NATIONAL GUIDELINES FOR MANAGEMENT OF TUBERCULOSIS

NATIONAL TB CONTROL PROGRAMME
DEPARTMENT OF PUBLIC HEALTH
MINISTRY OF HEALTH
BHUTAN

Sixth Edition, 2016

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Foreword

Tuberculosis (TB) which is caused by *Mycobacterium tuberculosis* still remains a public health problem all across the globe causing morbidity and mortality among the general population. In 2015, about 9.6 million fell ill with TB and 1.5 million died from the disease globally.

For a population of approximately 0.7million people, a total of 975 TB cases were reported as per 2015 data. As per the WHO estimates, we should be having a total of 1300 TB incident cases in the country. With the comparison of WHO estimates versus notified incident TB cases, there is still a gap of 325 cases.

Since the development of 5th Edition of TB guideline in 2010, many new developments and updates have taken place across the globe in terms of diagnosis, treatment and management of Tuberculosis. To revise and update the existing TB guideline was very necessary to adapt and align our treatment and management protocols as per the End TB Strategy of WHO and international standards.

This guideline has been developed considering the End TB Strategy, case definitions and reporting framework for tuberculosis of 2013 revision of WHO. The guideline describes the components of TB in our country's context based on global information, laboratory network, case finding, diagnosis, treatment initiation and management of TB in special situations, TB and co-morbid conditions, Latent TB Infection (LTBI), infection control measures, management of first line TB drugs, monitoring and supervision including recording and reporting of treatment outcomes of patients with TB. The guideline also describes for the use of GeneXpert machines for various groups of patients who may be at risk of developing drug resistant TB.

While TB today remains a public health concern, it is important for every one of us to remember that most TB patients can be cured with the standard six-month first-line treatment regimen. Therefore, our focus of care should be to reduce the burden of TB cases through early diagnosis and prompt initiation of treatment with vigorous follow up and monitoring.

I hope that this guideline will be useful in our day to day's work. I trust that each and every one of you will make the best use of this guideline for the effective management of TB cases. The Ministry of Health looks forward to your commitment in delivering your services to the needs of our TB patients.

Dr. Ugen Dophu
SECRETARY

Abbreviations and acronyms

AC	-	Amplification Control
AFB	-	Acid-Fast Bacilli
AIDS	-	Acquired Immunodeficiency Syndrome
ALT	-	Alanine Aminotransferase
ART	-	Antiretroviral Therapy
AST	-	Aspartate Aminotransferase
BCG	-	Bacillus Calmette–Guérin
BHMIS-	-	Bhutan Health Management and Information System
BHU	-	Basic Health Unit
BMU	-	Basic Management Unit
CC	-	Conjunate Control zone
CEM	-	Cohort Event Monitoring
CMO	-	Chief Medical Officer
CNS	-	Central Nervous System
CP	-	Continuation Phase
CPT	-	Cotrimoxazole Preventive Therapy
CSF	-	Cerebrospinal Fluid
CSO	-	Civil Society Organization
CXR	-	Chest X-Ray
DHO	-	District Health Officer
DoMS	-	Department of Medical Services
DoMSHI-	-	Department of Medical Supplies and Health
DOT	-	Directly-Observed Therapy
DOTS	-	Core Approach underpinning the Stop TB strategy for TB control
DRS	-	Drug Resistance Surveillance
DR-TB-	-	Drug Resistant Tuberculosis
DST	-	Drug Susceptibility Testing
EPTB	-	Extra-Pulmonary Tuberculosis
EQA	-	External Quality Assurance
FDC	-	Fixed Dose Combination
FEFO	-	First Expiry First out
FQ	-	Fluoroquinolone
GDF	-	Global Drug Facility
HCDD	-	Health Care and Diagnostic Division
HIV	-	Human Immunodeficiency Virus
IEQAS	-	International External Quality Assurance System
IP	-	Intensive Phase
IPT	-	Isoniazid Preventive Therapy
IQC	-	International Quality Control
JDWNRH	-	Jigme Dorji Wangchuk National Referral Hospital
KFT	-	Kidney Function Test
LFT	-	Liver Function Test

LED	-	Light Emitting Diode
LPA	-	Line Probe Assays
LTBI	-	Latent Tuberculosis Infection
MDR	-	Multi-Drug Resistance
MDR-TB	-	Multi-Drug-Resistant Tuberculosis
MSD	-	Medical Supply Depot
M/XDR-TB	-	Multi- or Extensively Drug-Resistant Tuberculosis
NEQAS-	-	National External Quality Assurance System
NGO	-	Non Governmental Organization
NTCP	-	National TB control Programme
NTRL	-	National Tuberculosis Reference Laboratory
OR	-	Operational Research
PAS	-	Para-minosalicylic Acid
PCC	-	Probe Check Control
PHL	-	Public Health Laboratory
PMDT	-	Programmatic Management of Drug-Resistant Tuberculosis
PPD	-	Purified Protein Derivative
PTB	-	Pulmonary Tuberculosis
QA	-	Quality Assurance
QC	-	Quality Control
QI	-	Quality Improvement
RCDC	-	Royal Centre for Disease Control
rGLC	-	Regional Green Light Committee
RR	-	Rifampicin Resistance
SCC	-	Short-Course Chemotherapy
SGPT	-	Serum Glutamic-Pyruvic Transaminase
SLD	-	Second Line Drug
SL DST-	-	Second Line Drug Susceptibility Test
SNRL	-	Supranational Reference Laboratory
SOP	-	Standard Operating Procedure
TAT	-	Turn Around Time
TB	-	Tuberculosis
TbISS	-	Tuberculosis Information and Surveillance System
TSH	-	Thyroid Stimulating Hormone
TST	-	Tuberculin Skin Test
UVGI	-	Ultraviolet Germicidal Irradiation
VCT	-	Voluntary Counseling and Testing
WHO	-	World Health Organization
WRD	-	WHO Recommended Diagnostics
XDR-TB	-	Extensively Drug-Resistant Tuberculosis

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National TB Control Program, 2016

Anti-tuberculosis drug abbreviations			
DESCRIPTION	DRUG		ABBREVIATION
First-line anti-TB drugs			
Oral drugs	Isoniazid		H
	Rifampicin		R
	Ethambutol		E
	Pyrazinamide		Z
	Rifabutin		Rfb
	Rifapentine		Rpt
Injectable agent	(Streptomycin)		(S)
Second-line anti-TB drugs			
A. Fluoroquinolones (FQs)	Levofloxacin		Lfx
	Moxifloxacin		Mfx
	Gatifloxacin		Gfx
B. Injectable anti-TB drugs	Kanamycin		Km
	Amikacin		Am
	Capreomycin		Cm
	(Streptomycin)		(S)
C. Oral second-line anti-TB drugs	Ethionamide		Eto
	Prothionamide		Pto
	Cycloserine		Cs
	Terizidone		Trd
	Linezolid		Lzd
	Clofazimine		Cfz
D. **Add-on second-line agents** (not part of the core MDR-TB regimen)	D 1	Pyrazinamide	Z
		Ethambutol	E
		High dose Isoniazid	H
	D 2	Bedaquiline	Bdq
		Delamanid	Dlm
	D 3	p-aminosalicylic acid	PAS
		p-aminosalicylate sodium	PAS-Na
		Amoxicillin/Clavulanate	Amx/Clv
		Imipenem/Cilastatin	Ipm/Cln
		Meropenem	Mpm
		(Thioacetazone)	(T)

CHAPTER 1

Basic Facts about TB

TB is an infectious disease caused by the bacillus Mycobacterium tuberculosis. It usually affects the lungs (pulmonary TB) but can affect other sites as well (extra-pulmonary TB). When the tubercle bacilli enter the body of an individual but remain dormant without causing disease it is called a tuberculous infection. A person is said to have tuberculous disease when he/she starts manifesting symptoms and signs. Approximately 10% of people infected with bacillus but not suffering from any other concomitant immunosuppressive condition will develop the active disease during their lifetime. Overall, a relatively small proportion (5–15%) of the estimated 2–3 billion people infected globally with M. tuberculosis will develop TB disease during their lifetime. However, the probability of developing TB is much higher among people infected with HIV or other co-morbid conditions that compromise one's immunity.

The disease is spread via air when people who are sick with pulmonary TB expel bacteria, for example by coughing and sneezing.

TB situation

Although statistically Bhutan is considered a relatively low TB burden country compared to other countries, Tuberculosis remains a major health problem. For this reason, the Royal Government of Bhutan accords high priority to the National Tuberculosis Control Programme (NTCP).

In Bhutan it is estimated that the TB prevalence rate is 190/100,000 population while the TB Incidence rate is 164/100,000 population. The mortality rate due to TB is 9.5/100,000 population. (Source: SEARO regional TB report, 2016)

The TB control program in Bhutan has performed well as is evident by the stable treatment success rate for smear positive TB which is ≥90% since 2008 and the very low loss to follow-up (1%). However, possibly because of an increase in primary drug resistance, treatment failure has increased from 2% to 5% in the past 6-7 years. Case notification rate of all forms of TB was 143/100,000 population in 2014 while case notification rate of bacteriologically confirmed new and relapse TB was 59/100,000 population. In 2015, a total of 975 cases of all forms of TB were notified. There are 6 high

TB notification dzongkhags - Chukha, Mongar, Samtse, Sarpang, Thimphu, and Wangdue. These notification districts account for 80% of all notified TB cases.

Treatment success rate among new smear positive TB cases was 88% for the previous year cohort in 2014 (85% cured and 3% treatment completed) while the treatment success rate of all forms of TB was 90% (999 TB cases). It must be noted that the number of cases on treatment in Bhutan is small. Therefore, a small change in absolute numbers leads to significant changes in percentage.

Given the current estimates of incidence and trends noted so far, Bhutan is in a situation to prepare for elimination of TB and to further intensify efforts to reach the unreached populations.

MDR-TB situation

A drug resistance survey (DRS) was initiated in 2010 by Royal Centre for Disease Control formerly known as Public Health Laboratory (PHL) and the survey results were available in 2013. As per the DRS report, the proportion of MDR-TB cases was as follows:

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

The next DRS carried out by RCDC in 2014 revealed the proportion of MDR-TB cases as:

- New Cases- 10%
- Retreatment cases-37%

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

TB affects men and women equally but noticeably affects the younger age group (15-24). This age group which forms 35% of the total burden of TB falls in the economically active group.

Table No.1: Estimates of TB disease burden for 2014 *(SEARO TB report, 2016)*
Total population* - 745 153

Incidence of all forms of TB	1300 (1100–1400)
Incidence rate of all forms of TB (per 100 000 population per year)	164 (148–181)
Incidence rate HIV+TB only (per 100 000 population per year)	12 (9.4–15)
Prevalence of all forms of TB	1500 (570–2700)
Prevalence rate of all forms of TB (per 100 000 population)	190 (75–359)
TB death rate (of all forms of TB, excluding HIV per 100 000 population per year)	9.5 (5.1-15)
% of MDR-TB cases among new TB cases	2.2 (1.9–2.6)
% of MDR-TB cases among retreatment TB cases	35 (21–52)
Number of MDR-TB cases among notified new TB cases	12 (10–14)
Number of MDR-TB cases among notified retreatment TB cases	25 (15–37)

**Source: as per the Projections of Population and Housing Census of Bhutan, 2005. These figures differ from those published by the United Nations, Department of Economic and Social Affairs, Population Division (2015). World Population Prospects: The 2015 Revision, DVD Edition.*

Addressing the TB problem in Bhutan

The TB Control Program was initiated in 1976. After a pilot testing of short course chemotherapy (SCC) in 1988, SCC was implemented nationwide in 1994. This was followed in 1997 by a nationwide introduction of DOTS. The DOTS Strategy evolved into the Stop TB Strategy and in 2016 WHO has transitioned to a more inclusive and comprehensive End TB strategy. Bhutan has adapted the End TB strategy which is reflected in the updated guidelines and the national strategic plan. The three pillars of the strategy include a) integrated, patient-centred care and prevention b) bold policies and supportive systems and c) intensified research and innovation. The strategy is based on principles of government stewardship and accountability, with monitoring and evaluation; strong coalition with civil society organizations and community; protection and promotion of human rights, ethics, and equity; and adaptation of the strategy and targets at the country level, with global collaboration.

Structure and Broad Activities of National Tuberculosis Control Programme (NTCP)

The NTCP functions under the Department of Public Health and is fully integrated within the general health care system. At the national level, NTCP is managed by the Program Manager and assisted by a Program Officer. The NTCP is implemented at central, district and basic health unit levels of the health services.

The responsibilities of the NTCP at the central level are:

- Policy formulation
- Coordination with partners including funding agencies
- Planning and budgeting
- Mobilization of resources
- Human resources development and capacity building for TB control
- Coordination with national and international agencies for improving the technical capacity in the country to undertake TB related laboratory services, including quality assurance
- Coordination with DoMSHI and HCDD for procurement of anti-TB drugs and other supplies
- Coordination with other programmes and Dzongkhags
- Develop research agenda and coordination with academic institutes for undertaking operational research on TB
- Monitoring and supervision of NTCP activities at all levels, providing feedback and reporting to the Ministry of Health and related agencies.

District Level:

At the district level TB control activities are carried out by a team comprising of CMOs/Medical Superintendents/MOs, TB in-charges, district health officers and laboratory workers. The overall responsibilities of the TB control programme lies with the DHO and the Medical Officers. Their responsibilities include:

Diagnosis and treatment:

- Identification of people with symptoms of TB
- Diagnosis of TB in children and adults using available tools and following the algorithm as per the national guidelines
- Appropriate classification and registration of cases based on case definition
- Identifying cases that need to be tested for drug resistance as per national guidelines and appropriate referral
- Provide/ arrange directly observed treatment (DOT) to TB patients for the entire duration of TB treatment

- Sputum smear positive patients are encouraged to be treated in the hospitals for first two weeks of the treatment.
- Screen household and close contacts of all TB cases, specifically smear positive cases
- Initiate Isoniazid preventive treatment (IPT), or other preventive therapy recommended by WHO, in children and HIV positive contacts of infectious cases who do not have the active disease

Health education:

- Provide health education to all patients
- Carry out regular awareness programs about TB for the general public
- Impart training and refresher courses to all health workers

Follow up:

- Decentralisation of patients to respective BHUs for completion of treatment under direct observation
- Counsel the patient about importance of DOTS and to visit their respective BHU/Hospital at the end of every month for follow-up
- Ensure that follow up sputum samples are collected and examined as per NTCP guidelines
- Ensure early follow-up action for patients who interrupt treatment and resume their treatment as per NTCP guidelines
- Follow up, receive, and provide feedback on transferred/referred patients
- Monitor/ supervise and support the TB activities
- Prepare indents for drugs and other supplies
- Contact tracing to be done as per guideline

Recording and Reporting:

- Appropriate registration of all TB cases
- Maintain TB register and treatment cards/patient cards
- Prepare and submit monthly and quarterly NTCP reports to BHMIS
- Maintain separate records of IPT implementation and contact tracing
- Liaise between Dzongkhag/district hospital and BHU's in terms of logistic support and TB control related activities
- Ensure reports/feedback to the NTCP and BHUs

BHU Level:

The responsibilities of TB control program at basic health units are:

Diagnosis and treatment:

- Identify people with signs and symptoms of TB, collect sputum, and transfer specimen to the nearest district hospital for appropriate laboratory examination
- If the patient is willing to go themselves to the district hospital, the option should be provided
- Follow up patients as per the diagnostic algorithm wherever possible.
- Responsible for continuation of treatment both intensive and continuation phase under direct observation for the patients till completion of treatment

Follow up:

- Supervise and monitor treatment of all patients
- Ensure DOTS
- BHUs/Hospitals to identify and train suitable community DOT providers for those patients who are not within the easy reach of BHUs or Hospitals
- Trace any patients who interrupt treatment and manage their further treatment as per NTCP guidelines
- Contact tracing to be done as per guideline
- Indent drugs and other supplies in time
- Provide feedback on the transferred/referred cases

Health education:

- Provide health education and counselling to all TB patients and their family members at the beginning and on a regular basis
- Raise awareness about TB among general public in their catchment areas

Recording and reporting:

- Maintain records of patients transferred from the dzongkhag hospitals
- Provide feedback to the dzongkhag hospitals
- Prepare monthly TB reports on time and submit them to the dzonkhag

<u>Microscopy centre</u>

Diagnostic tasks

- Collect requisite number of sputum specimen from the patient with proper guidance
- Examine sputum specimens of all TB symptomatics referred for the same
- Examine follow up sputum samples of TB patients referred to the centre
- Report test results to referring clinician or medical officer

Referral tasks

- Ensure proper packaging and appropriate conditions for the transportation of sputum to the RCDC as and when required as per the national guidelines
- Proper storage of samples in case of any delay in transportation
- Coordinate with laboratory staff at the referred laboratory to verify receipt of samples as well as timely collection of results

Quality assurance

- Maintain microscopes and ensure proper storage of laboratory consumables
- Maintain sputum smear slides as per the EQA protocol and participate in QA activities

CHAPTER 2

Case Definitions and Treatment Outcomes

It is important to classify TB patients appropriately in order to determine the correct management. This includes classifying them into the appropriate treatment regimen and duration.

