	1	336	1008	50	1058	100	62	655
Clofazimine 100mg 100 cap jar	3	2	720	4320	216	4536	100	109	4966
Ethambutol HCl 400mg 672 tab bl	3	3	720	6480	324	6804	672	20	203
Linezolid 600mg 10 tab blister	3	1	720	2160	108	2268	10	14	3128
PAS sodium 5.52g eq. to 4g PAS	3	2	720	4320	216	4536	25	34	6124
Pyrazinamide 500mg 672 tab blister	3	2	720	4320	216	4536	672	21	142
Total									**15216**

Parameters

Quantification name:	DR-TB merged quantiffication.qtb	**Comment:**	DR-TB merged quantification based on: - Longer MDR regimen quantification - Shorter MDR regimen quantification
Name of Country/Region/Facility:	Bhutan		
Saved on:			
Name of the person performing the quantification:	NTCP/DoMSHI		
Inventory date:	11/4/2017		
Lead time:	4	months	
End date of quantification:	12/31/2018		
Quantification period:	13 months, 26 days		
Minimum months of stock:	4	months	
Maximum months of stock:	8	months	

Enrolled cases

	Mar-2016	Apr-2016	May-2016	Jun-2016	Jul-2016	Aug-2016	Sep-2016	Oct-2016	Nov-2016	Dec-2016	Jan-2017	Feb-2017	Mar-2017	Apr-2017	May-2017	Jun-2017	Jul-2017	Aug-2017	Sep-2017	Oct-2017	Nov-2017
SLD Bhutan 8Km(1000)Cs(250)Eto(250)Lfx(250)Z(400)/12Cs(250)Eto(250)Lfx(250)Z(400)	3	6	3	8	6	7	5	4	5	4	5	3	8	8	9	7	3	3	4	4	0
Shorter MDR-TB Regimen Bhutan (30-50kg)5Km(1000/4)Cfz(100)E(400)H(300)Mfx(400)Pto(250)Z(500)/5Mfx(400)Cfz(100)E(400)Z(500) 6Km(1000/4)Cfz(100)E(400)H(300)Mfx(400)Pto(250)Z(500)/5Cfz(100)E(400)Mfx(400)Z(500)										0	0	0	0	0	0	0	0	0	0	0	0

Expected cases

	Nov-2017	Dec-2017	Jan-2018	Feb-2018	Mar-2018	Apr-2018	May-2018	Jun-2018	Jul-2018	Aug-2018	Sep-2018	Oct-2018	Nov-2018	Dec-2018
SLD Bhutan 8Km(1000)Cs(250)Eto(250)Lfx(250)Z(400)/12Cs(250)Eto(250)Lfx(250)Z(400)	7	7	9	7	8	7	8	8	9	8	9	8	8	9
Shorter MDR-TB Regimen Bhutan (30-50kg)5Km(1000/4)Cfz(100)E(400)H(300)Mfx(400)Pto(250)Z(500)/5Mfx(400)Cfz(100)E(400)Z(500) 6Km(1000/4)Cfz(100)E(400)H(300)Mfx(400)Pto(250)Z(500)/5Cfz(100)E(400)Mfx(400)Z(500)	0	0	0	0	2	1	1	2	2	2	2	1	2	0

Stock of Medicines

Medicines	Stock on hand	Expiration date of the stock on hand	Stock on order	Expected receiving date	Expiration date of the stock on order (optional)	Batch number and/or comments
Km(1000/4) Kanamycin 1000mg/4ml Solution for injection	0	9/29/2018				
	0	10/30/2018				
	0	12/30/2018				
Cs(250) Cycloserine 250mg Capsule(s)	126,508	8/30/2018				
	12,200	5/30/2019				
	46,600	8/30/2019				
E(400) Ethambutol 400mg Film coated tablet(s)	0	2/27/2019				
	0	1/30/2020				
	0	2/28/2020				
Eto(250) Ethionamide 250mg Film coated tablet(s)	11,300	6/29/2018				
	10,300	7/30/2018				
	7,770	9/29/2018				
	14,100	1/30/2019				
	46,600	1/30/2020				
H(300) Isoniazid 300mg Film uncoated tablet(s)	0	1/30/2018				
	0	4/29/2018				
	0	8/30/2018				
	0	12/30/2018				
	0	2/28/2020				
	0	4/29/2020				
	0	11/29/2020				
Lfx(250) Levofloxacin 250mg Film coated tablet(s)	9,000	5/30/2020				
	11,500	12/30/2020				
	91,845	11/29/2021				
Z(400) Pyrazinamide 400mg Film uncoated tablet(s)	15,000	2/27/2018				
	8,500	8/30/2018				
	10,000	12/30/2019				
	2,398	5/30/2020				
Z(500) Pyrazinamide 500mg Film uncoated tablet(s)	0	8/30/2018				

Summary

Bhutan/NTCP/DoMSHI/ Comment: DR-TB merged quantification based on:

Medicine	On the inventory date Nov 4, 2017		Accelerated order period Nov 05, 2017 - Mar 04, 2018 (120 days)			Regular order period Mar 05, 2018 - Dec 31, 2018 (302 days)					Quantity to order Nov 05, 2017 - Dec 31, 2018 (422 days)		
	Stock on hand	Estim. months of stock (excl. on order)	Stock on order	Quantity dispensed	Quantity likely to expire	Stock on hand after accelerated order period	Stock on order	Quantity likely to expire	Estimated consumption (enrolled cases)	Estimated consumption (expected cases)	Accelerated order period	Regular order period	Total
Kanamycin 1000mg/4ml Solution for injection	0	0	0	0	0	0	0	0	569	17,469	10,595	18,084	0
Clofazimine 100mg Capsule(s)	0	0	0	0	0	0	0	0	0	2,684	456	3,631	0
Cycloserine 250mg Capsule(s)	185,308	14	0	40,593	0	144,715	0	19,804	50,094	67,662	0	32,463	0
Ethambutol 400mg Film coated tablet(s)	0	0	0	0	0	0	0	0	0	8,052	1,368	10,893	0
Ethionamide 250mg Film coated tablet(s)	90,070	8	0	40,593	0	49,477	0	0	50,094	67,662	0	107,897	0
Isoniazid 300mg Film uncoated tablet(s)	0	0	0	0	0	0	0	0	0	4,450	912	5,228	0
Levofloxacin 250mg Film coated tablet(s)	112,345	8	0	54,124	0	58,221	0	0	66,792	90,216	0	151,611	0
Moxifloxacin 400mg Film coated tablet(s)	0	0	0	0	0	0	0	0	0	5,368	912	7,262	0
Protionamide 250mg Film coated tablet(s)	0	0	0	0	0	0	0	0	0	6,675	1,368	7,842	0
Pyrazinamide 400mg Film uncoated tablet(s)	35,898	2	0	35,898	0	0	0	0	66,792	90,216	74,662	153,396	0
Pyrazinamide 500mg Film uncoated tablet(s)	0	0	0	0	0	0	0	0	0	10,736	1,824	14,524	0

"Bhutan/NTCP/DoMSHI/ Comment: DR-TB merged quantification based on:														
Medicine:	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18
Kanamycin 1000mg/4ml Solution for injection														
Stock on hand	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Min. qty. to prevent treatment interruption	1,035	1,144	1,188	1,056	1,336	1,468	1,663	1,705	1,977	2,038	1,900	2,065	2,020	2,021
Quantity likely to expire	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Stock on order	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Estimated consumption (enrolled cases)	874	780	567	336	286	208	108	0	0	0	0	0	0	0
Estimated consumption (expected cases)	161	364	621	720	1,050	1,260	1,555	1,705	1,977	2,038	1,900	2,065	2,020	2,021
Estimated consumption (total cases)	1,035	1,144	1,188	1,056	1,336	1,468	1,663	1,705	1,977	2,038	1,900	2,065	2,020	2,021
Clofazimine 100mg Capsule(s)														
Stock on hand	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Min. qty. to prevent treatment interruption	0	0	0	0	62	90	124	180	248	310	360	403	450	465
Quantity likely to expire	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Stock on order	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Estimated consumption (enrolled cases)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Estimated consumption (expected cases)	0	0	0	0	62	90	124	180	248	310	360	403	450	465
Estimated consumption (total cases)	0	0	0	0	62	90	124	180	248	310	360	403	450	465
Cycloserine 250mg Capsule(s)														
Stock on hand	185,308	176,797	166,567	155,779	146,119	135,238	124,708	113,548	102,388	90,484	58,404	46,164	33,051	20,361
Min. qty. to prevent treatment interruption	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Quantity likely to expire	0	0	0	0	0	0	0	0	0	19,804	0	0	0	0
Stock on order	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Estimated consumption (enrolled cases)	7,965	8,928	8,649	7,140	7,347	6,480	6,231	5,670	5,394	5,022	4,410	4,278	3,420	2,790
Estimated consumption (expected cases)	546	1,302	2,139	2,520	3,534	4,050	4,929	5,490	6,510	7,254	7,830	8,835	9,270	10,416
Estimated consumption (total cases)	8,511	10,230	10,788	9,660	10,881	10,530	11,160	11,160	11,904	12,276	12,240	13,113	12,690	13,206
Ethambutol 400mg Film coated tablet(s)														
Stock on hand	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Min. qty. to prevent treatment interruption	0	0	0	0	186	270	372	540	744	930	1,080	1,209	1,350	1,395
Quantity likely to expire	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Stock on order	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Estimated consumption (enrolled cases)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Estimated consumption (expected cases)	0	0	0	0	186	270	372	540	744	930	1,080	1,209	1,350	1,395

Estimated consumption (total cases)	0	0	0	0	186	270	372	540	744	930	1,080	1,209	1,350	1,395
Ethionamide 250mg Film coated tablet(s)														
Stock on hand	90,070	81,559	71,329	60,541	50,881	40,000	29,470	18,310	7,150	0	0	0	0	0
Min. qty. to prevent treatment interruption	0	0	0	0	0	0	0	0	4,754	12,276	12,240	13,113	12,690	13,206
Quantity likely to expire	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Stock on order	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Estimated consumption (enrolled cases)	7,965	8,928	8,649	7,140	7,347	6,480	6,231	5,670	5,394	5,022	4,410	4,278	3,420	2,790
Estimated consumption (expected cases)	546	1,302	2,139	2,520	3,534	4,050	4,929	5,490	6,510	7,254	7,830	8,835	9,270	10,416
Estimated consumption (total cases)	8,511	10,230	10,788	9,660	10,881	10,530	11,160	11,160	11,904	12,276	12,240	13,113	12,690	13,206
Isoniazid 300mg Film uncoated tablet(s)														
Stock on hand	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Min. qty. to prevent treatment interruption	0	0	0	0	124	180	248	360	496	620	600	620	660	558
Quantity likely to expire	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Stock on order	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Estimated consumption (enrolled cases)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Estimated consumption (expected cases)	0	0	0	0	124	180	248	360	496	620	600	620	660	558
Estimated consumption (total cases)	0	0	0	0	124	180	248	360	496	620	600	620	660	558
Levofloxacin 250mg Film coated tablet(s)														
Stock on hand	112,345	100,997	87,357	72,973	60,093	45,585	31,545	16,665	1,785	0	0	0	0	0
Min. qty. to prevent treatment interruption	0	0	0	0	0	0	0	0	14,087	16,368	16,320	17,484	16,920	17,608
Quantity likely to expire	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Stock on order	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Estimated consumption (enrolled cases)	10,620	11,904	11,532	9,520	9,796	8,640	8,308	7,560	7,192	6,696	5,880	5,704	4,560	3,720
Estimated consumption (expected cases)	728	1,736	2,852	3,360	4,712	5,400	6,572	7,320	8,680	9,672	10,440	11,780	12,360	13,888
Estimated consumption (total cases)	11,348	13,640	14,384	12,880	14,508	14,040	14,880	14,880	15,872	16,368	16,320	17,484	16,920	17,608
Moxifloxacin 400mg Film coated tablet(s)														
Stock on hand	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Min. qty. to prevent treatment interruption	0	0	0	0	124	180	248	360	496	620	720	806	900	930
Quantity likely to expire	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Stock on order	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Estimated consumption (enrolled cases)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Estimated consumption (expected cases)	0	0	0	0	124	180	248	360	496	620	720	806	900	930
Estimated consumption (total cases)	0	0	0	0	124	180	248	360	496	620	720	806	900	930

Protionamide 250mg Film coated tablet(s)														
Stock on hand	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Min. qty. to prevent treatment interruption	0	0	0	0	186	270	372	540	744	930	900	930	990	837
Quantity likely to expire	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Stock on order	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Estimated consumption (enrolled cases)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Estimated consumption (expected cases)	0	0	0	0	186	270	372	540	744	930	900	930	990	837
Estimated consumption (total cases)	0	0	0	0	186	270	372	540	744	930	900	930	990	837
Pyrazinamide 400mg Film uncoated tablet(s)														
Stock on hand	35,898	24,550	10,910	0	0	0	0	0	0	0	0	0	0	0
Min. qty. to prevent treatment interruption	0	0	3,474	12,880	14,508	14,040	14,880	14,880	15,872	16,368	16,320	17,484	16,920	17,608
Quantity likely to expire	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Stock on order	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Estimated consumption (enrolled cases)	10,620	11,904	11,532	9,520	9,796	8,640	8,308	7,560	7,192	6,696	5,880	5,704	4,560	3,720
Estimated consumption (expected cases)	728	1,736	2,852	3,360	4,712	5,400	6,572	7,320	8,680	9,672	10,440	11,780	12,360	13,888
Estimated consumption (total cases)	11,348	13,640	14,384	12,880	14,508	14,040	14,880	14,880	15,872	16,368	16,320	17,484	16,920	17,608
Pyrazinamide 500mg Film uncoated tablet(s)														
Stock on hand	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Min. qty. to prevent treatment interruption	0	0	0	0	248	360	496	720	992	1,240	1,440	1,612	1,800	1,860
Quantity likely to expire	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Stock on order	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Estimated consumption (enrolled cases)	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Estimated consumption (expected cases)	0	0	0	0	248	360	496	720	992	1,240	1,440	1,612	1,800	1,860
Estimated consumption (total cases)	0	0	0	0	248	360	496	720	992	1,240	1,440	1,612	1,800	1,860

Case Report - Regimen

Bhutan/NTCP/DoMSHI/ Comment: DR-TB merged quantification based on:

Treatment regimen		Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18	Jul-18	Aug-18	Sep-18	Oct-18	Nov-18	Dec-18
SLD Bhutan	Enrolled Cases	105.00	96.00	93.00	85.00	79.00	72.00	67.00	63.00	58.00	54.00	49.00	46.00	38.00	30.00
	Expected Cases	7.00	14.00	23.00	30.00	38.00	45.00	53.00	61.00	70.00	78.00	87.00	95.00	103.00	112.00
	Total	112	110	116	115	117	117	120	124	128	132	136	141	141	142
Shorter MDR-TB Regimen Bhutan (30-50kg)5Km(1000/4)Cfz(100)E(400)H(300)Mfx(400)Pto(250)Z(500)/5Mfx(400)Cfz(100)E(400)Z(500)	Enrolled Cases	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Expected Cases	0.00	0.00	0.00	0.00	2.00	3.00	4.00	6.00	8.00	10.00	12.00	13.00	15.00	15.00
	Total	0	0	0	0	2	3	4	6	8	10	12	13	15	15
Grand total		**112**	**110**	**116**	**115**	**119**	**120**	**124**	**130**	**136**	**142**	**148**	**154**	**156**	**157**

Case Report - Medicine

"Bhutan/NTCP/DoMSHI/ Comment: DR-TB merged quantification based on:															
Medicine:		**Nov-17**	**Dec-17**	**Jan-18**	**Feb-18**	**Mar-18**	**Apr-18**	**May-18**	**Jun-18**	**Jul-18**	**Aug-18**	**Sep-18**	**Oct-18**	**Nov-18**	**Dec-18**
Kanamycin 1000mg/4ml Solution for injection	**Enrolled Cases**	38.00	30.00	21.00	14.00	11.00	8.00	4.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Expected Cases	7.00	14.00	23.00	30.00	40.00	48.00	57.00	67.00	78.00	74.00	74.00	75.00	76.00	76.00
	Total	45.00	44.00	44.00	44.00	51.00	56.00	61.00	67.00	78.00	74.00	74.00	75.00	76.00	76.00
Clofazimine 100mg Capsule(s)	**Enrolled Cases**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Expected Cases	0.00	0.00	0.00	0.00	2.00	3.00	4.00	6.00	8.00	10.00	12.00	13.00	15.00	15.00
	Total	0.00	0.00	0.00	0.00	2.00	3.00	4.00	6.00	8.00	10.00	12.00	13.00	15.00	15.00
Cycloserine 250mg Capsule(s)	**Enrolled Cases**	105.00	96.00	93.00	85.00	79.00	72.00	67.00	63.00	58.00	54.00	49.00	46.00	38.00	30.00
	Expected Cases	7.00	14.00	23.00	30.00	38.00	45.00	53.00	61.00	70.00	78.00	87.00	95.00	103.00	112.00
	Total	112.00	110.00	116.00	115.00	117.00	117.00	120.00	124.00	128.00	132.00	136.00	141.00	141.00	142.00
Ethambutol 400mg Film coated tablet(s)	**Enrolled Cases**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Expected Cases	0.00	0.00	0.00	0.00	2.00	3.00	4.00	6.00	8.00	10.00	12.00	13.00	15.00	15.00
	Total	0.00	0.00	0.00	0.00	2.00	3.00	4.00	6.00	8.00	10.00	12.00	13.00	15.00	15.00
Ethionamide 250mg Film coated tablet(s)	**Enrolled Cases**	105.00	96.00	93.00	85.00	79.00	72.00	67.00	63.00	58.00	54.00	49.00	46.00	38.00	30.00
	Expected Cases	7.00	14.00	23.00	30.00	38.00	45.00	53.00	61.00	70.00	78.00	87.00	95.00	103.00	112.00
	Total	112.00	110.00	116.00	115.00	117.00	117.00	120.00	124.00	128.00	132.00	136.00	141.00	141.00	142.00
Isoniazid 300mg Film uncoated tablet(s)	**Enrolled Cases**	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Expected Cases	0.00	0.00	0.00	0.00	2.00	3.00	4.00	6.00	8.00	10.00	10.00	10.00	11.00	9.00
	Total	0.00	0.00	0.00	0.00	2.00	3.00	4.00	6.00	8.00	10.00	10.00	10.00	11.00	9.00

Levofloxacin 250mg Film coated tablet(s)	Enrolled Cases	105.00	96.00	93.00	85.00	79.00	72.00	67.00	63.00	58.00	54.00	49.00	46.00	38.00	30.00
	Expected Cases	7.00	14.00	23.00	30.00	38.00	45.00	53.00	61.00	70.00	78.00	87.00	95.00	103.00	112.00
	Total	112.00	110.00	116.00	115.00	117.00	117.00	120.00	124.00	128.00	132.00	136.00	141.00	141.00	142.00
Moxifloxacin 400mg Film coated tablet(s)	Enrolled Cases	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Expected Cases	0.00	0.00	0.00	0.00	2.00	3.00	4.00	6.00	8.00	10.00	12.00	13.00	15.00	15.00
	Total	0.00	0.00	0.00	0.00	2.00	3.00	4.00	6.00	8.00	10.00	12.00	13.00	15.00	15.00
Protionamide 250mg Film coated tablet(s)	Enrolled Cases	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Expected Cases	0.00	0.00	0.00	0.00	2.00	3.00	4.00	6.00	8.00	10.00	10.00	10.00	11.00	9.00
	Total	0.00	0.00	0.00	0.00	2.00	3.00	4.00	6.00	8.00	10.00	10.00	10.00	11.00	9.00
Pyrazinamide 400mg Film uncoated tablet(s)	Enrolled Cases	105.00	96.00	93.00	85.00	79.00	72.00	67.00	63.00	58.00	54.00	49.00	46.00	38.00	30.00
	Expected Cases	7.00	14.00	23.00	30.00	38.00	45.00	53.00	61.00	70.00	78.00	87.00	95.00	103.00	112.00
	Total	112.00	110.00	116.00	115.00	117.00	117.00	120.00	124.00	128.00	132.00	136.00	141.00	141.00	142.00
Pyrazinamide 500mg Film uncoated tablet(s)	Enrolled Cases	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
	Expected Cases	0.00	0.00	0.00	0.00	2.00	3.00	4.00	6.00	8.00	10.00	12.00	13.00	15.00	15.00
	Total	0.00	0.00	0.00	0.00	2.00	3.00	4.00	6.00	8.00	10.00	12.00	13.00	15.00	15.00