Presumptive TB

A case of presumptive TB is a person who presents with symptoms or signs suggestive of TB, particularly cough for two weeks or more, unexplained weight loss, night sweats, or coughing of blood but who is yet to have a TB related investigation carried out.

Case of tuberculosis

This could be either a **bacteriologically confirmed TB case** or a **clinically diagnosed TB case:**

1. **A bacteriologically confirmed TB case** is one where a biological specimen (such as sputum, CSF, lymph node aspirate etc) is positive by smear microscopy, culture, or WHO recommended Rapid Diagnostics (WRD) - such as Xpert MTB/RIF. All such cases should be notified, regardless of initiation of TB treatment.

   a) Smear-positive pulmonary tuberculosis:
   - A patient with at least two sputum smears positive for AFB by direct smear microscopy;

   OR

   - A patient with at least one sputum smear positive for AFB by microscopy and Chest X-ray findings suggestive of TB.

   b) Culture positive:

   A patient with or without sputum smear positive for AFB but sputum or any biological specimen testing positive by culture for *M. tuberculosis*

   c) WRD positive:

   A patient with or without sputum smear positive for AFB but sputum or any biological specimen testing positive on Xpert MTB/RIF for M. tuberculosis. In some cases Xpert MTB/RIF may be used as first test on biological specimen without subjecting the sample to microscopy examination as described later.

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

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

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

Classification based on anatomical site of the disease

Pulmonary tuberculosis (PTB)

Any bacteriologically confirmed or clinically diagnosed case of TB that involves the lung parenchyma or the trachea-bronchial tree with or without the involvement of any other organs in the body. Miliary TB is classified as PTB because there are lesions in the lungs.

Extra- pulmonary tuberculosis (EPTB)

Any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges, tuberculous intra-thoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lung parenchyma, constitutes a case of EPTB. However, in cases of pleural involvement and/ or lymph node involvement, involvement of the lungs should be ruled out. As already stated, in case of lung involvement, even in the absence of symptoms, the case is classified as a pulmonary TB case.

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

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

In order to identify and to prescribe appropriate treatment to those patients at increased risk of acquired drug resistance, a case should be defined according to whether or not the patient has previously received TB treatment. The registration group focuses only on history of previous treatment irrespective of bacteriological confirmation or site of the disease.

Accordingly, all patients can be categorized as 'New' patients or 'Previously Treated' patients.

They are defined as follows:

New: A patient who has never taken treatment for TB or a patient who has taken anti-tuberculosis drugs for less than one month.

New patients may have positive or negative bacteriology and may have disease at any anatomical site.

Previously treated patients:

Those who have received 1 month or more of anti-TB drugs in the past are classified as "previously treated" patients. They may have positive or negative bacteriology and may have the disease at any anatomical site. They are further classified by the outcome of their most recent course of treatment as 'relapse', 'treatment after failure' and 'treatment after loss to follow up'.

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

b) **Treatment after failure:** Patients who have previously been treated for TB and whose treatment failed during or at the end of their most recent course of TB treatment.

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

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

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

New and relapse cases of TB are considered **incident** TB cases.

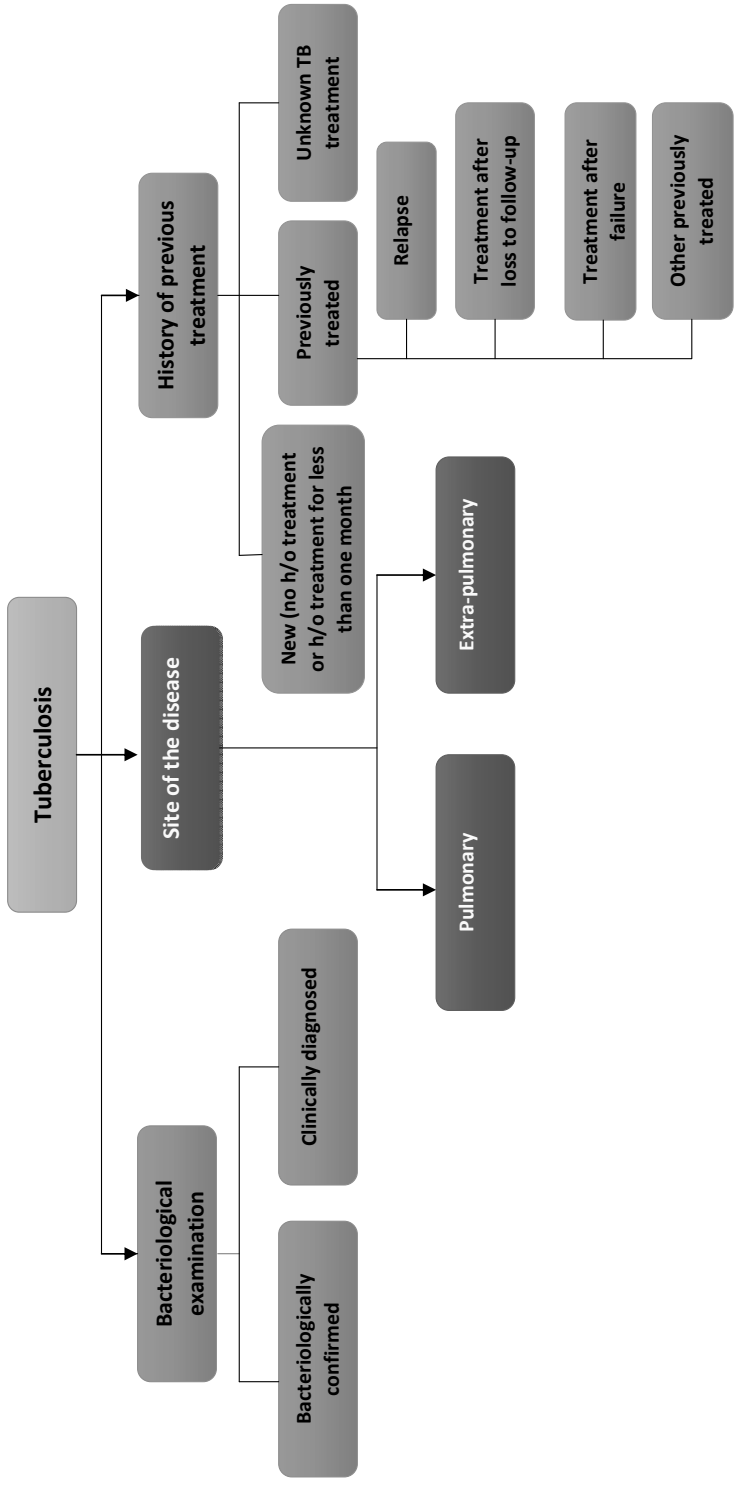


Figure 1: Classification of Tuberculosis

Classification based on HIV status

a) **HIV-positive** TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB who also has a positive result from an HIV confirmatory test.

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

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

Classification based on drug resistance

Cases are classified in categories based on drug susceptibility testing (DST) of clinical isolates confirmed to be *M. tuberculosis:*

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

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

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

d) **Extensively Drug Resistant (XDR-TB):** When a TB patient's infecting isolates of M. tuberculosis are resistant in vitro to both rifampicin and isoniazid along with resistance to any quinolone and one of the second-line injectable anti-TB drugs.

e) **Rifampicin resistance (RR):** Resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs except Isoniazid.

Treatment outcomes

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

- patients treated for drug-susceptible TB;
- patients treated for drug-resistant TB using second-line treatment

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

Treatment outcomes for TB patients (excluding patients treated for RR-TB or MDR-TB using the second line anti-TB drugs)

All bacteriologically confirmed and clinically diagnosed TB cases should be assigned an outcome from this list **except** those with RR-TB or MDR-TB, who are placed on a second-line drug regimen.

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

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

CHAPTER 3

Case Finding

In Bhutan, TB case finding is mainly passive. This means that cases reported to health facilities with signs and symptoms of TB are referred for appropriate laboratory tests. However in marginalised and vulnerable populations or those that have limited access to TB services, the programme would consider undertaking active case finding. Active case finding will also be carried out among contacts of TB cases.

Signs and symptoms of TB

The highest priority for TB control is early identification and successful treatment of all patients suffering from TB. The disease should be suspected in all patients presenting with a history of prolonged cough, typically 2 weeks or more. In addition, the patient may also present with following symptoms:

- Respiratory symptoms: shortness of breath, chest pain, coughing up of blood
- General symptoms: loss of weight, loss of appetite, fever and night sweats

Bacteriological confirmation should always be requested for a patient who has had a cough for two weeks or longer, even if in the absence of any other symptom. In certain cases, the patient may present with constitutional symptoms other than cough.

Signs and symptoms of extra-pulmonary TB depend on the site involved. Most common examples are:

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

The diagnosis of extra-pulmonary TB should always be made by a physician or specialist and often requires special examinations such as X-ray examinations, biopsies and FNAC. Sputum for AFB, Chest X-ray along with VCT should be done in all EPTB cases during the initial diagnosis. Wherever possible, the biological specimen should be sent for bacteriological confirmation using

Xpert MTB/RIF, Culture and/or smear examination as per the diagnostic algorithm and availability of tests.

Active screening

Mass screening for TB is not recommended. However, screening among contacts, high risk groups, and unreached populations could be carried out. The main purposes of contact screening and management are twofold-first, to identify contacts of all ages with undiagnosed TB disease and second, to provide preventive therapy for contacts without TB disease who are susceptible to developing the disease following recent infection. Close contacts of all TB patients (adults and children above 5 years) irrespective of sputum findings should be screened for symptoms of TB. Those who have symptoms suggestive of TB should be investigated with sputum smears, chest X-ray, or other relevant investigation (e.g. in EPTB) irrespective of the duration of the symptoms. Contact investigations should also be conducted when the index case has any of the following characteristics:

- has multi-drug-resistant TB (MDR-TB)
- is a person living with HIV infection or
- is a child < 5 years of age

Close contact: A person who is not in the household with the index case but shared an enclosed space, such as a social gathering place, workplace, or facility for extended periods during the day with them during the 3 months before commencement of the current treatment episode.

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

To identify incident cases, the TB control programme would conduct follow-up screening of contacts for up to 2 years at 6 monthly intervals. The follow-up screening is to be coordinated by the TB In-charges along with the BHU staff.

Contact investigation should include:

- Detailed medical history
- Clinical examination
- Sputum examination if cough is a symptom or appropriate biological specimen using smear, Xpert MTB/RIF and/or Culture as considered appropriate as per the guidelines. This includes samples from extra-pulmonary sites for microbiology and pathology investigations

- Chest X-ray
- Mantoux test (where indicated)

All children under the age of 5 years, whether they have symptoms or not, should be screened with a chest X-ray and the Mantoux test.

Presumptive TB Register: Sample of a Presumptive TB Register is shown in Annexure 1.

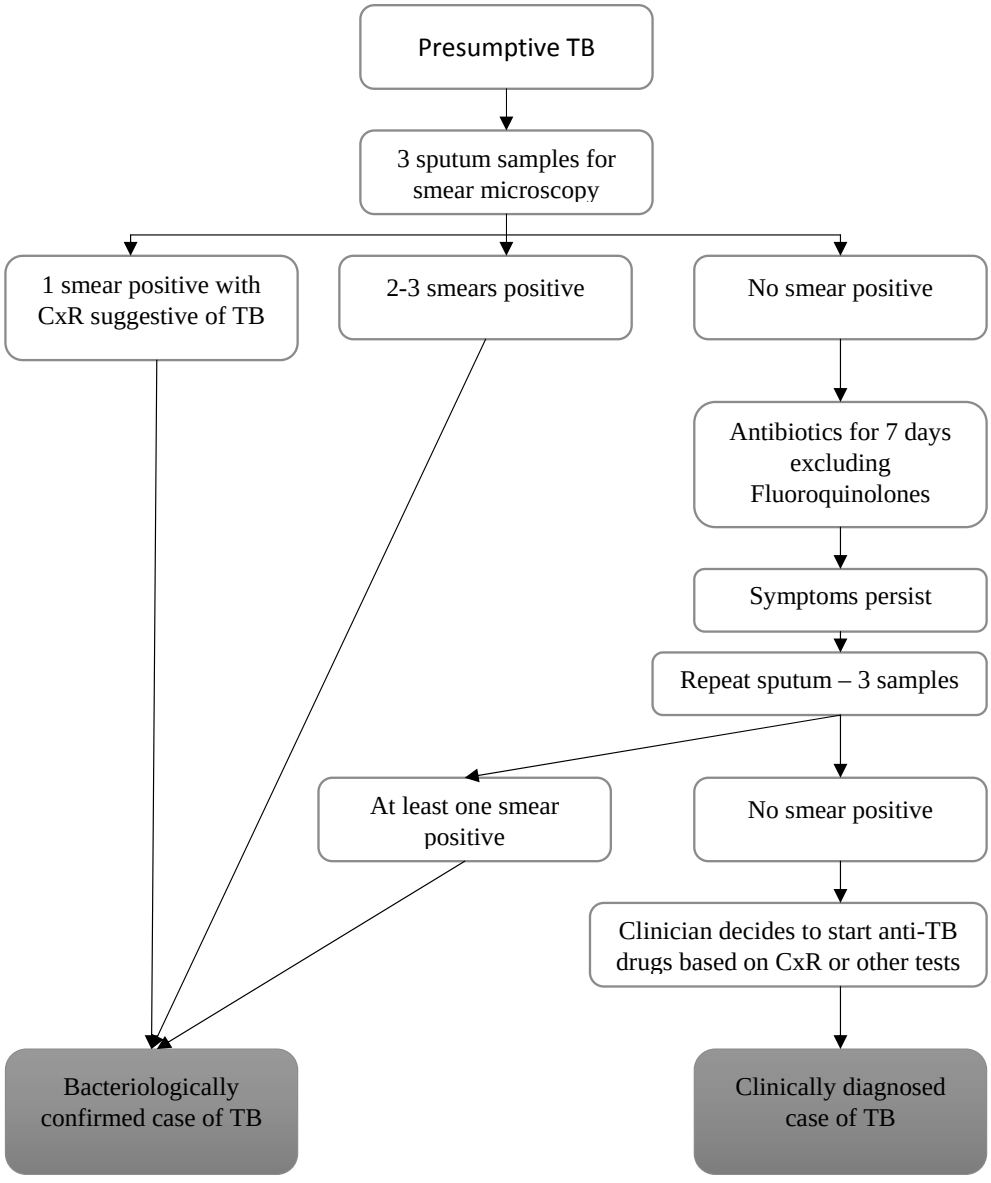
All the patients identified at the health centre with symptoms suggestive of TB and referred for sputum/biological sample examination should be recorded in this register.

The register is useful:

- To review the case finding activity of the health institution.
- To monitor whether TB symptomatics have been referred to the laboratory and the results of laboratory examinations have been returned for all samples sent.
- Whether the identified case of presumptive TB was referred for correct diagnostic test as per the national algorithm.

Whenever a presumptive TB case is identified, it should be recorded in the register. The referring medical officer or an officer assigned the duty should be responsible for maintaining this register. The head of the health facility may entrust these responsibilities to any other officer depending on the situation in the particular health facility. The person responsible for the register should ensure that, if available, full name, complete address, and contact telephone number are entered in the register legibly. This will assure that bacteriologically confirmed patients can be located if he/she does not return for the results.

Figure 2: Diagnosis of Pulmonary TB



CAPTER 4

Diagnostics

Sputum smear examination

The most cost-effective tool for screening pulmonary TB suspects is a microscopy examination of their sputum by the Ziehl-Neelsen method. Over 65% of pulmonary TB patients are smear-positive and will be detected by this method. The number of bacilli in the sputum of the remaining pulmonary TB patients is too low to be detected with this method. Another method of sputum examination is fluorescent staining which utilizes basically the same approach as the Z-N staining. In this approach, carbolfuchsin is replaced by a fluorescent dye (auramine-O, rhodamine, auramine-rhodamine, acridine orange etc), the acid for decolourisation is milder, and the counter stain, though nonessential, is useful in quenching background fluorescence.

Three sputum specimens should be collected from a TB suspect (Spot – Morning– Spot) for diagnosis and two specimens (Morning – Spot) during follow up.

Sputum collection and Transportation:

a) At the first visit, collect a sputum specimen from every presumptive TB case (including presumptive extra-pulmonary TB). A supervised spot sputum specimen is collected at this first level.
b) Fill in the sputum smear request form and record lab number/name of the patient on the sputum container (not on the lid). Make sure that there is a detailed address of the patients for easy tracing if he/she fails to return.
c) Give the patient clear instructions on how to produce good sputum from within the chest. If needed, gently tap at the back or advise to take warm fluid. While supervising sputum collection, the health worker should stand next to the patient, NOT in front of him, in a well ventilated area e.g. at a window or corridor.
d) Check that the specimen is of good quality (not saliva). If not, collect another sample.
e) Give the patient a sputum container and ask him to come back the following day with an early morning sputum specimen. Properly advise patient on the procedures of sputum collection.
f) The following day when the patient returns with the early morning sample, collect another supervised spot sputum specimen.

g) Send the specimen to the laboratory with the laboratory request form. If the sample cannot be sent to the laboratory immediately, it must be stored in a cool place out of direct sunlight. If the laboratory is in a different location, the sample should be packed and transported properly within one week. Alternatively, slides can be prepared at the health centre and sent to the laboratory.

h) For culture, the specimen should be packed properly and sent maintaining the cold chain to the laboratory.

Steps in smear preparation:

1. Write the laboratory serial number and I, II, III or a, b, c for spot identifier on the edge of a clean unused glass slide with a diamond pen on a non-frosted slide and pencil on a frosted slide.
2. Use muco-purulent, opaque, greyish or yellowish portion for the smear preparation. Transfer an appropriate portion of the specimen to the slide by using an applicator stick or wire loop (if using wire loop, clean it using an alcohol sand jar before heat flaming). Collect a match head sized particle of thick sputum. Do not use mucus or saliva.
3. Spread the sputum evenly on glass slide. Use the bamboo stick to make smear about 2cms by 3cms in size. Spread it evenly – not too thick and not too thin.
4. Dry the smear at room temperature. Do not leave it in direct sunlight. DO NOT use a flame to dry it.
5. When the slide is completely dry, fix it. Pass the smear 3 times through the flame of a spirit lamp, for 5 seconds each time. Do not put the slide in the flame before it is completely dry. Store the smear in a slide box if you cannot stain it straight away.

Steps in staining the smear with ZN stain:

a) Place the unstained slides on the slide rack, with the smeared slide on the uppermost rack, about 1 cm apart and the edge with the serial number towards you.

b) Cover the whole surface of the slide with a 1% carbolfuchsin. (The carbolfuchsin should be filtered during reagent preparation).

c) Heat the slide gently from underneath with a spirit burner until the stain begins to steam gently. Repeat twice. DO NOT let the stain boil or dry on the slide. Leave the warm stain for a minimum of 5 minutes.

d) Rinse each slide with tap water until the fresh stain has been washed away.

e) Cover the slide with a decolorizing solution (25% sulphuric acid or 3% acid-alcohol) and leave for 3 minutes until the slide is completely decolorized.
f) Rinse each slide with tap water. Wipe the underside of the slide gently to remove any remaining stain. If the decolourization is incomplete, repeat the step.
g) Cover the slide with 0.1% methylene blue counter stain for 60 seconds.
h) Rinse each slide gently with tap water.
i) Leave the slides to dry in a sheltered area, away from dust and direct sunlight. Do not heat or use blotting paper to dry the slides.

Steps to Examine the Smear:

1. Examine at least 100 fields with the oil immersion lens and a 10X eyepiece. This will take at least 5-10 minutes.
2. Record the result using the following classification:

Table No.2

What you see	What to report
No AFB in 100 fields	No AFB seen
1-9 AFB in 100 fields	Scanty (Record exact number of Bacilli)
10-99 AFB in 100 fields	1+
1-10 AFB per field, check 50 fields	2+
>10 AFB per field, check 20 fields	3+

Note: It is mandatory to examine 100 fields before declaring smear report as negative.

Steps in staining the smear with fluorescent stain:

a) Place the slides on a staining rack, with the smeared side facing up. The slides should not be touching each other.
b) Flood the slides with freshly filtered auramine-phenol. Let stand for 7-10 minutes.
c) Wash well with running water. Taking care to control the flow of water so as to prevent washing away the smear.
d) Decolorize by covering completely with acid-alcohol for 2 minutes. Perform this twice.
e) Like before, wash well with running water to wash away the acid alcohol.
f) For 30 seconds counter stain with 0.1% potassium permanganate.
g) Wash, as before, with water and let the slide stand at a slope for air drying.

Examination procedure and reporting of results for fluorescent staining:
Switch on the mercury vapour lamp. The bulb takes approximately 10 minutes to reach full intensity. To ensure that the microscope is correctly set up, first examine a known positive slide using the low power objective (magnification 100-150x). The bacilli will stand out against the dark background as slender bright yellow fluorescent rods. Rule out any artefacts. Grade positive smears into four degrees of positivity using the 20x, 25x objective along with the 10x eyepiece. Smear needs to be observed in a "linear pattern". For a trained and experienced lab technician, each smear would take approximately a minimum of 2 minutes for 100 fields or three horizontal sweeps. Smears are examined at a much lower magnifications (typically 250x) than the ZN-stained smears (1000x) if fluorescent staining is used. Therefore, each field examined under fluorescence microscopy has a larger area than that seen with a bright field microscopy. Thus, a report based on a fluorochrome-stained smear examined at 250x may contain a much larger numbers of bacilli than a similar report from the same specimen stained with carbol-fuchsin and examined at 1000x. For the purpose of uniformity among the examinations and for quantitative reporting of results, a method has been suggested (WHO Manual on Microscopy Part II). This method states that the number of acid-fast bacilli observed under fluorochrome staining could be divided by a "magnification correction factor" to yield an approximate number that might be observed if the same smear were observed under bright-field microscopy.

Comparative grading

Table No.3: - AFB grading based on IUALTD/WHO scale

IUATLD/WHO scale (1000x field = HPF) Result	Fluorescence (200–250x magnification: 1 length = 30 fields = 300 HPF)	Fluorescence (400x magnification: 1 length = 40 fields = 200 HPF)
No AFB seen	Zero AFB/1 length	Zero AFB/1 length
Scanty	1–29 AFB/1 length	1–19 AFB/1 length
1+	30–299 AFB/1 length	20–199 AFB/1 length
2+	10–100 AFB/1 field on average	5–50 AFB/1 field on average
3+	>100 AFB/1 field on average	>50 AFB/1 field on average

Write the smear result in the laboratory register and the smear request/ report form. If the result is positive, record the result in red.

If two or more slides are positive then the patient has pulmonary smear-positive tuberculosis. This indicates that you must refer the patient for treatment immediately. To prevent initial loss of follow-up, all smear-positive results must be communicated to the TB in-charge the same day.

False positivity, false negativity of sputum smears:

Much of the accuracy of the sputum examination depends on the preparation of the slide and the experience of the microscopist. Even in the hands of an experienced microscopist there are chances for the smear examinations to yield either false positive or false negative results.

a) A false positive can be the result of the following:

- Food particles.
- Precipitated stains.
- Saprophytic acid fast bacillus.
- Mycobacterium kansasii or Nocardia species.
- Spores of Bacillus subtilis.
- Fibres and pollen.
- Scratches on the glass slide.
- Contamination of sample from other sputum samples.

b) A false negative can be the result of the following:

- Poor collection of sputum sample, i.e. either there is inadequate sputum or only saliva.
- Not obtaining early morning samples.
- Exposure of sputum specimen to direct sunlight or other forms of destructive radiation, excessive heat or storage for prolonged periods under hot and dry conditions; all the above lead to the bacillus losing its acid fast property.
- False negative can also result from improper preparation of smear.
- Inadequate examination by either scanning too briefly or erratically or simply a reading error.

Disposal of used sputum containers and sputum:

All infectious waste should be ideally autoclaved at 121° C temperature for 15 minutes at 15 lbs pressure. If this isn't possible the rest of the sputum should preferably be burnt in a pit, otherwise throw it in a pit and cover it with soil, sand, bleaching powder, or some other disinfectants so as to minimize the risk of TB spread to others.

How reliable is smear microscopy?

If the sputum specimen is collected properly, a good slide is prepared and there is AFB in that specimen the chances of it being detected by microscopy is very high. However, the probability of detecting AFB in a smear is directly dependent on the concentration of bacteria in the smear.

Other methods used for diagnosing pulmonary TB:

Xpert MTB/RIF is an automated nucleic acid amplification test that is recommended by World Health Organization (WHO) for the early detection of TB and resistance to rifampicin. Rifampicin is one of the most important drugs used in the first line regimen for treating TB. Resistance to rifampicin is also used as a proxy indicator of multidrug resistance. The test takes around two hours and requires minimal man power to perform. Xpert MTB/RIF can detect TB bacilli at much lower concentrations compared to a smear microscopy and hence it is considered much more sensitive. At present, this test is only offered for following groups of patients:

- All new smear positive cases
- All cases with a history of TB treatment that are now presenting with symptoms suggestive of TB (retreatment cases). These includes both pulmonary and extra-pulmonary TB
- People living with HIV are at higher risk of morbidity and mortality due to TB. Given the urgency in detecting resistance to drugs, the samples from such patients are subjected to Xpert MTB/RIF testing.
- Symptomatic contacts of known DR-TB cases
- Diabetics, chronic kidney disease, drug users
- Sputum non-conversion - New PTB patients remaining positive at 2 months of treatment and Retreatment patients started on first line anti-TB drugs remaining positive at 3 months or later
- Patients with possible central nervous system TB
- Paediatric TB cases
- Elderly TB cases
- Health Care Workers
- Patients who return from abroad with active TB
- Prisoners, migrant workers, other congregate settings (hostel/ dormitory/nunneries/monasteries)
- Xpert MTB/RIF will also be used for diagnosis of extra-pulmonary TB (where appropriate).

With the wider availability of this test in future (expected by 2019) it will be used as an initial test in the diagnosis of all groups of patients.

Line probe assay

Line probe assay (LPA) is a molecular method for diagnosing TB and the most common genetic mutations causing resistance to rifampicin and isoniazid. This technology can provide results and a diagnosis of MDR-TB in 2 days directly from smear positive sputum specimens and from culture isolates. Turnaround time could be longer when the test is performed in batches of selected cultures. This test does not work well on smear negative specimens. Since this method is more demanding technically, it is used only at RCDC to confirm the diagnosis of MDR-TB alongside conventional DST.

As of now the LPA in Bhutan is used on culture isolates for diagnosing MDR-TB. LPA is also used on special request by the physicians on direct sputum samples for patients who are suggestive of MDR-TB.

The following groups of patients will be preferred for LPA:

1. All cases of rifampicin resistance detected by GeneXpert MTB/RIF will be subjected to LPA to see for isoniazid sensitivity.
2. All retreatment and high risk DR-TB cases at start of the treatment.
3. High risk DR-TB cases found not to be Rifampicin resistant on GeneXpert and in whom LPA was not performed earlier for early confirmation of resistance to Isoniazid.
4. In low risk cases with Rifampicin resistance found through GeneXpert testing, using another sample.

MTB culture

TB sputum culture is more sensitive than sputum smear examination. It is mainly indicated in case of:

- Diagnosis of smear negative cases or smear-negative relapse cases.
- Suspected drug resistance to study antibiotic sensitivity pattern.

In Bhutan, TB culture is done on solid media (Lowenstein-Jensen) and liquid media (BACTEC MGIT 960 Liquid Culture System). If solid media is used, time to growth detection is about six to eight weeks and DST results would be available after another four weeks. In liquid media time to growth detection is about four to six weeks and DST results would be available after another two to four weeks. The probability of finding acid-fast bacilli in sputum smears by microscopy is directly related to the concentrations of bacilli in the sputum. Sputum microscopy is likely to be positive when there are at least 5000 to 10,000 organisms per ml of sputum. At concentrations below 1000 organisms per ml of the sputum, the chance of observing acid-fast bacilli in a smear is less than 10%. In contrast, a properly performed culture can detect organisms even at concentrations between 10 to 100 organisms per ml.

Chest X-Ray

X-Ray is a good screening tool but does not confirm a diagnosis. Chest X-Ray (CXR) findings do not specifically indicate pulmonary tuberculosis because there are other chest diseases which may show the same changes on a CXR. It may be used in patients in whom 3 sputum smear examinations are negative. It is difficult to differentiate between active TB and other conditions through the use of CXR. Therefore, CXR findings suggestive of pulmonary TB should be clinically corroborated along with the decision by the Medical Officer to treat.

Mantoux text

The Mantoux test or tuberculin test (PPD) is of use in children below five years. The Mantoux test is only as an ancillary investigation used to diagnose active tuberculosis only after performing examination of other biological specimen like sputum. Mantoux test should not be used as a screening test on contacts or others.

Technique of Mantoux test

Several preparations of Tuberculin are available. The Mantoux test is an intradermal injection of 0.1 ml of tuberculin into the anterior aspect of the left forearm. The transverse diameter of the induration is measured after 48-72 hours.

Interpretation of Mantoux test depends on two factors:

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

Induration of diameter ≥5 mm is considered positive in:

- HIV-positive individuals including children;
- Severely malnourished children.
- Severely immunocompromisd people (chronic kidney disease on dialysis, organ transplant recipients and those on high dose steroids or anti-TNF).

Induration of diameter ≥10 mm is considered positive in:

- All other children (whether or not they have received BCG vaccination) and adults.

Causes of false positive tests:

- Incorrect interpretation of test.
- Past TB disease.

- BCG vaccination.
- Primary TB infection.
- Infection with non-tuberculous mycobacteria.

Causes of false negative results:

- Incorrect administration or interpretation of test.
- HIV infection and other immunocompromising situations.
- Improper storage of tuberculin .
- Viral infections (e.g. measles, varicella).
- Vaccinated with live viral vaccines (within 6 weeks).
- Malnutrition.
- Bacterial infections (e.g. typhoid, leprosy, pertussis).
- Immunosuppressive medications (e.g. corticosteroids).
- Neonatal patient.
- Primary immunodeficiencies.
- Diseases of lymphoid tissue (e.g. Hodgkin's disease, lymphoma, leukaemia, sarcoidosis).
- Low protein states.
- Severe TB.
- Diabetes and other.

Diagnosis of TB in special situations

This section deals with diagnosis in situations where it is suspected that TB is involving other organs of the body with or without the involvement of the lung parenchyma. In all cases where lung parenchyma is involved, the disease should be reported as pulmonary TB irrespective of the site from where biological sample is taken. The common methodology to diagnose TB at sites other than the lungs is by using a biopsy or tissue aspirate.

Tissue Biopsy

Tissue biopsy is useful in the diagnosis of extra-pulmonary TB (EPTB). A biopsy will also exclude other pathological processes like malignancy. A biopsy should be attempted in suspected EPTB cases if a lesion is amenable to biopsy and when a confirmed diagnosis cannot be made using Xpert MTB/RIF on tissue aspirate or when there is no clinical progress even after giving effective TB treatment for 2 months or more. In pulmonary TB (PTB), lung biopsy may be indicated in the diagnosis of miliary TB or in cases of lung lesions atypical of TB when the sputum is negative for AFB. Histology will reveal granulomatous inflammation with central caseation and cell infiltration with lymphocytes, epithelioid cells, and Langerhan's giant cells. Biopsy specimens collected

in normal saline can be cultured for MTB. When an adequate amount of sample can be obtained, direct smear for AFB and Xpert MTB/RIF can also be done on biopsy samples. Xpert MTB/RIF is recommended in addition to MTB culture for diagnosis of TB in EPTB cases (except pleural effusion, blood, urine and stools).

Tissue aspirate

Cytology and direct smear for AFB can be done on aspirates from extra pulmonary sites such as lymph nodes and collections of pus. If an adequate amount (at least 0.8 ml) of aspirate is obtained, Xpert MTB/RIF can be performed which, if positive, confirms the diagnosis microbiologically. For MTB culture and Xpert MTB/RIF at least 1 ml of aspirate would be required.