Quantity and Costs

Schedule of orders: Monthly							
Consolidated regular order(s)							
Medicines	**Quantity needed (in units)**	**Adjustment (% of quantity needed)**	**Pack size (enter 1 for units)**	**Pack price or unit price (USD/$)**	**Adjusted quantity to order (in units)**	**Adjusted quantity to order rounded up to pack size**	**Cost (USD/$)**
Km(1000/4) Kanamycin 1000mg/4ml Solution for injection	18,084	100.00	-	-	18,084	-	-
Cfz(100) Clofazimine 100mg Capsule(s)	3,631	100.00	-	-	3,631	-	-
Cs(250) Cycloserine 250mg Capsule(s)	32,463	100.00	-	-	32,463	-	-
E(400) Ethambutol 400mg Film coated tablet(s)	10,893	100.00	-	-	10,893	-	-
Eto(250) Ethionamide 250mg Film coated tablet(s)	107,897	100.00	-	-	107,897	-	-
H(300) Isoniazid 300mg Film uncoated tablet(s)	5,228	100.00	-	-	5,228	-	-
Lfx(250) Levofloxacin 250mg Film coated tablet(s)	151,611	100.00	-	-	151,611	-	-
Mfx(400) Moxifloxacin 400mg Film coated tablet(s)	7,262	100.00	-	-	7,262	-	-
Pto(250) Protionamide 250mg Film coated tablet(s)	7,842	100.00	-	-	7,842	-	-
Z(400) Pyrazinamide 400mg Film uncoated tablet(s)	153,396	100.00	-	-	153,396	-	-
Z(500) Pyrazinamide 500mg Film uncoated tablet(s)	14,524	100.00	-	-	14,524	-	-
Cost of medicines							**0.00**

Consolidated accelerated order(s)							
Medicines	**Quantity needed (in units)**	**Adjustment (% of quantity needed)**	**Pack size (enter 1 for units)**	**Pack price or unit price (USD/$)**	**Adjusted quantity to order (in units)**	**Adjusted quantity to order rounded up to pack size**	**Cost (USD/$)**
Km(1000/4) Kanamycin 1000mg/4ml Solution for injection	10,595	100.00	-	-	10,595	-	-
Cfz(100) Clofazimine 100mg Capsule(s)	456	100.00	-	-	456	-	-
Cs(250) Cycloserine 250mg Capsule(s)	-	100.00	-	-	-	-	-
E(400) Ethambutol 400mg Film coated tablet(s)	1,368	100.00	-	-	1,368	-	-
Eto(250) Ethionamide 250mg Film coated tablet(s)	-	100.00	-	-	-	-	-
H(300) Isoniazid 300mg Film uncoated tablet(s)	912	100.00	-	-	912	-	-
Lfx(250) Levofloxacin 250mg Film coated tablet(s)	-	100.00	-	-	-	-	-
Mfx(400) Moxifloxacin 400mg Film coated tablet(s)	912	100.00	-	-	912	-	-
Pto(250) Protionamide 250mg Film coated tablet(s)	1,368	100.00	-	-	1,368	-	-
Z(400) Pyrazinamide 400mg Film uncoated tablet(s)	74,662	100.00	-	-	74,662	-	-
Z(500) Pyrazinamide 500mg Film uncoated tablet(s)	1,824	100.00	-	-	1,824	-	-
Cost of medicines							**0.00**

Consolidated total order(s)			
Medicines	**Quantity needed (in units)**	**Adjusted quantity to order (in units)**	**Cost (USD/$)**
Km(1000/4) Kanamycin 1000mg/4ml Solution for injection	28,679	-	-
Cfz(100) Clofazimine 100mg Capsule(s)	4,087	-	-
Cs(250) Cycloserine 250mg Capsule(s)	32,463	-	-
E(400) Ethambutol 400mg Film coated tablet(s)	12,261	-	-
Eto(250) Ethionamide 250mg Film coated tablet(s)	107,897	-	-
H(300) Isoniazid 300mg Film uncoated tablet(s)	6,140	-	-
Lfx(250) Levofloxacin 250mg Film coated tablet(s)	151,611	-	-
Mfx(400) Moxifloxacin 400mg Film coated tablet(s)	8,174	-	-
Pto(250) Protionamide 250mg Film coated tablet(s)	9,210	-	-
Z(400) Pyrazinamide 400mg Film uncoated tablet(s)	228,058	-	-
Z(500) Pyrazinamide 500mg Film uncoated tablet(s)	16,348	-	-
Total cost of medicines			**0.00**

Additional and Total Costs

Schedule of orders: Monthly	
Consolidated regular order(s)	
Name of the order item	**Value (USD/$)**
Freight	-
Insurance	-
Estimated pre-shipment inspection	-
Procurement agent fee	-
Customs clearance	-
Cost of medicines	**0.00**
Additional cost	**0.00**
Total cost of regular orders	**0.00**
Consolidated accelerated order(s)	
Name of the order item	**Value (USD/$)**
Freight	-
Insurance	-
Estimated pre-shipment inspection	-
Procurement agent fee	-
Customs clearance	-
Cost of medicines	0.00
Additional cost	0.00
Total cost of accelerated orders	**0.00**
Total cost of medicines	**0.00**
Total of other costs	**0.00**
Grand total cost of all orders	**0.00**

Schedule of orders: Monthly			
Accelerated order # 1	Order date:	As soon as possible (should have been ordered on Jun, 30 2017)	
	Delivery date:	As soon as possible (should have been delivered on Nov, 05 2017)	
Medicines	Adjusted quantity to order (in units)	Adjusted quantity to order rounded up to pack size	Cost (USD/$)
Km(1000/4) Kanamycin 1000mg/4ml Solution for injection	4,423.00	0.00	0.00
Z(400) Pyrazinamide 400mg Film uncoated tablet(s)	16,354.00	0.00	0.00
Cost of medicines			**0.00**
Additional cost			**0.00**
Cost of order:			**0.00**

Accelerated order # 2	Order date:	As soon as possible (should have been ordered on Jul, 31 2017)	
	Delivery date:	As soon as possible (should have been delivered on Nov, 30 2017)	
Medicines	Adjusted quantity to order (in units)	Adjusted quantity to order rounded up to pack size	Cost (USD/$)
Km(1000/4) Kanamycin 1000mg/4ml Solution for injection	1,336.00	0.00	0.00
Cfz(100) Clofazimine 100mg Capsule(s)	62.00	0.00	0.00
E(400) Ethambutol 400mg Film coated tablet(s)	186.00	0.00	0.00
H(300) Isoniazid 300mg Film uncoated tablet(s)	124.00	0.00	0.00
Mfx(400) Moxifloxacin 400mg Film coated tablet(s)	124.00	0.00	0.00
Pto(250) Protionamide 250mg Film coated tablet(s)	186.00	0.00	0.00
Z(400) Pyrazinamide 400mg Film uncoated tablet(s)	14,508.00	0.00	0.00
Z(500) Pyrazinamide 500mg Film uncoated tablet(s)	248.00	0.00	0.00
Cost of medicines			**0.00**
Additional cost			**0.00**
Cost of order:			**0.00**

Accelerated order # 3	Order date:	As soon as possible (should have been ordered on Aug, 31 2017)	
	Delivery date:	As soon as possible (should have been delivered on Dec, 31 2017)	
Medicines	**Adjusted quantity to order (in units)**	**Adjusted quantity to order rounded up to pack size**	**Cost (USD/$)**
Km(1000/4) Kanamycin 1000mg/4ml Solution for injection	1,468.00	0.00	0.00
Cfz(100) Clofazimine 100mg Capsule(s)	90.00	0.00	0.00
E(400) Ethambutol 400mg Film coated tablet(s)	270.00	0.00	0.00
H(300) Isoniazid 300mg Film un-coated tablet(s)	180.00	0.00	0.00
Mfx(400) Moxifloxacin 400mg Film coated tablet(s)	180.00	0.00	0.00
Pto(250) Protionamide 250mg Film coated tablet(s)	270.00	0.00	0.00
Z(400) Pyrazinamide 400mg Film uncoated tablet(s)	14,040.00	0.00	0.00
Z(500) Pyrazinamide 500mg Film uncoated tablet(s)	360.00	0.00	0.00
Cost of medicines			**0.00**
Additional cost			**0.00**
Cost of order:			**0.00**

Accelerated order # 4	Order date:	As soon as possible (should have been ordered on Sep, 30 2017)	
	Delivery date:	As soon as possible (should have been delivered on Jan, 31 2018)	
Medicines	**Adjusted quantity to order (in units)**	**Adjusted quantity to order rounded up to pack size**	**Cost (USD/$)**
Km(1000/4) Kanamycin 1000mg/4ml Solution for injection	1,663.00	0.00	0.00
Cfz(100) Clofazimine 100mg Capsule(s)	124.00	0.00	0.00
E(400) Ethambutol 400mg Film coated tablet(s)	372.00	0.00	0.00
H(300) Isoniazid 300mg Film un-coated tablet(s)	248.00	0.00	0.00
Mfx(400) Moxifloxacin 400mg Film coated tablet(s)	248.00	0.00	0.00
Pto(250) Protionamide 250mg Film coated tablet(s)	372.00	0.00	0.00
Z(400) Pyrazinamide 400mg Film uncoated tablet(s)	14,880.00	0.00	0.00
Z(500) Pyrazinamide 500mg Film uncoated tablet(s)	496.00	0.00	0.00
Cost of medicines			**0.00**
Additional cost			**0.00**
Cost of order:			**0.00**