Diagnosing TB in special situations:

Miliary (disseminated) TB

Miliary TB results from wide spread blood borne dissemination of TB bacilli. Although in children it is often the consequence of a recent (primary) infection, in adults it may be due to either recent infection or reactivation of old disseminated foci.

Patients present with constitutional features rather than respiratory symptoms. They may have hepatosplenomegaly and choroidal tubercles on fundoscopy. Often the presentation is associated with a fever of unknown origin and wasting may be marked. A rare presentation seen in the elderly is cryptic military tuberculosis. It has a chronic course and remains undiagnosed unless there is a high degree of suspicion. An acute septicaemic, non-reactive form of miliary tuberculosis occurs very rarely and is due to a massive haematogenous spread of tubercle bacilli.

Diagnosis is based on CXR. It shows diffuse, uniformly distributed, small miliary shadows. "Miliary" means "like small millet seeds". Various haematological abnormalities may also be seen. These include anaemia, leukopenia, neutrophilic leucocytosis, and leukemoid blood reactions. Liver function tests may also be abnormal. Bacteriological confirmation (smear or culture) is sometimes possible from sputum, cerebrospinal fluid, bone marrow, the liver, or blood. Granulomas are evident in liver or bone marrow biopsy specimens from many patients. Broncho alveolar lavage is more likely to permit bacteriological confirmation. Miliary tuberculosis with lung parenchymal involvement is classified as Pulmonary TB.

Tuberculous serous effusions (pleural, pericardial, ascites)

The presentation is usually with constitutional and local features. Microscopy of the aspirate from tuberculous serous effusions rarely shows AFB because the fluid forms as an inflammatory reaction to TB lesions in the serous membrane. TB culture, even if available, is of no immediate help. The white cell content is variable, usually with predominant lymphocytes and monocytes. The aspirate is an exudate (i.e. protein content is more than30 g/l; it is easily determined by leaving the aspirate standing and if "spider clots" develop in the specimen, it is an exudate). Interpret with caution the laboratory result of protein concentration in any aspirated fluid. If there has been a delay in laboratory analysis, a protein clot may have formed in the sample. The laboratory result may then be falsely low.

Tuberculous pleural effusion:

The clinical and CXR diagnosis of a pleural effusion is straight forward. In case of doubt, an ultrasound can confirm the presence of fluid in the pleural space. Always perform diagnostic pleural aspiration if a patient has a pleural effusion. The fluid is usually straw-coloured. The white cell count is usually high with predominant lymphocytes. Occasionally the fluid is blood-stained. On aspiration, the presence of pus indicates an empyema (purulent effusion). If facilities are available, closed pleural biopsy using an Abrams needle will be useful for histological diagnosis. Since the distribution of TB lesions in the pleura is patchy, the diagnostic yield of closed pleural biopsy is about 75%. Multiple biopsies increase the diagnostic yield. A small open pleural biopsy increases the yield even further. Pleural effusion with lung parenchymal involvement is classified as Pulmonary TB.

Tuberculous pericardial effusion:

The diagnosis usually rests on suggestive constitutional and cardiovascular features and investigation findings (ECG, chest CXR and echocardiography).

Tuberculous ascites:

Ascites results from peritoneal TB. Routes of spread of TB to the peritoneum include the following: a) from tuberculous mesenteric lymph nodes; b) from intestinal TB (pulmonary TB patients may develop intestinal ulcers and fistulae as a result of swallowing infected sputum); c) blood-borne. Patients present with constitutional features and ascites. There may be palpable abdominal masses (mesenteric lymph nodes). Aspirated fluid is exudative with high protein content and leucocytosis with predominantly lymphocytes. The yield of direct smear and culture for AFB is relatively low; culture of a large volume ascitic fluid can increase the yield. Ultrasound may show features consistent

with TB, including enlarged mesenteric or retroperitoneal lymph nodes. Definitive diagnosis rests on a peritoneal biopsy. Blind percutaneous needle biopsy of the peritoneum has a low pickup rate and a high complication rate. In experienced hands, laparoscopy under anaesthesia has a high pick-up rate. Laparoscopy enables direct visualization and biopsy of peritoneal TB lesions. Laparotomy will confirm the diagnosis in nearly every case but is too invasive for routine use.

Gastro-intestinal TB

Any portion of the gastrointestinal tract may be affected by tuberculosis. The terminal ileum and caecum are the sites most commonly involved. Abdominal pain (at times similar to that of appendicitis), chronic diarrhoea, subacute obstruction, hematochezia, and a right iliac fossa mass are common presentations. Fever, weight loss, and night sweats are also frequent. A 'doughy abdomen' due to extensive intra-abdominal inflammation may also be detected. Diagnosis rests on a barium examination of the small and large intestine or on a colonoscopy or CT abdomen.

Tuberculous meningitis

Diagnosis of neurological TB is difficult. High protein content in CSF with high lymphocyte count, although not a confirmatory test, suggest TB etiology. Xpert MTB/RIF is a sensitive rapid molecular diagnostic test on CSF which should be performed as a first line investigation whenever neuro TB with meningeal involvement is suspected. At least 0.5 ml of CSF should be sent for the Xpert MTB/RIF test. Direct microscopy for AFB on CSF has poor sensitivity. Mycobacterial culture can also be done and needs at least 1 ml of the specimen.

Spinal TB (Pott's disease)

TB of the spine is important. For the patient with a missed diagnosis of thoracic or cervical spinal TB the disastrous consequence is paralysis. The sites most commonly involved are the lower thoracic vertebrae (with T-10 being the most common) and the upper lumbar spine. The cervical spine can also be affected. TB starts in an intervertebral disc and spreads along the anterior and longitudinal ligaments, before involving the adjacent vertebral bodies. With an advanced disease, a collapse of vertebral bodies results in kyphosis (gibbus). A para-vertebral cold abscess may also be formed. This may track to sites such as the lower thoracic cage or below the inguinal ligament (Psoas abscess).

A plain X-ray of the spine is usually indicative of diagnosis. The typical appearance is erosion of the anterior edges of the superior and inferior borders of adjacent vertebral bodies. The disc space is narrowed. A CT scan or an MRI can reveal the lesions more correctly. Aspiration of the abscess or bone biopsy confirms the tuberculosis etiology by histopathology and culture. The main differential diagnoses are malignancy and pyogenic spinal infections. Malignant deposits in the spine tend to erode the pedicles and spinal bodies, leaving the disc intact. Pyogenic infection tends to be more acute than TB and presents with more severe pain.

Joint TB

Weight bearing joints are mostly affected. Tuberculosis of the hip joints causes pain and limping. TB of the knee produces pain and swelling. A history of previous trauma is often elicited. Systemic symptoms are present in about half of the patients. Pulmonary TB is detected in approximately half of these patients. Radiological abnormalities include bone erosions, joint space narrowing, and ultimately joint destruction. A confirmatory diagnosis requires synovial biopsy.

Genito-urinary TB

Tuberculosis can involve any parts of the genito-urinary tract. Genito-urinary TB is usually due to haematogenous seeding following primary infection. Local symptoms predominate. Urinary frequency, dysuria, haematuria, and loin pain are common presentations. However, patient may be asymptomatic with the disease only being discovered after severe destructive lesions of the kidneys have developed. Urinalysis gives abnormal result in 90% of cases, revealing pyuria and haematuria. Sterile pyuria first raises the suspicion of renal tuberculosis. An intravenous pyelography helps in the diagnosis. Calcification and ureteric stricture are also suggestive findings. AFB from a centrifuged urine specimen helps in the diagnosis. Culture of three morning urine specimens yields a definitive diagnosis in nearly 90% cases. Severe ureteric strictures may lead to hydronephrosis and renal damage.

Genital tuberculosis is more common in female than in male patients. In female patients, it affects the fallopian tubes and endometrium and may cause infertility, pelvic pain, and menstrual irregularities. Diagnosis requires a biopsy and/or a culture of specimens obtained by dilatation and curettage (D and C). In male patients, tuberculosis preferentially affects the epididymis (producing a slight tender mass). Orchitis and prostatitis may also develop.
In almost half of the cases of genitourinary tuberculosis, urinary tract disease is also present.

Hepatic/Splenic TB

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

Less common forms

Tuberculosis may cause chorioretinitis, uveitis, panopthalmitis, phlyctenular conjunctivitis and retinal vasculitis. In the nasopharynx, tuberculosis may simulate Wegener's granulomatosis. Cutaneous manifestations of tuberculosis include primary infection due to direct inoculation, abscess, chronic ulcers, scrofuloderma, lupus vulgaris, miliary lesions, and erythema nodosum. Adrenal tuberculosis is a manifestation of advanced disease presenting as sign of adrenal insufficiency.

Diagnosis of tuberculosis in children

In 2014, an estimated 1 million children became ill with TB and 140 000 children died of TB worldwide. TB illness in children is often missed or overlooked due to non-specific symptoms and difficulties in diagnosis such as obtaining sputum from children. Children with vulnerable immune systems, such as the very young, HIV-infected, or severely malnourished are most at risk for falling ill or dying from TB. Infants and children are at increased risk of developing severe disseminated disease, such as TB meningitis or miliary,TB those are associated with high mortality. Adolescents are at particular risk of developing adult-type disease, i.e. often sputum smear positive and highly infectious TB.

Children with TB are often poor and live in vulnerable communities where there may be a lack of access to health care. New-born children of women with TB are at increased risk of contracting TB. Risks are very high for HIV-infected mothers and children.

Since only a small proportion of children have sputum smear positive tuberculosis and many children cannot produce sputum for examination, diagnosis of TB in children is often difficult. Detailed clinical history of symptoms and contact with a known or likely case of tuberculosis followed by thorough clinical examination should precede diagnostic tests in children. Diagnosis of TB in children should be considered in the following situations.

- Respiratory symptoms for more than two weeks and not responding to broad-spectrum antibiotics.

- Undiagnosed illness continuing for more than 2- 4 weeks.
- Unexplained fever.
- Meningitis not responding to antibiotic treatment or sub acute in onset and/or raised intracranial pressure.
- History of contact with an infectious pulmonary TB case, particularly in the same household.
- An abnormal chest X –ray.
- A positive Tuberculin skin test.
- Unexplained weight loss or failure to gain weight in spite of adequate nutrition.
- Fatigue, reduced playfulness, decreased activity.
- Failure to thrive in an infant.
- Enlarged lymph nodes (especially non painful), abdominal mass, ascites, CNS signs, signs of pleural or pericardial effusion, enlarged joints.
- Gibbus deformity of spine.

The diagnosis should be based on:

- Careful history (including history of TB contact and symptoms consistent with TB).
- Clinical examination (including growth assessment).
- Tuberculin skin testing.
- Chest X-ray .
- Bacteriological confirmation whenever possible – In case of suspected PTB, early morning sputum (where a good sample can be obtained) or sputum obtained after nebulisation with normal/ hypertonic saline and/or gastric aspirates can be sent for Xpert MTB/RIF, culture and/or smear examination.
- Other investigations relevant for suspected pulmonary TB and suspected extra-pulmonary TB.
- HIV testing.

Bacteriological confirmation for tuberculosis in children:

As per the recent WHO guidelines on Xpert MTB/RIF as well as the childhood TB guidelines, the following recommendations are included for diagnosing TB in children.

- Xpert MTB/RIF should be used, rather than conventional microscopy and culture, as the initial diagnostic test in children suspected of having MDR TB or HIV-associated TB.

- Xpert MTB/RIF may be used, rather than conventional microscopy and culture, as the initial test in all children suspected of having TB.

- Xpert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture, and/or histopathology) for testing of specific non-respiratory specimens (lymph nodes and other tissues) from children suspected of having extra-pulmonary TB.

- Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test in testing cerebrospinal fluid specimens from children suspected of having TB meningitis.

- Interferon-gamma release assays (IGRAs) should not replace the tuberculin skin test (TST) for the diagnosis of latent TB infection in children or for the diagnostic work-up of children (irrespective of HIV status) suspected of TB disease.

- Routine HIV testing should be offered to all patients, including children, diagnosed with TB.

Smear microscopy for AFB can be used as an initial test only when the Xpert MTB/RIF test is not immediately available and for the older children who can expectorate an adequate volume of sputum. Even when sputum smear is AFB negative or microscopy facility is not readily available, an early morning sputum sample should be transported to the nearest laboratory with facilities for Xpert MTB/RIF test and culture for *M. tuberculosis.*

Since most young children swallow the sputum, gastric aspirate or induced sputum may be obtained early in the morning and sent for Xpert MTB/RIF test and culture for *M. tuberculosis.*

Organisation of 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. It can also be done by isolating the bacteria by culture and conducting drug susceptibility testing (DST) using solid or liquid media.

Early detection of drug resistance allows for the use of appropriate treatment regimens for patients. This has an important impact on improved TB control. 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, the development of rapid methods for DST is crucial.

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

Diagnostic facilities available in the country

There is a three tier laboratory network in the country to support the diagnosis of TB and drug resistant TB. The laboratory services at the dzongkhag, regional, and national level are as follows:

- Dzongkhag level/BHU I – microscopy and shipment of sputum for rapid DST at Regional level.
- Regional level – Microscopy, Xpert MTB/RIF testing and shipment of sputum to RCDC for culture and DST.
- National level – Microscopy and Xpert MTB/RIF testing at the Jigme Dorji Wangchuk National Referral Hospital (JDWNRH), and LPA, culture & DST at National Tuberculosis Reference Laboratory (NTRL), RCDC.

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

The collection and transportation of sputum from all screening categories should possibly happen on the same day. The sputum will be transported to the nearest site undertaking the Xpert MTB/RIF testing by the Laboratory technician or a person designated by the hospital In-charge. In case of a delay in transportation, the sample will be kept in cold conditions using a cold-box or a refrigerator. The delay is not expected to be more than 5 days. Standard biohazard packing will be used to pack the samples. All sputum smear positive samples will also be transported in similar manner to the RCDC as was being done before.

The transportation of the sputum specimen will be done preferably using the hospital utility vehicle or ambulance. If this is not possible then another method, such as a courier will be used. However, the decision and the responsibility of transporting the samples as early as possible within the prescribed time frame will lie with hospital administration.

Laboratory technician at the testing site and the TB In-charge will be responsible for ensuring the availability of Xpert MTB/RIF results within 2 days.

After getting results of the first specimen, sputum for RR cases will be collected and transported in a similar manner for both LPA and conventional culture and DST to RCDC if sample was not sent earlier. LPA will be used to determine the sensitivity to Isoniazid; isoniazid to be added to the MDR-TB treatment regimen if MTB is found sensitive to it. For culture only, the turnaround time for results is expected to be not more than 6 weeks (if using liquid culture). If the samples need to be further sub-cultured, it will take around 2-8 weeks in solid after which DST can be performed in liquid. This takes another 2 weeks. All cases started on second line TB treatment will be offered second line DST. To ensure this, TB In-charges will coordinate with treating physicians.

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 laboratory service include:

- **Training and competence assessment of the staf**f - 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 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 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:

o **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 (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

- **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 comprise 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-TB 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 analysing actual and potential defects.

- **Quality indicator monitoring** - provided in table

- **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 No.4: 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
(a) Equipment down time	No equipment downtime leading to service interruption
Turnaround time	
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 No.5: 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 4–8 weeks 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.	2-24 hrs

Laboratory biosafety

Essential measures to be in place and enforced for laboratory biosafety include:

- Appropriate layout of the laboratory in line with the techniques implemented:
  - Containment rooms.
  - Biosafety cabinets.
  - Aerosol-containment centrifuges.
  - Ventilation systems providing directional airflow.
- Effective and specific administrative controls.
  - Standard operating procedures.
  - Waste management procedures.
  - Accident management plans.
  - Health monitoring of the staff.
- Proper practices and procedures for general laboratory safety.
- Personal protective equipment appropriate for the techniques being performed.

Second line DST (SL-DST)

It is expected that at least 60 MDR-TB cases will be enrolled each year. The programme aims to offer SL-DST to all cases initiated on second line treatment. In-country capacity for SL-DST will be developed. However till such capacity is in place, samples will be sent to SNRL Bangkok for SL-DST. In case of resource constraints in sending samples, the following cases will be prioritised for SL-DST:

- Patients having history of prior use of SLDs specifically fluoroquinolones or injectables.
- History of contact with known or suspected XDR-TB cases.
- Migrant workers and bridge population (those nationals who have possibly contracted MDR-TB outside the country during a recent visit to neighbouring countries).

CHAPTER 5

Treating a Case of Tuberculosis

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

Aims of treatment

The aims of treating TB are:

- To cure the patient of TB.
- To prevent death from active TB or its late effects.
- To prevent relapse of TB.
- To decrease transmission of TB to others.
- To prevent the development of acquired drug resistance.

Basic Principles of TB treatment

The basic principles of good TB treatment are:

- Right combination of drugs to kill different bacterial populations.
- Drugs are given for the right duration (several months) to kill the bacilli.
- Drugs are given in the right dosages to achieve therapeutic but not toxic effect.

Previously treated TB patients

At the time of registration, each patient meeting the case definition is also classified according to whether or not he or she has previously received TB treatment, and if so, what the outcome was (if known). It is important to identify as previously treated TB patients are at increased risk of drug resistance including MDR-TB. At the start of therapy, specimens should be obtained for Xpert MTB/RIF, culture and DST from all previously treated TB patients.

Treatment depends on whether the patient has relapsed or is returning after default or prior treatment has failed. The distinctions between new and previously treated patients, and among the subgroups of previously treated patients, are also essential for monitoring the TB epidemic and programme performance.

New patients may have positive or negative bacteriology and may have the disease at any anatomical site.

Previously treated patients are further classified by the outcome of their most recent course of treatment.

Patients whose sputum is smear positive at the end of (or returning from) a second or subsequent course of treatment are classified by the outcome of their most recent treatment course: relapsed, loss to follow-up or failed.

Fixed-dose combinations (FDCs)

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

a) Prescription errors are likely to occur less frequently because dosage recommendations are more straightforward and adjustment of dosage according to patient weight is easier.
b) The number of tablets to ingest is smaller and may thus encourage patient's adherence. A new TB patient of 35-54 kg bodyweight has to take three tablets of 4-FDC daily during the intensive phase of treatment.
c) Drug resistance is less likely to occur; patients swallow all drugs and cannot skip any particular drug.

FDCs have the disadvantage that if severe side-effects occur, all drugs have to be stopped and the patient has to continue treatment with single drugs, excluding the drug(s) which might be responsible for the side-effect.

In order to manage side effects, 5% of single drugs will be supplied together with FDCs.

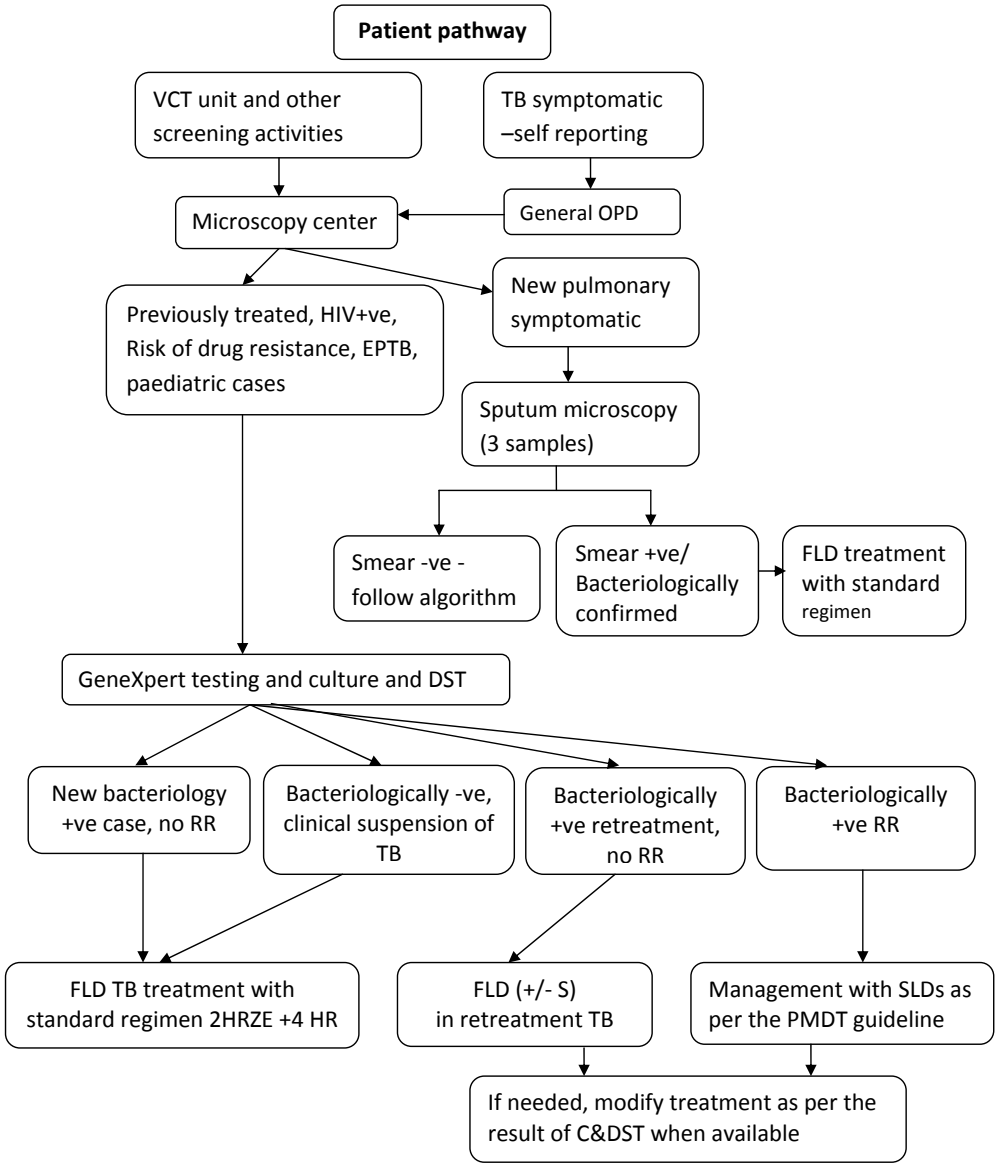
Standardized Regimens

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

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

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

Figure 3: Algorithm for diagnosis and treatment



Treatment phases

Effective chemotherapy consists of two phases:

(a) The intensive phase administered daily for two months in new cases and three months in re-treatment cases. The aim of this phase is to rapidly reduce and eliminate the multiplying bacilli without allowing the development of acquired resistance to the prescribed drugs. The infectious patients quickly become non-infectious (within approximately two weeks).

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

Table No.6: Case definitions, Treatment Categories and Recommended Regimens

Case Definition	Treatment Category	Treatment Regimen	
		Intensive Phase	Continuation Phase
New cases • Pulmonary • Extra pulmonary TB	New	2 (HRZE)	4 (HR)
Previously treated cases without drug resistance • Relapse • Treatment after failure • Treatment after loss to follow up • Other previously treated cases	Retreatment*	3 (HRZE) Add S for 2 months if there is perceived risk of mono/poly resistance	5 (HRE)

* Sputum specimen from all retreatment cases would be subjected to Xpert MTB/RIF testing and would simultaneously be sent for Culture and DST (C & DST). In case the results of Xpert MTB/RIF are reported MTB positive/rifampicin resistance (RR) not detected, and the clinician decides to initiate the patient on TB treatment, standard first line anti-TB drugs HRZE on IP and HR in CP should be administered. *However, where the treating Physician considers the risk of having drug resistance as high (e.g. repeated treatment interruption, treatment failure of first line drugs), Streptomycin may be added to the first line regimen for initial two months of treatment while awaiting results of complete DST.* The regimen may be modified again as per the drug sensitivity pattern after the results of C & DST are obtained. Medical experts or chest physician may consider adding FQ in accordance with PMDT guidelines specifically when resistance to Isoniazid is being suspected. In case the results of Xpert MTB/RIF are reported MTB positive/ RR detected or there is any drug resistance found on C & DST, then the algorithm as per the PMDT guidelines needs to be followed under the guidance of experts.

Table No.7: Number of FDC tablets used in TB treatment in adults according to body weight

	Body weight (kg)***			
Treatment regimen	<35	35-54	>55	Duration of treatment
New Patients				
Intensive phase-daily HRZE tablet (4FDC)	2	3	4	2 months
Continuation phase-daily HR tablet (2FDC)	2	3	4	4 months
Previously treated patients*				
Intensive phase – daily				
HRZE tablet (4FDC)	2	3	4	3 months
Streptomycin** im	0.5g	0.75g	1g	2 months
Continuation phase-daily HRE tablet (3FDC)	2	3	4	5 months

**For retreatment cases, the use of additional drugs like Streptomycin would be added depending on history, risk assessment (treatment failure and repeated treatment interruption) and available DST reports. If there is documented resistance to any drug/s PMDT guidelines should be followed*

***Patients over 60 years, the dose of streptomycin is 0.5 g, irrespective of the weight*

**** For patients over 70 kg bodyweight, additional 400 mg Pyrazinamide may be added by the clinician in the intensive phase. Change the number of drugs if the weight band changes overtime.*

For weight based dosing of individual drugs see annexure 2.

In certain cases duration of treatment may be longer than usual. In spinal TB, TB meningitis and severe disseminated TB, treatment is for a minimum of one year. However, decision for the duration of treatment including extending treatment duration lies with the treating physicians.

FDC tablets are composed as follows:

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

Start of treatment

Treatment should be started as soon as possible after a confirmed diagnosis has been made. The treating doctor should categorize the patient. The TB in-charge should fill in the treatment card and TB register. They should also maintain other documents related to the diagnosis of the patients. After the confirmation of diagnosis, treatment will be started at the health facility. Bacteriologically positive pulmonary TB cases are encouraged to be admitted for around 2 weeks in isolation ward and remaining part of the treatment will be followed-up by the designated DOT provider.

Clinically diagnosed pulmonary and extra-pulmonary cases will continue their treatment at hospitals/BHUs/ and by the designated DOT provider. The TB in-charge should review and cross check the TB register weekly with the laboratory register to ensure that all patients diagnosed in the laboratory are registered and enrolled for treatment. Patients who are bacteriologically confirmed TB cases, according to the laboratory register, but did not begin treatment should be traced immediately after the laboratory results are available. For effective tracing of patients, proper address and contact numbers should be noted in the laboratory register during the first visit.

Treatment regimens in special situations

The treatment of TB in pregnancy and breast feeding, liver disorders, and renal failure is discussed below.

Pregnancy and breast feeding

Women of childbearing age should be asked about current or planned pregnancy before starting TB treatment. A pregnant woman should be advised that successful treatment of TB with the standard regimen is important for a successful pregnancy outcome. With the exception of streptomycin, the first line anti-TB drugs are safe for use in pregnancy. Streptomycin, however, is ototoxic to the foetus and should not be used during pregnancy.

A breast feeding woman who has TB should receive a full course of TB treatment. Timely and properly applied chemotherapy is the best way to prevent transmission of tubercle bacilli to the baby. Mother and baby should possibly be isolated, however the baby should continue to breast feed. After active TB in the baby has been ruled out, the baby should be given 6 months of isoniazid preventive therapy, followed by a BCG vaccination. Mother should use face mask while breast feeding and breast feed in a well ventilated room. Pyridoxine supplementation is recommended for all pregnant or breast feeding women taking isoniazid.

Management of newborns born to mother with TB during pregnancy and/ or in close contact with Tuberculosis in neonatal period

Newborns may acquire tuberculosis by the following means:

1. Trans-placental spread through the umbilical vein to the fetal liver
2. Aspiration or ingestion of infected amniotic fluid
3. Airborne inoculation from the close contacts (family members or nursing personnel)

Therefore all newborns that were exposed to tuberculosis during pregnancy should be screened for active tuberculosis. This will include neonates born to mother with pulmonary TB (both sputum positive or negative) or disseminated TB, to mother treated or untreated, and to mother with or without current ATT drugs. All newborns in close contact with a person with sputum positive TB during must also be screened for active tuberculosis.

The following are the screening tests to be done in any neonates born to mother with TB:

1. Chest Xray
2. Mantoux test (PPD)
3. Ultrasound of liver and spleen
4. Gastric aspirate for AFB and culture (3 samples)
5. Gene Xpert (in one gastric aspirate sample) if there is any high risk of transmission:
    a. Mother with disseminated TB during pregnancy
    b. Mother with extrapulmonary TB (except TB lymph node and Pleural TB) during pregnancy
    c. Mother has received ATT for < 2 weeks before delivery
    d. No negative sputum report at delivery
    e. Close post natal contact with sputum positive.

Isoniazid (INH) Prophylaxis:

1. Whom to give prophylaxis? To any of the following two scenarios:
    a. Asymptomatic newborn with any high risk of transmission and all above screening tests for active TB negative
    b. Asymptomatic newborn with positive PPD and rest of the above screening tests for active tuberculosis negative.
2. Dose of INH: 10mg/kg/day, once daily (range 10-15mg/kg/day)
3. When to start on INH? : Start after getting all the reports on above tests (except culture)
4. Duration of INH prophylaxis: Six months

5. Pyridoxine: any neonates on INH prophylaxis, should receive supplemental pyridoxine of 1mg/kg/day once a day

If mother/contact has resistant TB:

1) INH resistant: give Rifampicin (10-15mg/kg/day) for 6 months.
2) Rifampicin resistant: give INH until culture results are known.
3) MDR-TB: no prophylaxis and ensure close clinical follow-up.

BCG Vaccine:

BCG vaccination should be given at birth even if INH prophylaxis is planned, once active TB at birth has been ruled out.

Breast feeding:

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

Isolation

Isolate newborn as much as possible while admitted in hospital during investigations as congenital TB is highly infectious and family attendants may be contagious if active TB has not been ruled out yet.

Follow up

Follow up with doctor at 3 weeks, 6 weeks and then every month for clinical assessment till completion of INH prophylaxis to rule out signs and symptoms of active TB.

Placental examination

If tuberculosis is suspected or confirmed, please examine placenta, send for microscopy, histology and culture in the nearest referral hospital.

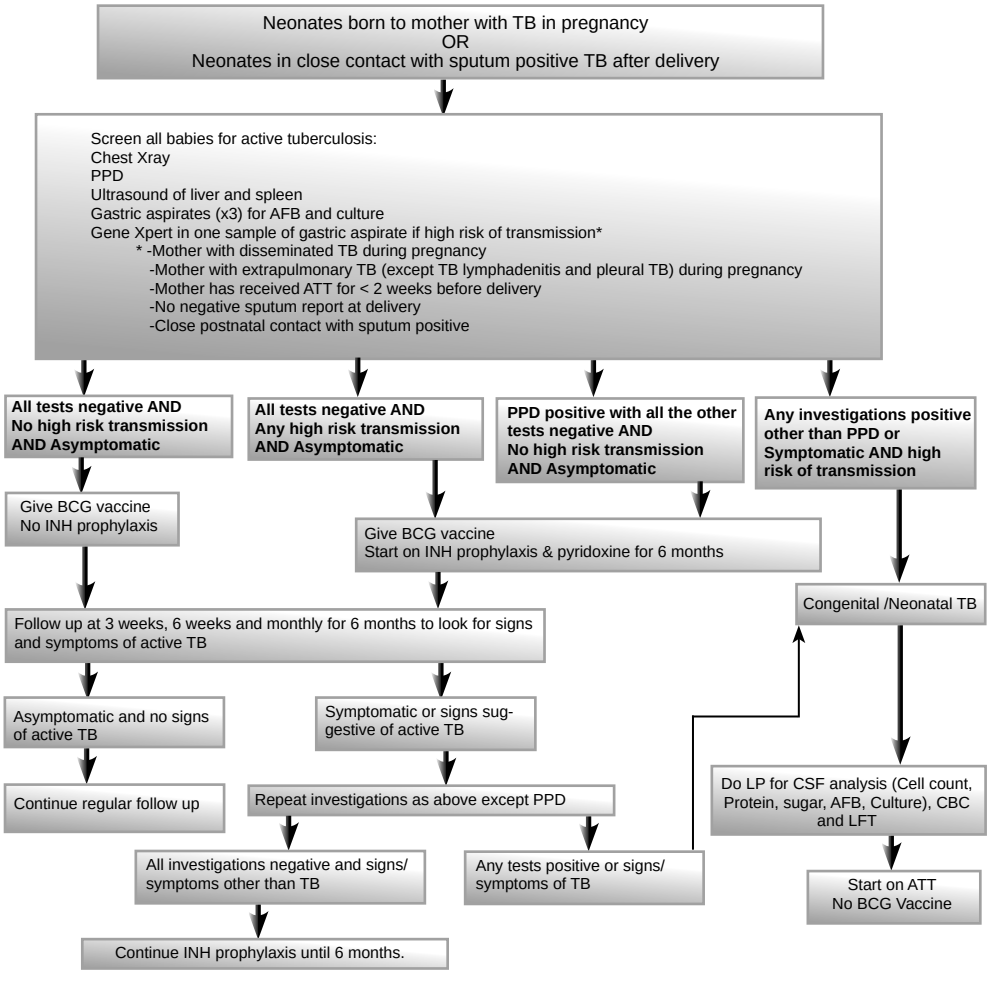
Management of neonate with active tuberculosis (Congenital/Neonatal tuberculosis)

The clinical presentation of congenital/neonatal tuberculosis is nonspecific but is usually marked by multiple organ involvement. Active TB develops between 2 and end of 4 weeks of age. The neonate may look acutely or chronically ill and will present with non-specific symptoms such as fever, lethargy,

respiratory distress or non-responsive pneumonia, hepatosplenomegaly, or failure to thrive.