Accelerated order # 5	Order date:	Oct, 31 2017	
	Delivery date:	Feb, 28 2018	
Medicines	**Adjusted quantity to order (in units)**	**Adjusted quantity to order rounded up to pack size**	**Cost (USD/$)**
Km(1000/4) Kanamycin 1000mg/4ml Solution for injection	1,705.00	0.00	0.00
Cfz(100) Clofazimine 100mg Capsule(s)	180.00	0.00	0.00
E(400) Ethambutol 400mg Film coated tablet(s)	540.00	0.00	0.00
H(300) Isoniazid 300mg Film un-coated tablet(s)	360.00	0.00	0.00
Mfx(400) Moxifloxacin 400mg Film coated tablet(s)	360.00	0.00	0.00
Pto(250) Protionamide 250mg Film coated tablet(s)	540.00	0.00	0.00
Z(400) Pyrazinamide 400mg Film uncoated tablet(s)	14,880.00	0.00	0.00
Z(500) Pyrazinamide 500mg Film uncoated tablet(s)	720.00	0.00	0.00
Cost of medicines			**0.00**
Additional cost			**0.00**
Cost of order:			**0.00**

Regular order # 1	Order date:	Nov, 30 2017	
	Delivery date:	Mar, 31 2018	
Medicines	**Adjusted quantity to order (in units)**	**Adjusted quantity to order rounded up to pack size**	**Cost (USD/$)**
Km(1000/4) Kanamycin 1000mg/4ml Solution for injection	1,977.00	0.00	0.00
Cfz(100) Clofazimine 100mg Capsule(s)	248.00	0.00	0.00
E(400) Ethambutol 400mg Film coated tablet(s)	744.00	0.00	0.00
Eto(250) Ethionamide 250mg Film coated tablet(s)	4,754.00	0.00	0.00
H(300) Isoniazid 300mg Film un-coated tablet(s)	496.00	0.00	0.00
Lfx(250) Levofloxacin 250mg Film coated tablet(s)	14,087.00	0.00	0.00
Mfx(400) Moxifloxacin 400mg Film coated tablet(s)	496.00	0.00	0.00
Pto(250) Protionamide 250mg Film coated tablet(s)	744.00	0.00	0.00
Z(400) Pyrazinamide 400mg Film uncoated tablet(s)	15,872.00	0.00	0.00
Z(500) Pyrazinamide 500mg Film uncoated tablet(s)	992.00	0.00	0.00
Cost of medicines			**0.00**
Additional cost			**0.00**
Cost of order:			**0.00**

Regular order # 2	Order date:	Dec, 31 2017	
	Delivery date:	Apr, 30 2018	
Medicines	**Adjusted quantity to order (in units)**	**Adjusted quantity to order rounded up to pack size**	**Cost (USD/$)**
Km(1000/4) Kanamycin 1000mg/4ml Solution for injection	2,038.00	0.00	0.00
Cfz(100) Clofazimine 100mg Capsule(s)	310.00	0.00	0.00
E(400) Ethambutol 400mg Film coated tablet(s)	930.00	0.00	0.00
Eto(250) Ethionamide 250mg Film coated tablet(s)	12,276.00	0.00	0.00
H(300) Isoniazid 300mg Film uncoated tablet(s)	620.00	0.00	0.00
Lfx(250) Levofloxacin 250mg Film coated tablet(s)	16,368.00	0.00	0.00
Mfx(400) Moxifloxacin 400mg Film coated tablet(s)	620.00	0.00	0.00
Pto(250) Protionamide 250mg Film coated tablet(s)	930.00	0.00	0.00
Z(400) Pyrazinamide 400mg Film uncoated tablet(s)	16,368.00	0.00	0.00
Z(500) Pyrazinamide 500mg Film uncoated tablet(s)	1,240.00	0.00	0.00
Cost of medicines			**0.00**
Additional cost			**0.00**
Cost of order:			**0.00**

Regular order # 3	Order date:	Jan, 31 2018	
	Delivery date:	May, 31 2018	
Medicines	**Adjusted quantity to order (in units)**	**Adjusted quantity to order rounded up to pack size**	**Cost (USD/$)**
Km(1000/4) Kanamycin 1000mg/4ml Solution for injection	1,900.00	0.00	0.00
Cfz(100) Clofazimine 100mg Capsule(s)	360.00	0.00	0.00
E(400) Ethambutol 400mg Film coated tablet(s)	1,080.00	0.00	0.00
Eto(250) Ethionamide 250mg Film coated tablet(s)	12,240.00	0.00	0.00
H(300) Isoniazid 300mg Film un-coated tablet(s)	600.00	0.00	0.00
Lfx(250) Levofloxacin 250mg Film coated tablet(s)	16,320.00	0.00	0.00
Mfx(400) Moxifloxacin 400mg Film coated tablet(s)	720.00	0.00	0.00
Pto(250) Protionamide 250mg Film coated tablet(s)	900.00	0.00	0.00
Z(400) Pyrazinamide 400mg Film uncoated tablet(s)	16,320.00	0.00	0.00
Z(500) Pyrazinamide 500mg Film uncoated tablet(s)	1,440.00	0.00	0.00
Cost of medicines			**0.00**
Additional cost			**0.00**
Cost of order:			**0.00**

Regular order # 4	Order date:	Feb, 28 2018	
	Delivery date:	Jun, 30 2018	
Medicines	**Adjusted quantity to order (in units)**	**Adjusted quantity to order rounded up to pack size**	**Cost (USD/$)**
Km(1000/4) Kanamycin 1000mg/4ml Solution for injection	2,065.00	0.00	0.00
Cfz(100) Clofazimine 100mg Capsule(s)	403.00	0.00	0.00
E(400) Ethambutol 400mg Film coated tablet(s)	1,209.00	0.00	0.00
Eto(250) Ethionamide 250mg Film coated tablet(s)	13,113.00	0.00	0.00
H(300) Isoniazid 300mg Film un-coated tablet(s)	620.00	0.00	0.00
Lfx(250) Levofloxacin 250mg Film coated tablet(s)	17,484.00	0.00	0.00
Mfx(400) Moxifloxacin 400mg Film coated tablet(s)	806.00	0.00	0.00
Pto(250) Protionamide 250mg Film coated tablet(s)	930.00	0.00	0.00
Z(400) Pyrazinamide 400mg Film uncoated tablet(s)	17,484.00	0.00	0.00
Z(500) Pyrazinamide 500mg Film uncoated tablet(s)	1,612.00	0.00	0.00
Cost of medicines			**0.00**
Additional cost			**0.00**
Cost of order:			**0.00**

Regular order # 5	Order date:	Mar, 31 2018	
	Delivery date:	Jul, 31 2018	
Medicines	Adjusted quantity to order (in units)	Adjusted quantity to order rounded up to pack size	Cost (USD/$)
Km(1000/4) Kanamycin 1000mg/4ml Solution for injection	2,020.00	0.00	0.00
Cfz(100) Clofazimine 100mg Capsule(s)	450.00	0.00	0.00
E(400) Ethambutol 400mg Film coated tablet(s)	1,350.00	0.00	0.00
Eto(250) Ethionamide 250mg Film coated tablet(s)	12,690.00	0.00	0.00
H(300) Isoniazid 300mg Film un-coated tablet(s)	660.00	0.00	0.00
Lfx(250) Levofloxacin 250mg Film coated tablet(s)	16,920.00	0.00	0.00
Mfx(400) Moxifloxacin 400mg Film coated tablet(s)	900.00	0.00	0.00
Pto(250) Protionamide 250mg Film coated tablet(s)	990.00	0.00	0.00
Z(400) Pyrazinamide 400mg Film uncoated tablet(s)	16,920.00	0.00	0.00
Z(500) Pyrazinamide 500mg Film uncoated tablet(s)	1,800.00	0.00	0.00
Cost of medicines			**0.00**
Additional cost			**0.00**
Cost of order:			**0.00**

Regular order # 6	Order date:	Apr, 30 2018	
	Delivery date:	Aug, 31 2018	
Medicines	**Adjusted quantity to order (in units)**	**Adjusted quantity to order rounded up to pack size**	**Cost (USD/$)**
Km(1000/4) Kanamycin 1000mg/4ml Solution for injection	2,021.00	0.00	0.00
Cfz(100) Clofazimine 100mg Capsule(s)	465.00	0.00	0.00
E(400) Ethambutol 400mg Film coated tablet(s)	1,395.00	0.00	0.00
Eto(250) Ethionamide 250mg Film coated tablet(s)	13,206.00	0.00	0.00
H(300) Isoniazid 300mg Film uncoated tablet(s)	558.00	0.00	0.00
Lfx(250) Levofloxacin 250mg Film coated tablet(s)	17,608.00	0.00	0.00
Mfx(400) Moxifloxacin 400mg Film coated tablet(s)	930.00	0.00	0.00
Pto(250) Protionamide 250mg Film coated tablet(s)	837.00	0.00	0.00
Z(400) Pyrazinamide 400mg Film uncoated tablet(s)	17,608.00	0.00	0.00
Z(500) Pyrazinamide 500mg Film uncoated tablet(s)	1,860.00	0.00	0.00
Cost of medicines			**0.00**
Additional cost			**0.00**
Cost of order:			**0.00**

Regular order # 7	Order date:	May, 31 2018	
	Delivery date:	Sep, 30 2018	
Medicines	Adjusted quantity to order (in units)	Adjusted quantity to order rounded up to pack size	Cost (USD/$)
Km(1000/4) Kanamycin 1000mg/4ml Solution for injection	2,021.00	0.00	0.00
Cfz(100) Clofazimine 100mg Capsule(s)	465.00	0.00	0.00
Cs(250) Cycloserine 250mg Capsule(s)	6,051.00	0.00	0.00
E(400) Ethambutol 400mg Film coated tablet(s)	1,395.00	0.00	0.00
Eto(250) Ethionamide 250mg Film coated tablet(s)	13,206.00	0.00	0.00
H(300) Isoniazid 300mg Film uncoated tablet(s)	558.00	0.00	0.00
Lfx(250) Levofloxacin 250mg Film coated tablet(s)	17,608.00	0.00	0.00
Mfx(400) Moxifloxacin 400mg Film coated tablet(s)	930.00	0.00	0.00
Pto(250) Protionamide 250mg Film coated tablet(s)	837.00	0.00	0.00
Z(400) Pyrazinamide 400mg Film uncoated tablet(s)	17,608.00	0.00	0.00
Z(500) Pyrazinamide 500mg Film uncoated tablet(s)	1,860.00	0.00	0.00
Cost of medicines			**0.00**
Additional cost			**0.00**
Cost of order:			**0.00**