If TB is confirmed or neonate is symptomatic, suggestive of TB a complete course of TB treatment must be given. Any above investigations other than PPD are positive, do lumbar puncture for CSF analysis to rule out tubercular meningitis, CBC and LFT prior to ATT therapy.
Start on ATT with standard 2HRZE/4HR regime.
If it is TB meningitis, start on steroid at 2mg/kg/day for 4 weeks and taper over 2 weeks (1mg/kg/day for 1 week and 0.5mg/kg/day for another week and stop) and ATT (2HRZE followed by 7 to 10 months of HR).

Approach algorithm of neonates born to mother with TB in pregnancy and in close contact with active TB during neonatal period



Liver disorders

Patients with the following conditions can receive the usual TB regimens provided that there is no clinical evidence of chronic liver disease, hepatitis virus carriage, a past history of acute hepatitis, or current excessive alcohol consumption. Hepatotoxic reactions to anti-TB drugs may be more common among these patients and should therefore be anticipated.

In patients with unstable or advanced liver disease, liver function tests should be done at the start of treatment, if possible. The following regimens should be considered if the serum alanine aminotransferase level is more than 3 times normal before the initiation of treatment. The more unstable or severe the liver disease, the fewer hepatotoxic drugs should be used.

Note that TB itself may involve the liver and cause abnormal liver function.

It may be possible to defer TB treatment until the acute hepatitis has resolved in some cases of concurrent acute (i.e. viral) hepatitis not related to TB or TB treatment.

Possible regimens include:

- Two hepatotoxic drugs (rather than the three in the standard regimen):
- 9 months of isoniazid and rifampicin, plus ethambutol (until or unless isoniazid susceptibility is documented).
- 2 months of isoniazid, rifampicin, streptomycin and ethambutol, followed by 6 months of isoniazid and rifampicin.
- 6–9 months of rifampicin, pyrazinamide and ethambutol.
- One hepatotoxic drug:
- 2 months of isoniazid, ethambutol and streptomycin, followed by 10 months of isoniazid and ethambutol.
- No hepatotoxic drugs:
- 18-24 months of streptomycin, ethambutol and a fluoroquinolone.
- (note: streptomycin is also for a minimum of 18 months)

Expert consultation is advised in treating patients with advanced or unstable liver disease.

Clinical monitoring (and liver function tests, if possible) should be performed during treatment of all patients with pre-existing liver disease.

Renal failure and severe renal insufficiency

The recommended initial TB treatment regimen for patients with renal failure or severe renal insufficiency is 2 months of isoniazid, rifampicin, pyrazinamide

and ethambutol, followed by 4 months of isoniazid and rifampicin. No change in dosing is necessary because Isoniazid and ri¬fampicin are eliminated by biliary excretion. There is significant renal excretion of ethambutol and metabolites of pyrazinamide, and therefore doses should be adjusted. It is recommended that pyrazinamide at 25 mg/kg and ethambutol at 15 mg/kg is administered three times a week.

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

Streptomycin should be avoided in patients with renal failure because of an increased risk of nephrotoxicity and ototoxicity. If streptomycin must be used, the dosage is 15 mg/kg, two or three times per week, to a maximum of 1 gram per dose.

Management of TB in children

The basic principles for management of TB in children remain the same as those in adults. The first line drugs are similar and the duration of therapy in the intensive and the continuation phase also remain the same. The children on treatment must have rigorous monitoring and care in terms of dosage.

New Paediatric FDC formulations

HRZ - isoniazid 50mg + rifampicin 75mg + pyrazinamide 150mg
HR - isoniazid 50mg + rifampicin 75mg

The child-friendly fixed dose combinations offer the following advantages:

- Correct, WHO-recommended dose – no need for breaking, crushing or chopping of tablets
- Quickly dispersible in liquid - easy for children of all ages to take
- Palatable flavours
- Expected to improve treatment adherence and outcomes

Table No.8: Paediatric formulation fixed dose combination drugs dosages according to the body weight.

	Weight (Kg)*				
	4- 7	8-11	12-15	16-24	>25
Intensive phase – daily					
HRZ(E) (50mg +75 mg + 150 mg) +(100mg)	1	2	3	4	
	Ethambutol should be added in the intensive phase for children with extensive disease or living in settings where the prevalence of HIV or of isoniazid resistance is high				Use adult formulation
Continuation phase – daily					
HR (50 mg +75 mg)	1	2	3	4	

*** rounded off to nearest Kg**

For weight based dosing of individual drugs see annexure 3.

CHAPTER 6

Management of Adverse Drug Effects

First line anti-TB drugs are generally considered safe. Most TB patients complete their treatment without any significant adverse drugs effects. A few patients, however, experience adverse effects although most of them are minor. Occasionally patients discontinue treatment due to major or even minor adverse effects. For this reason it is important that patients are clinically monitored during the treatment so that adverse effects can be detected promptly and managed properly. Routine laboratory monitoring is not necessary.

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

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

Table No.9: Symptom based management of side-effects of Anti-TB drugs

Side-effects	Drug(s) responsible	Management
MINOR SIDE-EFFECTS - CONTINUE DRUGS		
1. Anorexia, nausea, abdominal pain	Rifampicin, INH, Pyrazinamide	Give drugs with small meals or last thing at night. If patient doesn't get better, exclude hepatitis.
2. Joint pain	Pyrazinamide	Give paracetamol or Aspirin/NSAIDs like ibuprofen
3. Burning, numbness or tingling sensation in the hands or feet	Isoniazid	Pyridoxine 50-75 mg daily*.
4. Orange/red urine	Rifampicin	Reassurance
5. Minor rash with itching	Any drug	Anti-histamines like cetrizine, promethazine

MAJOR SIDE-EFFECTS - STOP DRUGS RESPONSIBLE REFER FOR EVALUATION		
1. Itching of skin, severe rash	Any drug	Stop anti-TB drugs
2. Deafness	Streptomycin	Stop streptomycin
3. Dizziness, vertigo, nystagmus	Streptomycin	Stop streptomycin
4. Nausea , vomiting, deterioration of appetite +/-Jaundice (other causes of hepatitis excluded)	INH, Rifampicin and Pyrazinamide	Stop anti-TB drugs. Perform liver function test
5. Visual impairment	Ethambutol	Stop ethambutol
6. Shock, purpura, acute renal failure, haemolytic anaemia	Rifampicin	Stop rifampicin **(Never give again)**

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

Management of Hepatitis

- Most anti-TB drugs can damage the liver. The most commonly responsible ones are Isoniazid, pyrazinamide and rifampicin.
- When a patient develops hepatitis during anti-TB treatment, it is important to rule out other possible causes of hepatitis before deciding that the hepatitis is drug-induced.
- Mild transient increases in serum transaminases may occur during the initial treatment of TB. This rise is not more than 2-3 folds the normal rise. This subsequently falls to normal levels despite the continuation of anti-TB drugs. Provided serum bilirubin level remains normal, an elevated transaminase level is not an indication to stop anti-TB drugs.
- Pre-treatment baseline liver function tests (LFTs) should ideally be done in all patients. Since this may not be practical, the test should at least be done on those who are at a higher risk of developing drug-induced hepatitis e.g. known chronic alcoholics, pre-existing liver disease, pregnant mothers, elderly, and severely ill patients.
- Liver function tests should be performed when patient is having symptoms & signs suggestive of hepatitis. i.e. nausea, vomiting with or without icterus or hepatomegaly.

- If drug-induced hepatitis is diagnosed, all anti-TB drugs should be stopped and patient may need admission to a hospital for supportive treatment. Repeat the liver function tests after 1-2 weeks.

- Anti TB drugs should be re-introduced once liver function tests come back to normal. This should be done sequentially in the order of rifampicin, isoniazid and pyrazinamide with daily monitoring of the patient's clinical condition and at least weekly monitoring of LFT (see below). Re-introduction of rifampicin, isoniazid, and pyrazinamide can be done under streptomycin and ethambutol cover. In patients who have experienced jaundice, it is advisable to avoid pyrazinamide.

- It may be possible to completely withdraw anti TB drugs in patients with TB lymphadenitis, TB pleural effusion, sputum negative PTB with limited lung involvement and who are not very ill. Sometimes tuberculosis disease is so severe that all anti TB drugs cannot be withdrawn. In such situations, patient should be treated with two of the least hepatotoxic drugs, i.e., streptomycin and ethambutol (provided the patient is not allergic to these drugs), until the LFTs come back to normal. However, because ethambutol and streptomycin is a weak combination, it may not be adequate for a severely ill patient. In such a situation alternatives are:

    1. Streptomycin, INH, and ethambutol – when serum bilirubin is high but transaminases are normal.

    2. Streptomycin, ethambutol, and quinolone (ofloxacin/ levofloxacin) when both serum bilirubin and transaminases are high. Consultant Respiratory Physician's advice should be sought in such a situation. Streptomycin will continue for a minimum of 18 months while using regimen of streptomycin, ethambutol and a floroquinolone.

- Once LFTs return to normal, doses of the original drugs can be reintroduced sequentially in the order of rifampicin, isoniazid and pyrazinamide. There should be daily monitoring of the patient's clinical condition and at least weekly monitoring of LFTs. If symptoms recur early, LFTs should be repeated before one week. Rifampicin should be introduced initially at 75 mg/day increasing to reach the maximum dose in 3-4 days. If there are no complaints, isoniazid should be added at 50 mg/day and the dose should increase sequentially to reach the

full dose in 3-4 days. If the patient tolerates both drugs pyrazinamide should be added in the same way - starting with a dose of 250 mg/day.

- If there is no further reaction, standard chemotherapy can be continued and any alternative drugs that had been temporarily introduced can then be withdrawn.

- If the patient complains of a recurrence of symptoms suggestive of hepatitis during this procedure, LFTs should be repeated, and if found to be abnormal the most recently added drug should be withdrawn. It may not be possible to reintroduce it. A suitable alternative drug regimen should be used on the advice of and under the supervision of a Chest Physician or Medical Specialist in case the standard treatment cannot be recommenced. If both rifampicin and pyrazinamide need to be excluded from the regimen, the option is to give 2SHE/10HE. In case pyrazinamide alone is to be excluded, the option is 2HRE/7HR. In case INH is to be excluded, the option is to give a regimen of 2RZE followed by RE for 6-8 months.

Generally, anti-TB drug induced hepatitis almost always occurs during the first 6-8 weeks of treatment but standard treatment can be recommenced in most patients.

CHAPTER 7
Management of TB with Co-morbidities

TB-HIV co-infection

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

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

Features of HIV related TB

TB usually occurs earlier in the course of HIV infection compared to other opportunistic infections associated with HIV. It may, however, occur at any stage of HIV infection as the result of a rapid progression of a recently acquired or latent infection. Among HIV infected people, TB infection results in a transient drop in CD4 count and a progression of the HIV infection.

As the HIV infection progresses, the CD4 lymphocyte count declines and the immune system is less efficient in preventing the growth and spread of M. tuberculosis. As a result, disseminated and extra-pulmonary disease is more common in HIV positive patients than in HIV negative patients. Nevertheless, pulmonary TB is still the most common form of TB seen in HIV infected patients, with or without concomitant extra-pulmonary TB.

Pulmonary TB

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

Table No.10: Features of PTB in HIV infection depending on the stage

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

Diagnosis

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

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

If TB is suspected in HIV infected people, their sputum should preferably be tested using Xpert MTB/RIF and followed by C & DST. If Xpert is not available, smear microscopy may be performed. Other investigations include chest-x ray, tissue biopsy, aspirations from suspected extra-pulmonary sites for cytology, histology, direct smear, and culture for *mycobacteria* and Xpert MTB/RIF.

Important points to remember in the treatment of HIV associated TB

- In a TB/HIV co-infection, the priority is to treat TB. Current WHO guidelines recommend that TB treatment should be commenced first and ART commenced within the first 8 weeks of starting anti-TB treatment. ART should be commenced within two weeks in the case of severe immunosuppression (CD4<50) and in very ill patients.

- Generally, anti-TB treatment in HIV positive patients is the same as for HIV negative TB patients.

- It is important that these patients receive Directly Observed Treatment. (DOT). To maintain confidentiality, HIV status need not be divulged to the DOT provider. Effective treatment using quality drugs under observation can cure TB, prevent the spread of the disease, and prolong the life of HIV patients.

- It is more common for adverse reactions to occur in HIV positive patients due to anti-TB drugs and for drug interactions to occur between anti-TB and anti-retroviral drugs.
- When patients on anti-TB drugs are started on anti-retroviral drugs paradoxical exacerbation of symptoms, signs, and radiographic manifestations of TB may be seen. This is known as Immune Reconstitution Inflammatory Syndrome (IRIS).
- The rate of recurrence of TB after completion of treatment is higher in HIV positive patients than in HIV negative TB patients.
- The case fatality rate is higher in HIV positive TB patients than in HIV negative TB patients. The excess deaths in TB/HIV patients are partly due to the tuberculosis disease itself and partly due to other HIV related problems.
- Bearing in mind the higher rates of morbidity and mortality in cases of co-infection, all HIV positive cases should undergo Xpert MTB/RIF for detection of TB disease and resistance to Rifampicin on relevant biological specimens.

Screening of TB patients for HIV

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

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

ART should be started in HIV positive child with active TB disease as soon as possible and within eight weeks of the initiation of anti-tuberculosis treatment regardless of the CD4 count.

Screening of HIV patients for TB

All HIV infected patients should be screened for TB at the time of the diagnosis and whenever it is suspected. Using the standard referral form patients are referred from HIV Clinics to the Microscopy Centre/Xpert testing centre for

this purpose. For those patients who are found to have tuberculous disease, anti-TB treatment should be commenced immediately. All HIV positive cases should undergo Xpert MTB/RIF as an initial test to detect TB disease and resistance to Rifampicin.

HIV patients who are already on ART and diagnosed subsequently with TB may need a change in ART regimen when they start anti-TB drugs. When such a situation arises, close consultation between the VCT/HIV treatment and care unit, TB In-charge, and the medical officer should take place. Modifications of treatment may be required as per the HIV/ART guidelines in place.

TB treatment and anti-retroviral therapy (ART)

Rifampicin stimulates the activity of cytochrome P450 which metabolizes protease inhibitors (PIs) e.g. saquinavir, ritonavir, indinavir, nelfinavir, amprenavir) and non-nucleoside reverse transcriptase inhibitors (NNRTI), except for efavirenz (EFV). PIs and NNRTIs also enhance or inhibit the same enzyme system and this may result in decreased blood levels of rifampicin and the anti-retrovirals resulting in both being ineffective. The preferred ART regimen is Tenofovir + Lamivudine or Emtricitabine + Efavirenz (TDF + 3TC (or FTC) + EFV). In case of suspected drug interaction or a special situation, the case should be jointly reviewed by the TB and HIV programmes.

To strengthen collaborations, the following activities will be undertaken

- Joint review of the programmes at National and sub-national level twice a year.
- TB training modules will have a section on TB-HIV co-infection and vice-versa. The training on relevant section will be held in coordination with both programmes.
- Both programmes will plan joint supervisory visits, once a year from the national level and twice a year at the dzongkhag level.

Tuberculosis and Diabetes

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

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

Cross-referral between the two programmes will be strengthened and jointly monitored. TB patients should be referred for diabetes evaluations and diabetes patients should be evaluated for symptoms of TB.

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

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

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

Tuberculosis and liver disease

This section covers TB treatment in patients with pre-existing liver disease. See chapter 6 for detection and management of TB drug induced hepatitis. Prior to commencement of ATT, LFT (serum bilirubin, SGPT) should be done on all patients with a history of liver disease (including patients who abuse alcohol, carriers of the hepatitis virus, past history of acute/chronic hepatitis, alcoholic/non-alcoholic cirrhosis, and a fatty liver). Provided there is no clinical and bio chemical evidence of liver function impairment, patients can receive the usual TB regimens. However, hepatotoxicity to anti-tuberculosis drugs may be more common among patients with liver function impairment and should therefore be anticipated.

If pre-treatment serum bilirubin and SGPT are abnormal, such patients should be managed as per guidelines for anti-TB drug induced hepatotoxicity given in chapter 6.

Tuberculosis and Renal insufficiency

For patients with renal failure or severe renal insufficiency, the recommended initial TB treatment regimen is two months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampicin. No change in dosing is necessary for isoniazid and rifampicin as they are eliminated by biliary excretion. Ethambutol and metabolites of pyrazinamide have significant renal excretion and thus, dosing adjustments are required.

Because of an increased risk of nephrotoxicity and ototoxicity, streptomycin should be avoided in patients with renal failure. For details see treatment regimens in special situations (chapter 5). To avoid premature drug removal, treatment can be given immediately after haemodialysis. With this strategy there is a possible risk of raised ethambutol and pyrazinamide drug levels between dialysis sessions. Alternatively, treatment can be given 4–6 h before dialysis, increasing the possibility of premature drug removal but reducing possible ethambutol or pyrazinamide toxicity. The choice of strategy may be influenced by a need to ensure adherence (when post dialysis offers the opportunity for directly observed therapy), practical issues (post dialysis for morning shift patients), and expected pharmacokinetics or drug interactions.

Rifampicin in particular can interact with immunosuppressive regimens, increasing the chance of graft rejection. Doses of mycophenolate mofetil, tacrolimus, and cyclosporine may therefore need adjustment. Corticosteroid doses should be doubled in patients of renal allograft recipient receiving rifampicin on immunosuppressive regimens.

Important drug interactions

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

Commonly used drugs affected by rifampicin

Rifampicin substantially decreases the concentrations of certain drugs. They are:

- Anti-infectives (including certain antiretroviral drugs): mefloquine, antifungal agents, clarithromycin, erythromycin, doxycycline, atovaquone, chloramphenicol.

- Hormone therapy including ethinylestradiol, norethindrone, tamoxifen, and levothyroxine.
- Methadone.
- Warfarin.
- Cyclosporine.
- Corticosteroids.
- Anticonvulsants (including phenytoin).
- Cardiovascular agents including digoxin (among patients with renal insufficiency), verapamil, nifedipine, diltiazem, propranolol, metoprolol, enalapril, losartan, quinidine, mexilitine, tocainide, propafenone.
- Theophylline.
- Sulfonylurea.
- Hypolipidemics including simvastatin and fluvastatin.
- Nortriptyline, haloperidol, quetiapine, benzodiazepines (diazepam, triazolam, zolpidem, buspirone).

Pulmonary and extra-pulmonary disease should be treated with the same regimens. As per the WHO guidelines for the treatment of TB, some experts recommend 12 months of treatment for TB meningitis because of the serious risk of disability and mortality, and minimum of 12 months of treatment for TB of bones or joints because of the difficulties related to assessing treatment response. Unless drug resistance is suspected, adjuvant corticosteroid treatment is recommended for TB meningitis and pericarditis. In tuberculous meningitis, ethambutol should be replaced by streptomycin. Surgery plays little role in the treatment of extra-pulmonary TB except for it's requirement for diagnosis. Surgery is reserved for the management of late complications of the disease such as hydrocephalus, obstructive uropathy, constrictive pericarditis, and neurological involvement from Pott’s disease (spinal TB). For large fluctuant tense lymph nodes aspiration, incision or drainage appear beneficial.

CHAPTER 8

Patient Centred Care and Treatment Adherence

Patient adherence to treatment is a key factor in treatment success. For various reasons a proportion of patients stop treatment before completion. However, strict adherence to treatment should be ensured to cure the patients and to prevent the development of drug-resistant TB. Directly observed treatment (DOT) is a very important component in the internationally recommended policy package for TB control. DOT means that an observer watches the patient swallow their drugs. This is essential for the completion of treatment and recovery from TB. DOT ensures that the patient takes the right anti-TB drugs, in the right doses, at the right intervals and for the right time period. All patients, irrespective of their treatment category, should receive all doses of the anti-TB drugs under DOT.

Ambulatory versus hospital treatment

Over 95% of the TB patients can be treated using ambulatory care. Hospitalization itself has little or no effect on the outcome of the treatment except in severe forms of tuberculosis. However, all sputum positive patients are encouraged to be admitted for at least two weeks to allow for monitoring of side effects, patient education and DOT awareness. Longer hospitalization may be necessary if the patient cannot receive ambulatory treatment under direct observation. In-patient treatment may also be necessary (often only for a short period) for severely ill patients, e.g. spontaneous pneumothorax (air in the inter-pleural space resulting in collapse of the lung) or for those with other associated serious diseases.

DOT providers

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

Medical officer, TB in-charge in consultation with local health workers and along with patients should identify the DOT provider. The name and address of the DOT provider should be recorded on the patient's treatment card. The DOT provider should be mutually acceptable, accessible to the patient and should agree to be accountable to the health system.

The medical officer or TB in-charge has to ensure that the DOT provider receives the filled-in copy of the Treatment Card and the patient's card.

Drug supplies to DOT providers

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

Regularity of treatment

DOT providers should make sure that the patients swallow the drugs according to prescription. They should trace absentees and prevent patients from becoming defaulters.

If a patient misses a dose of the treatment he/she must be traced immediately to resume DOT without delay. To ensure easy tracing of patients, the detailed address should be filled in the Tuberculosis Treatment Card and TB Register. Mobile number of the patient should be included if available.

Addressing social determinants of TB

People with TB and their households often face severe economic hardship related to the direct and indirect costs of illness and health care such as income loss, health-care costs and transport expenses. Adverse social consequences may include stigmatization and social isolation, interruption of studies, loss of employment or divorce. These negative consequences often extend to the family of individuals ill with TB and indirectly to the wider community. This can create a negative economic impact on the whole society. Even when TB diagnosis and treatment are offered free of charge, social protection measures are needed to alleviate the burden of income loss and non-medical costs of seeking and staying in care. Social protection should cover the special needs associated with TB through the following policies:

- Legislation to protect people with TB from discrimination such as expulsion from workplaces, educational institutions, health institutions, transport systems, housing or deportation
- Other instruments to protect and promote human rights including addressing stigma with special attention to gender, ethnicity and protection of vulnerable groups

Poverty is a powerful determinant of TB. Crowded, polluted, and poorly ventilated living and working environments are direct risk factors for TB transmission. Malnutrition is an important risk factor for developing the active disease. Poverty is also associated with poor general health knowledge and a lack of empowerment to act on that knowledge. This could lead to the exposure of several TB risk factors such as HIV, smoking and alcohol abuse. Poverty alleviation reduces the prospect of TB transmission and progression from infection to disease. It also helps improve access to health services and adherence to the recommended treatment. Actions on the determinants of ill health through "health-in-all-policies" approaches will benefit TB care and prevention.

The required social, economic, and public health policies include those that:

- Pursue overarching poverty reduction strategies and expanded social protection.
- Reduce food insecurity.
- Improve living conditions, including in prisons and other congregate settings
- Improve environment and working conditions, including reduced exposure to silica and indoor air pollution.
- Address the social, financial, and health situation of migrants.
- Promote healthy diets and lifestyles, including reduction of smoking and harmful use of alcohol and drugs.

Nutrition support

Nutritional status is often poor in patients suffering from Tuberculosis. The wasting commonly found in patients with active TB is most likely the result of a combination of factors. These include a decreased appetite, a diminished food intake and increased losses and altered metabolism associated with the inflammatory and immune response.

TB's effect on the nutritional status of an individual are severe weight loss (loss of lean and fat mass), altered protein metabolism, micronutrient deficiencies (such as Vitamins A, D, E, C, minerals like zinc and selenium) and anaemia. Good nutritional status has an impact on a patient's "quality of life" and their ability to return back to normal life.

This guideline provides a protocol that can easily be followed by health staff in the provision of outpatient and inpatient care to the patients for the effective treatment of acute malnutrition. This guideline will help to improve the case management and outcome among patients.

Nutritional support includes the following components:

(a) Nutritional assessment to determine nutritional status and necessary referrals or intervention.
(b) Nutrition education and counselling on symptom-management and improved dietary intake during and after TB treatment.
(c) Targeted micronutrient supplementation (e.g., vitamin B6).
(d) Food support for treatment of malnutrition in TB patients.

Nutritional assessment to determine nutritional status and necessary referrals or intervention

Nutrition screening of TB patients

i. Take the weight and height of all patients except in pregnant women on the first visit.
ii. Calculate the Body Mass Index (BMI).
BMI = Weight in kgs/(height in meters)2.
iii. Determine the nutritional status of the adult male, non pregnant women as follows:

Classification	BMI (kg/m2) Principal cut-off points
Severe under nutrition	< 16.0
Moderate under nutrition	16.0-16.99
Mild under nutrition	17.0-18.49
Normal	18.5-24.9
Overweight or obese	>=25.0

iv. In children between 5-18 years use the BMI for age and sex charts to determine the nutritional status and for children below 5 years the weight for height growth chart provided by the Ministry of Health.
v. If weight and height can not be measured (e.g- elderly with kyphosis) and in pregnant women, measure Mid Upper Arm Circumference (MUAC) to determine the current nutritional status.
a. MUAC < 19cm - Severe Undernutrition.
b. MUAC 19-21.9cm - Moderate Undernutrition.

Treatment plan:

It depends on the current nutritional status. Nutrition supplements and special diet are recommended in consultation with a nutrition specialist in cases with moderate to severe undernutrition.

Tobacco Smoking and Tuberculosis:

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

For further details on tobacco cessation please refer to the national tobacco cessation guidelines.

CHAPTER 9
Monitoring Treatment

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

New pulmonary TB (PTB) patients

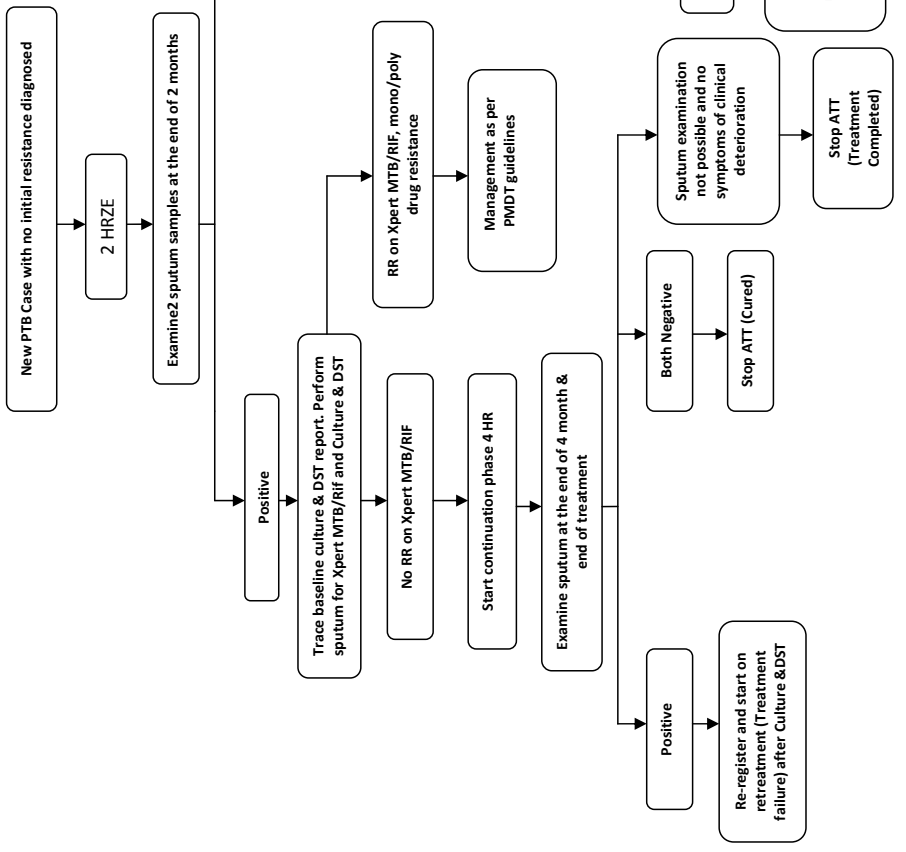
- Sputum examination should be done after 2 months of completing the intensive phase. If the smear is positive, confirm patient's compliance to treatment and trace report of culture and DST sent at baseline. If results of DST are not available, shift the treatment to continuation phase. Perform Xpert MTB/RIF test as well as culture and DST examination on sputum. The cultures should be tested both for DST and using LPA.

- To document the cure, a follow-up sputum examination should be done at the end of 4th month and on treatment completion or during the last month (6th month). Positive sputum at any stage during the treatment should call for Xpert MTB/RIF tests and Culture and DST to rule out drug resistance as early as possible.

- All sputum negative cases will be subjected to repeat smear examination at the end of two months to ensure that they remain negative. If positive, Xpert MTB/RIF and culture and DST will be done and managed accordingly. No follow up sputum examination is required if the smear is negative at the end of two months and patient is clinically improved.

- Sputum examination for AFB should be done if indicated for any TB patient during the course of treatment.

Figure 4: Treatment and follow-up of new PTB cases

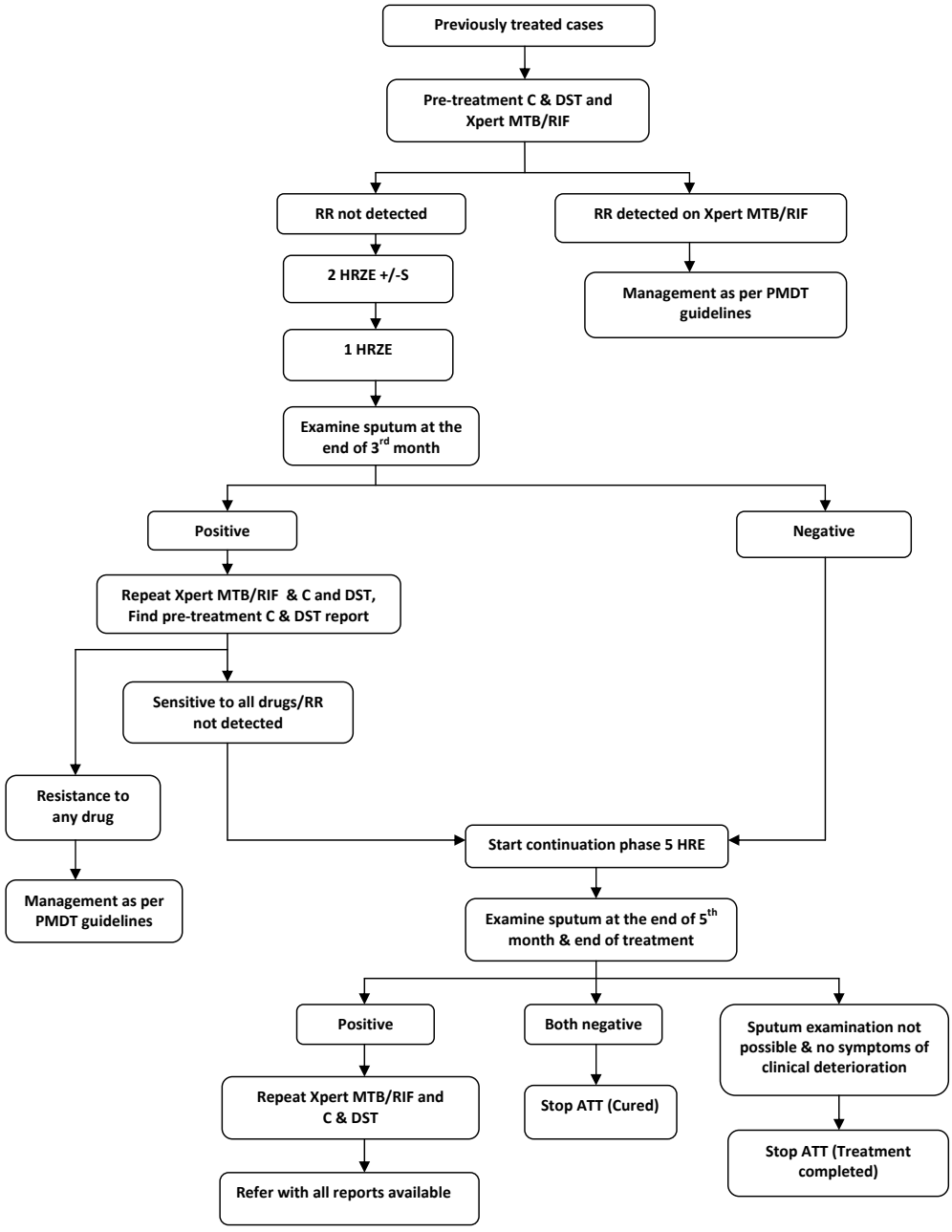


Re-treatment smear-positive patients (Relapse and treatment after loss to follow-up):

The follow-up is done with a sputum examination similar to that in new cases. However, the timing of the tests varies. Moreover, retreatment cases are considered to be at greater risk for drug resistance. Hence, they should be screened for resistance at the start of the treatment as well as at any time during the treatment when the sputum is positive on microscopy.