Regular order # 8	Order date:	Jun, 30 2018	
	Delivery date:	Oct, 31 2018	
Medicines	**Adjusted quantity to order (in units)**	**Adjusted quantity to order rounded up to pack size**	**Cost (USD/$)**
Km(1000/4) Kanamycin 1000mg/4ml Solution for injection	2,021.00	0.00	0.00
Cfz(100) Clofazimine 100mg Capsule(s)	465.00	0.00	0.00
Cs(250) Cycloserine 250mg Capsule(s)	13,206.00	0.00	0.00
E(400) Ethambutol 400mg Film coated tablet(s)	1,395.00	0.00	0.00
Eto(250) Ethionamide 250mg Film coated tablet(s)	13,206.00	0.00	0.00
H(300) Isoniazid 300mg Film un-coated tablet(s)	558.00	0.00	0.00
Lfx(250) Levofloxacin 250mg Film coated tablet(s)	17,608.00	0.00	0.00
Mfx(400) Moxifloxacin 400mg Film coated tablet(s)	930.00	0.00	0.00
Pto(250) Protionamide 250mg Film coated tablet(s)	837.00	0.00	0.00
Z(400) Pyrazinamide 400mg Film uncoated tablet(s)	17,608.00	0.00	0.00
Z(500) Pyrazinamide 500mg Film uncoated tablet(s)	1,860.00	0.00	0.00
Cost of medicines			**0.00**
Additional cost			**0.00**
Cost of order:			**0.00**

Regular order # 9	Order date:	Jul, 31 2018	
	Delivery date:	Nov, 30 2018	
Medicines	Adjusted quantity to order (in units)	Adjusted quantity to order rounded up to pack size	Cost (USD/$)
Km(1000/4) Kanamycin 1000mg/4ml Solution for injection	2,021.00	0.00	0.00
Cfz(100) Clofazimine 100mg Capsule(s)	465.00	0.00	0.00
Cs(250) Cycloserine 250mg Capsule(s)	13,206.00	0.00	0.00
E(400) Ethambutol 400mg Film coated tablet(s)	1,395.00	0.00	0.00
Eto(250) Ethionamide 250mg Film coated tablet(s)	13,206.00	0.00	0.00
H(300) Isoniazid 300mg Film uncoated tablet(s)	558.00	0.00	0.00
Lfx(250) Levofloxacin 250mg Film coated tablet(s)	17,608.00	0.00	0.00
Mfx(400) Moxifloxacin 400mg Film coated tablet(s)	930.00	0.00	0.00
Pto(250) Protionamide 250mg Film coated tablet(s)	837.00	0.00	0.00
Z(400) Pyrazinamide 400mg Film uncoated tablet(s)	17,608.00	0.00	0.00
Z(500) Pyrazinamide 500mg Film uncoated tablet(s)	1,860.00	0.00	0.00
Cost of medicines			**0.00**
Additional cost			**0.00**
Cost of order:			**0.00**

"Bhutan/NTCP/DoMSHI/ Comment: DR-TB merged quantification based on:							
Km(1000/4) Kanamycin 1000mg/4ml Solution for injection							
Period	**Stock on hand**	**Estimated consumption (enrolled cases)**	**Estimated consumption (expected cases)**	**Estimated consumption (total cases)**	**Stock on order**	**Quantity likely to expire**	**Min. qty. to prevent treatment interruption**
Nov 05, 2017...Nov 30, 2017 (26 days)	0	874	161	1,035	0	0	1,035
Dec 01, 2017...Dec 31, 2017 (31 days)	0	780	364	1,144	0	0	1,144
Jan 01, 2018...Jan 31, 2018 (31 days)	0	567	621	1,188	0	0	1,188
Feb 01, 2018...Feb 28, 2018 (28 days)	0	336	720	1,056	0	0	1,056
Mar 01, 2018...Mar 31, 2018 (31 days)	0	286	1,050	1,336	0	0	1,336
Apr 01, 2018...Apr 30, 2018 (30 days)	0	208	1,260	1,468	0	0	1,468
May 01, 2018...May 31, 2018 (31 days)	0	108	1,555	1,663	0	0	1,663
Jun 01, 2018...Jun 30, 2018 (30 days)	0	0	1,705	1,705	0	0	1,705
Jul 01, 2018...Jul 31, 2018 (31 days)	0	0	1,977	1,977	0	0	1,977
Aug 01, 2018...Aug 31, 2018 (31 days)	0	0	2,038	2,038	0	0	2,038
Sep 01, 2018...Sep 30, 2018 (30 days)	0	0	1,900	1,900	0	0	1,900
Oct 01, 2018...Oct 31, 2018 (31 days)	0	0	2,065	2,065	0	0	2,065
Nov 01, 2018...Nov 30, 2018 (30 days)	0	0	2,020	2,020	0	0	2,020
Dec 01, 2018...Dec 31, 2018 (31 days)	0	0	2,021	2,021	0	0	2,021

"Bhutan/NTCP/DoMSHI/ Comment: DR-TB merged quantification based on:							
Cfz(100) Clofazimine 100mg Capsule(s)							
Period	**Stock on hand**	**Estimated consumption (enrolled cases)**	**Estimated consumption (expected cases)**	**Estimated consumption (total cases)**	**Stock on order**	**Quantity likely to expire**	**Min. qty. to prevent treatment interruption**
Nov 05, 2017...Nov 30, 2017 (26 days)	0	0	0	0	0	0	0
Dec 01, 2017...Dec 31, 2017 (31 days)	0	0	0	0	0	0	0
Jan 01, 2018...Jan 31, 2018 (31 days)	0	0	0	0	0	0	0
Feb 01, 2018...Feb 28, 2018 (28 days)	0	0	0	0	0	0	0
Mar 01, 2018...Mar 31, 2018 (31 days)	0	0	62	62	0	0	62
Apr 01, 2018...Apr 30, 2018 (30 days)	0	0	90	90	0	0	90
May 01, 2018...May 31, 2018 (31 days)	0	0	124	124	0	0	124
Jun 01, 2018...Jun 30, 2018 (30 days)	0	0	180	180	0	0	180
Jul 01, 2018...Jul 31, 2018 (31 days)	0	0	248	248	0	0	248
Aug 01, 2018...Aug 31, 2018 (31 days)	0	0	310	310	0	0	310
Sep 01, 2018...Sep 30, 2018 (30 days)	0	0	360	360	0	0	360
Oct 01, 2018...Oct 31, 2018 (31 days)	0	0	403	403	0	0	403
Nov 01, 2018...Nov 30, 2018 (30 days)	0	0	450	450	0	0	450
Dec 01, 2018...Dec 31, 2018 (31 days)	0	0	465	465	0	0	465

"Bhutan/NTCP/DoMSHI/ Comment: DR-TB merged quantification based on:							
Cs(250) Cycloserine 250mg Capsule(s)							
Period	**Stock on hand**	**Estimated consumption (enrolled cases)**	**Estimated consumption (expected cases)**	**Estimated consumption (total cases)**	**Stock on order**	**Quantity likely to expire**	**Min. qty. to prevent treatment interruption**
Nov 05, 2017...Nov 30, 2017 (26 days)	185,308	7,965	546	8,511	0	0	0
Dec 01, 2017...Dec 31, 2017 (31 days)	176,797	8,928	1,302	10,230	0	0	0
Jan 01, 2018...Jan 31, 2018 (31 days)	166,567	8,649	2,139	10,788	0	0	0
Feb 01, 2018...Feb 28, 2018 (28 days)	155,779	7,140	2,520	9,660	0	0	0
Mar 01, 2018...Mar 31, 2018 (31 days)	146,119	7,347	3,534	10,881	0	0	0
Apr 01, 2018...Apr 30, 2018 (30 days)	135,238	6,480	4,050	10,530	0	0	0
May 01, 2018...May 31, 2018 (31 days)	124,708	6,231	4,929	11,160	0	0	0
Jun 01, 2018...Jun 30, 2018 (30 days)	113,548	5,670	5,490	11,160	0	0	0
Jul 01, 2018...Jul 31, 2018 (31 days)	102,388	5,394	6,510	11,904	0	0	0
Aug 01, 2018...Aug 31, 2018 (31 days)	90,484	5,022	7,254	12,276	0	19,804	0
Sep 01, 2018...Sep 30, 2018 (30 days)	58,404	4,410	7,830	12,240	0	0	0
Oct 01, 2018...Oct 31, 2018 (31 days)	46,164	4,278	8,835	13,113	0	0	0
Nov 01, 2018...Nov 30, 2018 (30 days)	33,051	3,420	9,270	12,690	0	0	0
Dec 01, 2018...Dec 31, 2018 (31 days)	20,361	2,790	10,416	13,206	0	0	0

Chapter 11

Supervision, Monitoring and Evaluation including Recording and Reporting system for DR-TB

Programmatic management of drug resistant TB is complex. There is a need for constant support to implementing staff through supervision and monitoring so that all activities are implemented in accordance with the prescribed guidelines. Programme managers at all levels need to be actively involved in this process and their role is as important as the diagnostic and treatment aspects of management.

This chapter explains the parameters and activities necessary for monitoring interventions for management of care for tuberculosis (TB) patients infected with drug-resistant TB strains, including programme supervision, as well as planning and measurement of progress towards universal access.

Supervision

With the expansion of the PMDT and more patients being put on second-line treatment, there is a need to further strengthen and systematize the supervisory activities. The following schedule will be followed at each level. It needs to be added here that supervisory activities for PMDT can be combined with supervisory visits for TB programme as well as other activities if the concerned staff is visiting. However, the combination of visits should not compromise the supervisory needs and focus of PMDT.

- There will be biannual visit by National level to the Regional level.
- Quarterly supervisory visit by regional level to each district where a patient is undergoing treatment.
- Monthly visit by district level to each facility where an MDR-TB patient is being treated.

At each level the primary responsibility of visit will be with the programme manager/ In-charge at that level. Where possible, clinic and laboratory staffs may join the visit. A supervisory checklist will be used during the visit. The cost of travel expenses for the monitoring and supervision visits should be met from the regular budget of the respective hospitals to the extent possible.

Programme Review

Programme annual review meeting to discuss and review programme performance are already being held and will be further strengthened with the institution of TAC. External review of the PMDT will be held in coordination with partners especially the South East Asia Regional Green Light Committee (rGLC) either independently or, when possible, together with joint programme review.

Annual clinical review meetings will also be held out of which one will be combined with the PMDT review meeting. The aim of these meetings will be to apprise clinicians of the progress in programme performance as well as to provide a platform for sharing the clinical experience in managing MDR-TB cases specifically the complicated cases.

Monitoring – key indicators and target

Detection indicators

- TB patients with result for at least rifampicin DST (Target – 100% for both new smear positive and retreatment cases by 2016).
- Confirmed RR/MDR-TB cases tested for susceptibility to any fluoroquinolone and any second-line injectable drug (Target – 80% by 2017)
- Interval between presumption of RR-/MDR-TB and DST results (Target less than 5 days from the day of sample receipt by the respective laboratories when X-pert MTB/RIF test is used) and 8 -12 weeks for phenotypic Culture & DST from the day sample received by the Reference Lab at RCDC.

Enrolment indicators

- Confirmed RR/MDR-TB cases enrolled on MDR-TB treatment regimen (Target – 100%)
- Confirmed XDR-TB cases enrolled on XDR-TB treatment regimen (Target – 100% by 2017)
- Interval between RR/MDR-TB diagnosis and start of MDR-TB treatment (Target – less than 7 days)

Interim outcome

- RR/MDR-TB cases on MDR-TB treatment regimen with negative culture by six months (Target – 80%).

Final treatment outcome

- Treatment success rate for RR/MDR-TB (Target – more than 75%)

Recording and Reporting

Specific registers for laboratory and registration of MDR-TB cases are as follows:

- Form 01. Second-line TB treatment card;
- Form 02. Second-line TB treatment register;
- Form 03. Request for examination of biological specimen for TB;
- Form 04. Laboratory register for culture, X-pert MTB/RIF and drug susceptibility testing (DST)

The forms are provided in Annexure 5 of this guideline.

Chapter 12

Ethics in Management of Drug-resistant TB

TB particularly affects poor and 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* [3].

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.

3 Guidance on ethics of tuberculosis prevention, care and control. WHO. 2010

- **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.

Chapter 13

Role of Community Leaders and other Community Members

Full adherence to drug-resistant TB treatment is essential in preventing the amplification of resistance and in increasing the chances of cure. Adherence to MDR-TB therapy is particularly difficult because of the current lengthy recommended treatment regimens, the daily high pill burden, the frequent and serious drug adverse reactions, and the indirect social and economic costs to patients associated with access to care. Thus, MDR-TB patients are at increased risk of poor adherence to treatment.

While the public health system is the lead provider of services to patients, the system also faces limitations in terms of outreach, accessibility and forming close links with the patients. Therefore it is essential that community members may be involved to support patients in treatment adherence and provide necessary psychological support during the treatment as well as after treatment for integration back into the community and rehabilitation.

Role of community leaders and other community members

There are no non-governmental organizations (NGOs) and civil society organizations (CSOs) in Bhutan that are directly providing TB related services. Hence the NTCP has limited options for their involvement. 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 (Malaria programme) for support to MDR-TB patients.

The programme will sensitize these groups specifically in high TB notification areas and where there are existing MDR-TB patients on treatment. District health authorities in coordination with respective TB In-charge should seek the support of these groups for:

- Psychological support for MDR-TB patients.
- Reintegration of patient into society after discharge from hospital.

- Identification of a suitable DOT provider.
- Ensuring that DOT is carried out, any adverse events are notified and follow-up is carried as scheduled.
- Ensuring treatment adherence by exploring avenues of psycho-social support for the patient.

Annexures

Annexure 1 – Weight based dosing in adults for shorter regimen

Drug	Weight group		
	Less than 30 kg	30 kg to 50 kg	More than 50 kg
Gatifloxacin	400 mg	600 mg	800 mg
Maxifloxacin	400 mg	600 mg	800 mg
Clofazimine	50 mg	100 mg	100 mg
Ethambutol	800 mg	800 mg	1200 mg
Pyrazinamide	1000 mg	1500 mg	2000 mg
Isoniazid	300 mg	400 mg	600 mg
Prothionamide	250 mg	500 mg	750 mg
Kanamycin+	15 mg per kilogram body weight (maximum 1 g)		

+ For adults over 59 years of age, the dose will be reduced to 10 mg/kg (max dose 750 mg)

Annexure 2: Weight based dosing in adults for longer regimen

DRUGS	DAILY DOSE	30–35 KG	36–45 KG	46–55 KG	56–70 KG	>70 KG
Isoniazid	4–6 mg/kg once daily	150mg	200mg	300mg	300mg	300mg
Rifampicin	8–12 mg/kg once daily	300mg	450mg	450mg	600mg	600mg
Pyrazinamide	20–30 mg/kg once daily	800mg	1000mg	1200mg	1600mg	2000mg
Ethambutol	15–25 mg/kg once daily	600mg	800mg	1000mg	1200mg	1200mg
Rifabutin	5–10 mg/kg once daily	300mg	300mg	300mg	300mg	300mg
Levofloxacin	750–1000 mg once daily	750mg	750mg	1000mg	1000mg	1000mg
Moxifloxacin	400 mg once daily	400mg	400mg	400mg	400mg	400mg
Ethionamide	500–750 mg/day in 2 divided doses	500mg	500mg	750mg	750mg	1000mg
Prothionamide	500–750 mg/day in 2 divided doses	500mg	500mg	750mg	750mg	1000mg
Cycloserine	500–750mg/day in 2 divided doses	500mg	500mg	500mg	750mg	750mg
p-aminosalicylic acid	8 g/day in 2 divided doses	8g	8g	8g	8g	8–12g
Bedaquiline	400 mg once daily for 2 weeks then 200 mg 3 times per week					
Clofazimine	200–300 mg (2 first months) then 100 mg					
Linezolid	600 mg once daily	600mg	600mg	600mg	600mg	600mg
Amoxicillin/clavulanic acid7/1	80 mg/kg/day in 2 divided doses	2600mg	2600mg	2600mg	2600mg	2600mg
Amoxicillin/clavulanic acid8/1	80 mg/kg/day in 2 divided doses	3000mg	3000mg	3000mg	3000mg	3000mg

Weight based dosing injectables in adults							
Injectables	**Dosage**	**30–33 KG**	**34–40 KG**	**41–45 KG**	**46–50 KG**	**51–70 KG**	**>70 KG**
Streptomycin	12–18 mg/kg once daily	500mg	600mg	700mg	800mg	900mg	1000mg
Kanamycin	15–20 mg/kg once daily	500mg	625mg	750mg	875mg	1000mg	1000mg
Amikacin	15–20 mg/kg once daily	500mg	625mg	750mg	875mg	1000mg	1000 mg
Capreomycin	15–20 mg/kg once daily	500 mg	600 mg	750 mg	800 mg	1000 mg	1000 mg

Annexure 3 - Weight-based dosing for children

Isoniazid: 7–15 mg/kg for patients less than 30 kg; maximum dose 300 mg daily

Rifampicin: 10–20 mg/kg for patients less than 30 kg; maximum dose 600 mg daily

Ethambutol: 15–25 mg/kg, maximum dose 1200 mg daily

Pyrazinamide: 30–40 mg/kg for patients less than 30 kg; maximum dose 2000 mg daily

Levofloxacin: 5 years and under: 15–20 mg/kg split into two doses (morning and evening)

Over 5 years: 10–15 mg/kg once daily

Moxifloxacin: 7.5–10 mg/kg

Cycloserine: 10–20 mg/kg. For older children who cannot swallow capsules, the capsules can be opened and dissolved in 10 ml water to aid administration

Prothionamide/ethionamide: 15–20 mg/kg

PAS: 200–300 mg/kg for patients less than 30 kg

Injectables anti-TB drugs		
Drug	**Daily dose**	**Maximum daily dose**
Streptomycin	20–40 mg/kg once daily	1000mg
Amikacin	15–30 mg/kg once daily	1000mg
Kanamycin	15–30 mg/kg once daily	1000mg
Capreomycin	15–30 mg/kg once daily	1000mg

Annexure 4 – 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 includes:
		•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

Nausea and vomiting	Eto, Pto, PAS, Bdq H, E, Z, Amx/Clv, Cfz	– 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 refl ux) 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 flatulence	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, fl uoroquinolone 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 monitoringliver 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 hypo-magne 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 aminoglyco-side had been the prior injectable in the regimen.
		3. Discontinue the injectable agent if hearing loss continues despite dose adjustment and add 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 (see Chapter 12 on Social support).
		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, fl uoroquinolones	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 anti-psychotic 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[3]

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.

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 leaft 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

[3] *All subsequent managements are adapted from ‘endTB Clinical Guideline, MSF&PIH, version 3.2’*

Managing peripheral neuropathy

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

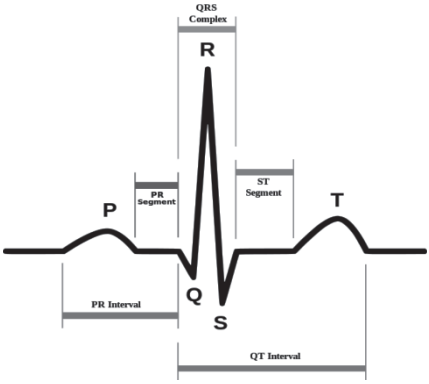
Prevalence (DR TB patients)	18% of patients in a trial with Lzd More common in patients with comorbidity, including HIV, alcohol use
How to detect?	Complete blood count, hemoglobin, platelets, white blood cells
Common causes	TB, Lzd, HIV, ART (AZT), alcohol (low platelets)
How to manage?	Iron supplementation, decrease dose of Lzd, transfusion or EPO if indicated, discontinue other medications.
Additional tests/precautions	Prevention: vitamin B6 Additional tests: Pregnancy testing, other comorbidities, 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 cinsider reduction of dose of Lzd to 300mg daily; 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 Grade1.	Stop Lzd immediately. Consider hemotransfusion or EPO. Restart at reduced dose once toxicity has decreased 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; hypo-thyroidism.
How to manage?	Assess for symptoms, repeat to confirm, review all medications; if >500 msec and does not cor-rect, d/c BDQ
Additional tests/precautions	Potassium, TSH



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

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

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 threat-ening
Prolonggation 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
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 of the affected eye (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 multi-drug regimen. *Cotrimoxazole 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 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/pre-cautions	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 neccessary.	Stop injectable temporarily. Start IV potassium replacement therapy in addition to oral. Replace magnesium and other electrolytes as neccessary.

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?	TSH levels (! High TSH = hypo-thyroidism)
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 diag-nostic obser-vations only; intervention not indicated	Symptomatic; thyroid replace-ment 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.

Annexure 5: Checklist for adverse effects monitoring of MDR-XDR-TB patients			
Sl No	Adverse effects	Action	Comments
1	Nausea and Vomitng	Rani dine/Omeprazole and metoclopramide. Divide the medicines throughout the day	If doesn't resolve within 2 to 3 days, do LFT and consult doctor.
2	Heart burn,acidity	Ranitidine, Omeprazole	
3	Diarrhoea	Oral Rehydra on Salt, Loperamide	Rule out other causes of diarrhoea and treat
4	Skin rashes, itching	Give Calamine lo-tion and an histamines (Cetrizine,promethiazine)	If severe rashes with swelling, stop treat-ment and consult doctor.
5	Anxiety	Counselling, diazepam	Seek consultation with doctor.
6	Depression	Counselling, Amitriptyline,Flouxetine	
7	Psychosis	Counselling, haloperidol,risperidone	If not managed, seek Psychiatrist's opinion
8	Seizures	Phenytoin, carbamazepine,valproic acid can be used.	Consult medical/chest physician
9	Jaundice	Do LFT, stop treatment	Consult medical/chest physician
10	Hypothyroidism	Most require thyroxine	Consult with doctor
11	Arthralgia (joint pain)	Use Ibuprofen, Indomethacin, do Serum Uric acid	

12	Electrolyte disturbances (hypokalemia)	Replace either with oral potassium chloride and if severe hypokalemia, hospitalize and give parental potassium.	Treat in consultation with doctor.
13	Nephrotoxicity (abnormal KFT)	Consult medical/chest physician	
14	Tinnitus and dizziness	Management need to change dose, do a Pure Tone Audiometry (PTA), add promethiazine	Seek ENT onsultation if possible. If worsening symptoms, consult medical/chest Physician
15	Hearing loss	Do a PTA. Compare with baseline PTA. Treatment might need to be changed.	Consult medical/chest physician
16	Peripheral neuropathy numbness, pain)	Increase Pyridoxine to 200mg per day. Add Brufen, Indomethacin. Gabapentin can also be used.	If worsening symptoms despite intervention, consult medical/chest Physician
17	Gynaecomas a (breast enlargement)	Counsel patient that resolution occurs after treatment is stopped.	
18	Alopecia (hair loss)	Consult patient that this is temporary.	
19	Oral Candidiasis	Nystatin paste, oral fluconazole	
20	Hypoglycemia	Consult doctor and treat.	

Annexure 6: Recording and Reporting forms

Form 01 - MDR-TB/XDR-TB treatment card

MDR-TB/XDR-TB Control Number:_____

Date of registration:_____

Name of Treatment Centre:_____

Patient Name:_____

Age:---------- Sex: M/F CID No:

Residential Address_____

Contact Number:_____

Name & address of DOT Provider and Contact Number:

Date of treatment started and regimen:

Initial Weight(kg): _____

Height(cm): _____

Site (circle one or both):

Pulmonary

Extrapulmonary

If extra-pulmonary, specify site:_____

Registration Group	Choose one only
New	
Relapse	
Treatment after loss to follow up	
Treatment after failure of first treatment with first-line drugs	
Treatment after failure of retreatment regimen with first-line drugs	
Other(previously treated without known outcome;previously treated extra-pulmonary	
Transfer in(from another second-line treatment centre)	

HIV INFORMATION

Y/N/Unknown

Date of Test:_____Result:_____

Started on ART(circle one): Y/N

Date:_____

Started on CPT(circle one): Y/N

Date:_____

Previous Tuberculosis Treatment Episodes			
TB Control Register No.(i.e for basic TB treatment)	Start Date(if Unknown put year)	Regimen(write regimen in drug abbreviations)	Outcome

Previous use of second-line drugs for more than one month? Yes/No/Unknown

If Yes, indicate in Table above.

Drug Abbreviations			
First-line Drugs	Second-line Drugs		
H=Isoniazid	Am=Amikacin	Eto=Ethionamide	Ctr=Clarithromycin
R=Rifampicin	Km=Kanamycin	Pto=Prothionamide	Cfz=Clofazimine
E=Ethambutol	Cm=Capreomycin	Cs=Cycloserine	Ipm=Imipenem
Z=Pyrazinamide	Mfx=Moxifloxacin		T=Thiacetazone
	Ofx=Ofloxacin	Amx/ Clv=Amoxicillin/ clavulanate	Bdq=Bedaquiline
	Gfx=Gatifloxacin		

Simplified Version

MDR-TB TREATMENT CARD

Name of Treatment Center…….....MDR –TB Control no……

Name of Patient……Age/Sex……CID No……

Occupation…….....Telephone No……

Local Address….....Permanent Address ….....

DOT Provider Name with telephone No……..

Date of registration…….....Date of treatment Started…….....

DRUGS REGIMEN…….....……..

Doses for longer Regimen; Z…….Ka……..Lfx……Cs…….Eto…….

Others…….....

Doses for shorter Regimen;Km…….....Mfx……...….Pto……...……Cfz…...…

Z….....….INH…….....E……Others……

DRUGS COLLECTION RECORD

Date	Issue		Next Due	Regimen	Body weight	Remarks
	From	To				
						(24 COLUMS)

Treatment out come	Date of decision
Cured	
Treatment completed	
Treatment failure	
Died	
Loss to follow up	
Not evaluated	

The card is in RED COLOR.

Month of treatment	Sputum Microscopy		
	Date *	Sample Number	Result
Prior**			
0			
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			

Month of treatment	Culture		
	Date*	Sample Number	Result
Prior**			
0			
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			
11			
12			
13			
14			
15			
16			
17			
18			
19			
20			

Drug -susceptibility testing(DST) Results §				
Drug	Date specimen(e.g., sputym) collected			
H				
R				
E				
S				
Am				
Km				
Cm				
FQ				
Other				
Other				
Other				

Notation method for DST
R=Resistant
S=susceptible
C=contaminated
Unk=Unknown

§ indicate near result if initial resistance was detected on line-probe assay or X-pert MTB/RIF

Notes:

*All dates in both tables are the dates the sputum was collected from the patient

**The date the sputum was collected that led to the patient being registered with RR/ MDR-TB (if performed)

Nation Method for recording smears:	
No AFB	0
1-9 AFB per 100 HPF	Scanty(and report number of AFB)
10-99 AFB per 100 HPF	+
1--10 AFB per HPF	++
> 10 AFB per HPF	+++

Notation Method for Recording Cultures:	
No growth reported	0
Fewer than 10 colonies	Report number of colonies
10-100 colonies	+
More than 100 colonies	++
Innumerable or confluent growth	+++

Notation Method for Recording X-pert MTB/RIF results:	
T	MTB detected, rifampicin resistance not detected
RR	MTB detected, rifampicin resistance detected
TI	MTB detected, rifampicin resistance indeterminate
N	MTB not detected
I	Invalid / no result / error

Second-line Treatment Regimen(Date of treatment started and dosage(mg), change of dosage and cessation of drugs): (weight band…….kg)

Date	H	R	E	S	Z(500mg)	Am	Km (vial-1gr)	Lfx	FQ(250 mg)	Pto/ Eto(250 mg)	CS(250mg)	PAS	Other	Other	Com-ments

Administration of Drugs(one row per month)

Month	Day																													Wt(kg), Lab, X-ray
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	

Mark in the boxes: V= Directly Observed

N=Not supervised

Ø= Drugs Not Taken

Split cell diagonally to record two administrations in one day.

If split doses are used mark the upper left half for the Morning dose and the lower right for the eveing dose

Administration of Drugs(one row per month): CONTINUED

Month	Day																													Wt(kg), Lab, X-ray
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	

Mark in the boxes	
Directly Observed	v
Not Supervised	N
Drugs Not Taken	Ø
"Split cell diagonally to record two administrations in one day	

Final outcome(circle one-red link)	Date
Cured	
Completed	
Treatment failed	
Died	
Lost to follow up	

Comments*: _____

_____

_____

_____

_____

* Any information on close contacts of patient may be entered here.

Form 02 - MDR-TB/XDR-TB treatment register (page 1 of 4)

MDR-TB/XDR-TB Control No.	Date of Registration	Name	Age	Sex	Residential Address	TB Control No. / Date of Registration	Site of Disease (P/EP)	Registration Group	Second-line drugs received previously (Y/N/Unk)	Date of Sample Collected for DST	Date of Sample Collected for DST	Date of DST result received	Result of Drug Susceptibility Testing(DST)[2] (R=resistant; S=susceptible; C=contaminated;----= Testing not alone)										
													H	R	E	S	Am/km	cm	FQ__	Other____	Other____	Other____	Other___

1=New; 2=Relapse; 3=After Loss to follow up; 4=After failure of first treatment with first-line drugs; 5=After failure of retreatment with first-line drugs; 6=Transfer in(from another second-line treatment centre); 7=Other

[2] Enter DST results that led to the patient being registered for second-line treatment. If DST is pending, complete when the results become available: R=resistant; S=Suceptible; C=contaminated; ----= Testing not done

First-line drug abbreviations: H=Isoniazid; R=Rifampicin; E=Ethambutol; S=Streptomycin; Z=Pyrazinamide

Second-line drug abbreviations: Am=Amikacin; Km=Kanamycin; Cm=Capreomycin; FQ=fluoroquinolone; Lfx=Levofloxacin; Mfx=Moxifloxacin; Ofx=Ofloxacin; Gfx=Gatifloxacin; Eto=Ethionamide; Pto=Prothionamide; Cs=Cycloserine; PAS=p=amino=salicyclic acid; Amx/Clv=Amoxicillin/clavulanate; Clr=Clarithromycin; Cfz=Clofazimine; Ipm=Imipenem; Lzd=Linezolid; T=Thiacetazone; Bdq=Bedaquiline

MDR-TB/XDR-TB treatment register(page 2 of 4)

Reasons for entering in MDR-TB/XDR-TB		Regimen(in drug initials)	Smear(S), Culture© or X-pert MTB/RIF(X) Results[3]										Smear(S), Culture© Results[3] during Treatment[3] CONTINUED															
RR-TB/MDR-TB confirmed	Presumptive RR-TB/MDR-TB		Start of treatment Month 0			Month 1		Month 2		Month 3		Month 4			Month 5		Month 6		Month 7		Month 8		Month 9		Month 10		Month 11		Month 12	
			S	C	X	S	C	S	C	S	C	S	C		S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C
		start date	Date			Date		Date		Date		Date			Date		Date		Date		Date		Date		Date		Date		Date	

[3](if more than one smear or culture or Xpert test done in a month, enter in the most recent positive result)

Smear results reported as follows: **0**=No AFB;

(1-9)=exact number if 1-9 AFB per 100HPF(scanty)

+ = 10-99 AFB per 100 HPF;

++ =1-10 AFB per HPF;

+++=>10 AFB per HPF

Xpert MTB/RIF test result reported as follows: T=MTB detected, rif resistance not detected;

RR= MTB detected, rif resistance detected;

TI= MTB detected, rif resistance indeterminate

N= MTB not detected;

I= Invalid/ no result/ error

Dates associated with the recorded examination results are dates of sample **collection.**

4 as per national policy.

MDR-TB/XDR-TB treatment register(page 3 of 4)

Smear(S) and Culture© Results during Treatment[3] CONTINUED																Smear(S) and Culture© results during treatment[3] CONTINUED															
Month 13		Month 14		Month 15		Month 16		Month 17		Month 18		Month 19		Month 20		Month 21		Month 22		Month 23		Month 24		Month 25		Month 26		Month 27		Month 28	
S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C
Date		Date		Date		Date		Date		Date		Date		Date		Date		Date		Date		Date		Date		Date		Date		Date	

MDR-TB/XDR-TB treatment register(page 4 of 4)

Smear(S) and Culture© Results during Treatment[3] CONTINUED																Final Outcome(Cured, Treatment completed, Treatment failed, Lost to follow up, Died, Not known)[5]	TB/HIV activities[6]			Remarks
Month 29		Month 30		Month 31		Month 32		Month 33		Month 34		Month 35		Month 36			HIV infection(Y/N/ Unk)[7]	On ART(Y/N)	On CPT(Y/N)	
S	C	S	C	S	C	S	C	S	C	S	C	S	C	S	C					
Date		Date		Date		Date		Date		Date		Date		Date		Date outcome assigned				

[5] Insert the outcome and the date when outcome was met. If patient "transfers out" make note in Remarks; if no definitive outcome is obtained indicate as Not Known or Lost to follow up depending on the way by which the patient separated from the services.

[6] TB/HIV data should also be copied back to the patient's record in the TB register because that is the source document for compiling the quarterly report on TB case management.

[7] Insert HIV status at time of TB diagnosis. **Y=** Yes, HIV infection; **N=**No HIV infection; **Unk=**HIV status unknown.

Form 03: Request for examination of biological specimen

Treatment Unit: _____ Date of request: _____

Patient Name: _____

Age (years): _____ Date of Birth: _____ Sex (mark one): ☐M ☐F

Patient Address: _____

_____ Patient Telephone: _____

Reason for examination (mark one):	Diagnostic	Presumptive RR-TB/ MDR-TB:	☐Y ☐N
	Follow-up	If follow-up, month of treatment:	
Specimen type:	Sputum	Other (specify):	
		HIV infection	☐Y ☐N ☐Unknown

Patient previously treated for TB (mark one):	☐Yes ☐No ☐Unknown
If information available specify if	
New	After failure of 1st treatment with 1st-line drugs
Relapse	After failure of retreatment regimen with 1st-line drugs
After Loss to follow-up	Other

Test requested:	Microscopy	Xpert MTB/RIF	Culture	Drug susceptibility	Line probe assay

Name, signature and telephone of requestor: _____

RESULTS (to be completed in the laboratory)

Microscopy results

Date sample collected (to be filled by requestor)	Specimen type	Laboratory serial number/s	Visual appearance (blood-stained, mucopurulent or saliva)	Result (check one)				
				Negative (0 AFB/ 100HPF)	1–9/100HPF (scanty; report number of AFB)	+ 10–99 AFB/100HPF	++ 1–10 AFB/HPF	+++ >10 AFB/ HPF

Examined by (Name & signature): _____ Date of result: _____

Xpert MTB/RIF test result (to be completed in the laboratory)

Date collected (to be filled by requestor)

M. tuberculosis			Rifampicin resistance		
Detected	Not detected	No result / Invalid / Error	Detected	Not detected	Indeterminate result

Examined by (Name & signature): _____ Date of result: _____

Culture results (to be completed in the laboratory)

Date sample collected (to be filled by requestor)	Media used (liquid or solid)	Laboratory serial number/s	Result (check one)						
			Negative (0 colonies)	1–9 <10 colonies	+ 10–100 colonies	++ >100 colonies	+++ Innumerable / confluent growth	NTM[1]	Contaminated

Examined by (Name & signature): _____ Date of result: _____

Drug-susceptibility test (DST) and line-probe assay (LPA) results (to be completed in the laboratory)

Date sample collected (to be filled by requestor)	Media used (liquid or solid media; direct or indirect LPA)	DST laboratory serial number/s	H	R	E	S	Amk	Km	Cm	FQ	Other	Other	Other	Other

R: Resistant; S: Susceptible; C: Contaminated; - Not done

Examined by (Name & signature): _____ Date of result: _____

1 Non-tuberculous mycobacteria

Form 4: Laboratpry Register For Culture, Xpert MTB/RIF and Drug Susceptibility Testing(DST)

Lab. Serial Number	Date of specimen received	Name of patient	Age	Sex	Address of patient	Treatment Unit	TB register No.	HIV infection (Y/N/Unk)*	Patient previously treated for TB(Y/N/Unk)*	Date of specimen collected	Date of specimen inoculated
1. New patients or patients starting a retreatment regimen: mark with a tick according to test used											
2. Patient on TB treatment; indicate months of treatment at which follow-up examination is performed.											
3. Culture result(Solid media) reported ad follows:											
No Growth reported											
<10 colonies		Report number of colonies									
10-100 colonies		+									
>100 colonies		++									
Immunerable or confluent growth		+++									

Form 5: LABORATORY REGISTER FOR CULTURE, XPERT MTB/RIF AND DRUG SUSCEPTIBILITY TESTING(DST)

Type of Examination			Result of Confirmatory Test of M.tuberculosis(Positive or Negative)	Culture sent for DST(Yes or No)	Name of Person Reporting Culture or Xpert MTB/RIF Results	Signature	Date of Result Reported	Comments
Diagnosis		Follow Up						
Culture	Xpert							
Date	Date	Month						

4. Xpert MTB/RIF results reported as follows:		
T	MTB detected, Rifampicin resistance not detected	
RR	MTB detected, Rifampicin resistance detected	
TI	MTB detected, Rifampicin resistance indeterminate	
N	MTB not detected	
I	Invalid/ no result/ error	

Six-monthly report on detection of TB cases with Rifampicin Resistance(RR-TB) and Multi-Drug Resistance(MDR-TB) Mono and poly resistance

Name of the Reporting Centre: **Name of the TB In-charge:**

Patients assessed during the six month period: **Date of Report submission:**

Reporting Period:

Risk Category	Number of TB cases						
List as many as exist in the national policy	Total	With results for susceptibility to rifampicin only	Resistant to rifampicin(RR) only	With results for susceptibility to both Isoniazid and Rifampicin	Resistant to both Isoniazid and Rifampicin(MDR-TB)	With MDR and tested for a fluoroquinolone and a 2nd line injectable	With XDR-TB
Treatment failure after initial treatment with first-line drugs							
Contact of a confirmed MDR-TB case							
Other risk categories as per national policy(specify)							
Mono resistance							
Poly resistance							
Total							

* from among cases tested for rifampicin +/- isoniazid(i.e. may include mono-resistant R cases).

NUMBER OF RR AND MDR-TB CASES WITH INFORMATION ON INTERVAL	INTERVAL BETWEEN PRESUMPTION OF RR-/MDR-TB AND DST RESULTS(IN DAYS)		
	MEAN	MINIMUM	MAXIMUM

Six-monthly report on enrolment of TB cases with Rifampicin Resistance(RR-TB) and Multi-Drug Resistance(MDR-TB) on second-line TB treatment poly and mono resistance

Name of the Reporting Centre: **Name of the TB In-charge:**

Patients assessed during the six month period: **Date of Report submission:**

Reporting Period: **Year:**

Type of TB Patient	Identified during assessment period	Enrolled on second-line treatment during period of assessment	With results for susceptibility to both Isoniazid and Rifampicin
All patients eligible for treatment*			
<15 years			
Female			
Confirmed RR-TB or MDR-TB			
Confirmed RR/MDR, HIV + on ART			
Confirmed RR/MDR, HIV+ not on ART			
Confirmed XDR-TB			
Confirmed mono resistance			
Confirmed poly resistance			

*** presumptive or confirmed RR-TB or MDR-TB**

NUMBER OF RR AND MDR-TB CASES WITH INFORMATION ON INTERVAL	INTERVAL BETWEEN PRESUMPTION OF RR-/MDR-TB AND DST RESULTS(IN DAYS)		
	MEAN	MINIMUM	MAXIMUM

Annual report of final outcomes of TB cases with Rifampicin Resistance(RR-TB), Multi-Drug Resistance(MDR-TB) and Extensive Drug Resistance(XDR-TB) on second-line TB treatment/mono and poly resistance

Name of the Reporting Centre: Name of the TB In-charge:

Date of Report Submission: Year of Treatment Start:

Reporting Period:

Type of TB Patient	Number of TB Cases						
	Started on treatment	Cured	Treatment Completed	Treatment Failed	Died	Lost to follow-up	Not Evaluated
All confirmed rifampicin resistant (RR-TB) and MDR-TB cases							
All confirmed XDR-TB cases							
All confirmed rifampicin resistant(RR-TB) and MDR-TB cases infected with HIV*							
Mono Resistance							
Poly Resistance							