- Do the sputum examination when the patient has completed the intensive phase, i.e., after 3 months. If the smear is negative, start the continuation phase. If the smear is positive after 3 months trace the culture and DST reports. Repeat Xpert MTB/RIF test on the sputum sample and send sputum for culture and DST again. If no RR is found, shift the treatment to the continuation phase. However, by this time the culture and DST results of the initial samples collected at the start of treatment should be available to guide the treatment decisions.
- In case there is persistent smear positivity but no resistance being detected on the rapid tests, consult the PMDT committee for further management.
- Follow up sputum examinations during the continuation phase should be done at 5 months and at the end of 8th month.

Figure 5: Treatment and follow up of re-treatment TB cases



Extra-pulmonary patients

In case of EPTB, no smear examination is necessary and the patients should be assessed clinically. Patient follow-up after completion of treatment is generally not needed. The weight of the patient is a useful indicator. However, if the patient develops any chest symptoms at any time during the course of treatment, a sputum examination may be requested to rule out pulmonary involvement.

Actions in case of interruption of TB treatment

If a patient misses an arranged appointment to receive treatment, the DOT provider should ensure that the patient is contacted within a day after missing treatment. The patient can be traced using the location information previously obtained. In order to take appropriate action and continue treatment it is important to find out the cause of the patient's absence. The management of patients who have interrupted treatment takes into consideration multiple factors. All possible support should be provided to enable patient to adhere to treatment. At no point should confrontation be used as health system and care delivery are equally responsible for patient non-adherence.

In general the long absence of a patient who has already started treatment puts them at greater risk of developing drug resistance. Management of such cases is explained in Table 11.

Principles in management of new patients who interrupt treatment

- A patient must complete all 60 doses of the intensive phase. If the treatment interruption is short, the patient has to continue his previous treatment. For example, if the patient took one month of treatment (30 doses before interruption), he will have one more month (30 doses) of the intensive phase to take. He will then, depending on follow-up sputum results, take the continuation phase of the treatment to completion.
- A patient who needs to "start again" will restart from the beginning and take complete duration irrespective of doses taken before the interruption.
- If more than 5 months since the start of treatment and the patient is smear positive, classify as treatment failure.

Table No.11: Management of treatment interruption among new cases

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

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

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

*** LPA test may be used in patients who are smear positive to test for both H and R sensitivity. In certain cases it can also be done on culture positive samples.

Table No.12: Management of treatment interruption among retreatment cases

Length of treatment	Length of interruption	Do a smear?	Result of smear	Register again as	Treatment
< 1 month	< 2 weeks	No	-	-	Continue retreatment regimen*
	2-8 weeks	No	-	-	Start again on retreatment regimen**
	> 8 weeks	Yes	Positive	Treatment after loss to follow-up	Start again on retreatment regimen**Check previous pre-treatment culture &DST reports. Request another culture if previous reports were negative. Repeat Xpert MTB/RIF
			Negative	-	Start again on retreatment regimen*
1-2 months	< 2 weeks	No	-	-	Continue retreatment regimen*
	2-8 weeks	Yes	Positive	-	1 extra month of intensive phase of retreatment regimen after a repeat Xpert MTB/RIF test and RR not found. Repeat culture if previous pre-treatment culture is negative
			Negative	-	Continue retreatment regimen*
	> 8 weeks	Yes	Positive	Treatment after loss to follow-up	Start again on retreatment regimen**after a repeat Xpert MTB/RIF test and RR not found. Repeat culture if previous pre-treatment culture is negative
			Negative	-	Continue retreatment regimen*
>2 months	<2 weeks	No	-	-	Continue retreatment regimen*
	2-8 weeks	Yes	Positive with no RR on Xpert MTB/RIF	-	Start again on retreatment regimen** after a repeat Xpert MTB/RIF test and RR not found. Repeat culture if previous pre-treatment culture is negative
			Negative	-	Continue retreatment regimen*
	> 8 weeks	Yes	Positive with no RR on Xpert MTB/RIF	Treatment after loss to follow-up	Start again on retreatment regimen** after a repeat Xpert MTB/RIF test and RR not found. Repeat culture if previous pre-treatment culture is negative
			Negative	-	Continue retreatment regimen*

Note: * A patient must complete all 90 doses of the initial intensive phase. Treatment taken before interruption is also counted.

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

*** LPA test may be used in patients who are smear positive to test for both H and R sensitivity. In certain cases it can also be done on culture positive samples.

CHAPTER 10

Management of DR-TB

Although the total number of cases of MDR-TB in Bhutan remains small, the high proportion of drug resistance is a cause of worry and needs urgent attention. The proportion is higher than the global and regional average.
This chapter will be dealing with diagnosis and management of DR-TB in brief. The management of DR-TB is covered in detail in the national guideline for the management of DR-TB 2016.

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

Acquired drug resistance: Acquired drug resistance is the result of inadequate, incomplete or poor treatment quality that allows for the selection of mutant resistant strains. If drug-susceptible TB is treated with a regimen exclusively based on a single effective TB medicine, there is a risk that bacteria with drug-resistant mutations will be selected and multiply further during the course of treatment, eventually becoming the dominant strain. If a person infected with a strain, initially resistant to a specific medicine is treated with that medicine plus only a single new additional medicine, then there is a risk of developing resistance to the additional medicine.

Simultaneous natural mutations in Mycobacterium tuberculosis resulting in resistance to more than one TB medicine are very rare. Therefore, appropriate treatment with a combination of several quality-assured TB medicines dramatically diminishes the risk of selection favouring resistant strains.

Poor treatment outcomes, including acquired drug-resistant TB can be caused by inappropriate treatment, inadequate drug quality or supply, and patient factors hampering adherence and treatment responses (Table 13).

Table No.13: Factors contributing to poor TB treatment outcomes

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

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. High prevalence of drug-resistant TB in the community increases the risk of drug-resistant TB exposure in the community. Undiagnosed, untreated or poorly treated drug-resistant TB contributes to a sustained high drug-resistant TB prevalence, as well as a high proportion of infectious drug-resistant TB cases among the community.

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 the transmission of drug-resistant TB. Infection control measures to prevent infection with drug-resistant TB are discussed in Chapter 12.

Organization and management of the DR-TB control programme in Bhutan
In Bhutan the services for drug-resistant TB are imparted by the TB control programme which is itself integrated in the general health services. There are 3 Referral hospitals, all dzongkhag hospitals and 5 BHU Grade I that functions as microscopy centres or diagnostic and treatment centres for TB. A total of 32 TB reporting centres report activities related to TB. BHU Grade II and below,

presumptive TB 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 including TB.

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

The programme has identified the National & Regional Referral hospitals as MDR-TB treatment sites. They acts as the main treatment initiation site having facilities for Xpert MTB/RIF. They also deals with all complicated cases and oversees other clinical MDR-TB services. Currently Gidakom hospital also functions as MDR-TB treatment site with hospitalisation facilities. MDR-TB treatment is initiated in these hospitals based on laboratory confirmed result. In future, these services will be expanded as per the PMDT expansion plan so as to improve outreach and access to programmatic management of drug resistant TB (PMDT) throughout the country.

Cases to be screened for drug resistance

As per the existing programme policy, all sputum smear positive patients are screened for drug-resistance. In addition the following will be screened.

Presumptive DR-TB cases – All the following categories of patients are high risk of drug-resistance and hence all the symptomatics will be screened directly with a rapid DST without the need to confirm TB using sputum microscopy

- All retreatment cases.
- All cases on first line drugs not converting at 2/3 months of treatment.
- Symptomatic contacts of MDR-TB cases including health care workers, children or those contacts who have suspicion of TB on physical examination by a physician.

Other risk groups and vulnerable groups

- Symptomatic HIV positive and those with known co-morbidity which may suppress immunity e.g. those with diabetes.

The following categories are also important for screening but given the constraint of resources, clinical judgement will be used to determine the need of direct screening of symptomatics using rapid DST.

- Elderly.
- Symptomatic children.
- Migrant workers specifically those in mining industry, cement industry and quarries.
- Bridge population.
- Symptomatics from areas where transmission rates are high: Prisons, Other congregate settings – hostels/dormitories/nunneries/monasteries.

Diagnosis

All sputum smear positive cases and symptomatics belonging to other screening categories as indicated above, will undergo Xpert MTB/RIF testing

- All rifampicin resistant (RR) cases in the high risk group will be started on Second-line treatment while waiting for drug susceptibility test (DST) results. Decision to add isoniazid will be taken upon receiving the results of DST to H by LPA.
- All low-risk cases found to be RR will undergo another rapid DST using Xpert MTB/RIF or LPA on a fresh sample and a decision will be made according to the algorithm given in figure 6.

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. TB-In-charge will oversee contact screening by BHU staff, health coordinator in institutional setting or other focal points in congregate settings. The 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 will be filed along with treatment records of the patient.

Diagnosing Paediatric TB and drug resistance among such cases

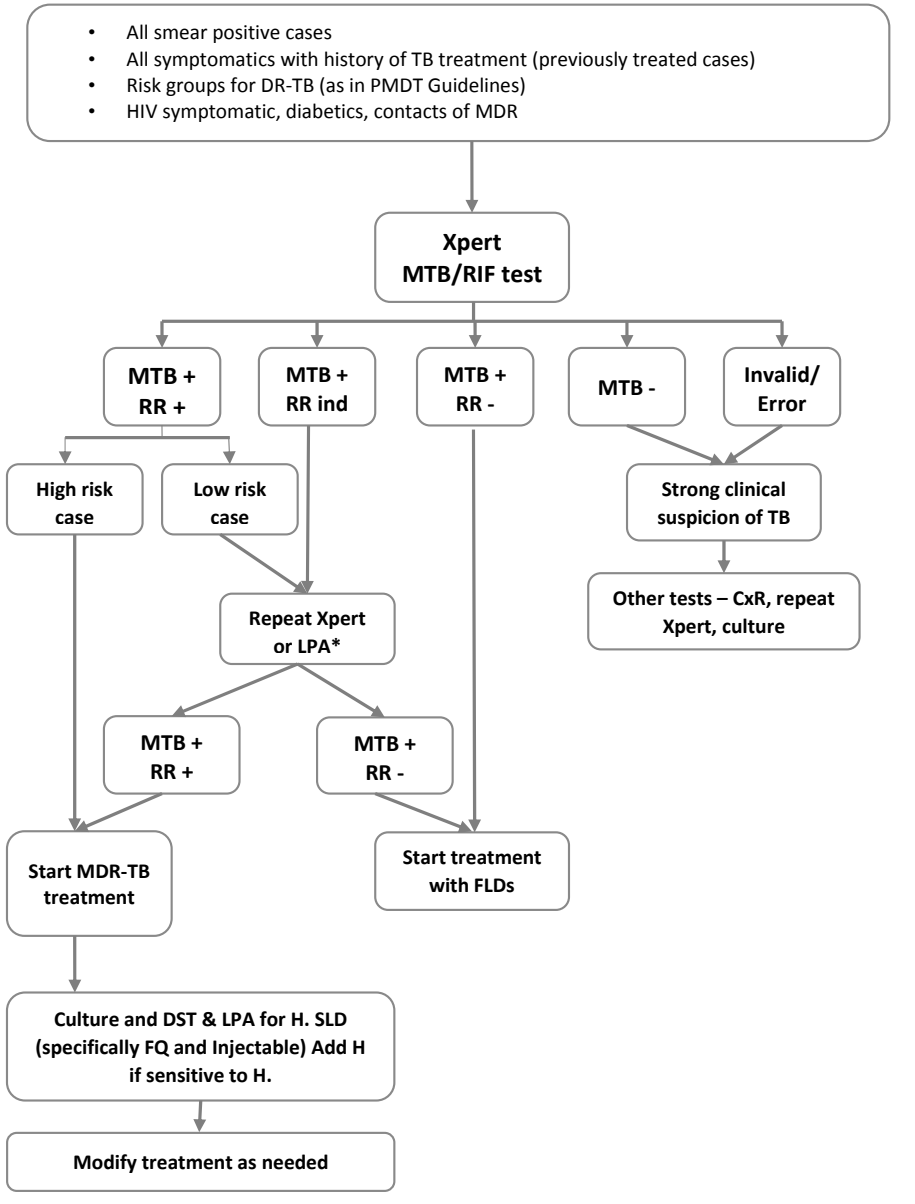
The presence of three or more of the following should strongly suggest a diagnosis of TB among paediatric cases

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

Specifically in cases in which a close family member has been 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 Xpert MTB/RIF or if not available, sputum smear microscopy, culture and DST) and HIV testing will be undertaken.

Sputum (or the available biological specimen) from all screening categories will be collected and transported by the Laboratory technician or a person designated by the hospital In-charge on the same day to the nearest site undertaking the Xpert MTB/RIF testing. In the case of a delay in transportation, the sample will be kept in cold conditions using a cold-box or refrigerator. The delay is not expected to be more than 5 days. Standard biohazard packing will be used to pack the samples.

Figure 6: algorithm for diagnosis of MDR-TB and treatment initiation



MTB – Mycobacterium tuberculosis; RR – Rifampicin resistance; FLD – First line drugs; DST – Drug susceptibility testing; tt – treatment; MDR – Multi drug resistance; FQ – fluoroquinolones; H – Isoniazid; SLD - second line drug

* Depending on the availability, either of the two tests may be used on a fresh sample of the sputum

Laboratory technician at the testing site and the TB In-charge will be responsible for ensuring the availability of Xpert MTB/RIF results within 2 days.

After getting results of the first specimen, sputum for RR cases will be collected and transported in a similar manner for both LPA and conventional culture and DST to RCDC if sample was not sent earlier. LPA will be used to determine the sensitivity to Isoniazid; isoniazid to be added to the MDR-TB treatment regimen if MTB is found sensitive to it. For culture only, the turnaround time for results is expected to be not more than 6 weeks (if using liquid culture). If the samples need to be further sub-cultured, it will take around 2-8 weeks in solid after which DST can be performed in liquid. This takes another 2 weeks. All cases started on second line TB treatment will be offered second line DST. To ensure this, TB In-charges will coordinate with treating physicians.

Process of enrolment

In the case that the rapid DST results (e.g. Xpert MTB/RIF) indicate an individual to be RR/MDR-TB, this person will immediately be initiated on second-line treatment at the National Referral Hospital or any of the regional referral hospitals by a chest physician or a medical specialist. In all such cases, MDR-TB registration numbers will be provided at any of the treatment initiation sites by the TB In-charge at that site. The patient will initially be admitted to the hospital for treatment observation and the 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 to discuss any associated co-morbidity or complications.

Baseline investigations

It is important to undertake some baseline investigations when initiating a case found to be RR/MDR-TB. These include:

- Mycobacterial cultures and DST to Isoniazid. Whenever possible, cases of RR-TB and MDR-TB would undergo SL-DST.
- Baseline potassium, creatinine, serum glucose and serum glutamic-pyruvic transaminase (SGPT/alanine transaminase (ALT)).
- HIV rapid testing. If HIV positive, the case will be referred for full blood count and CD4 (CD4% in children).
- Baseline full blood count.
- Pregnancy test for women of childbearing age.
- Routine baseline T4 and TSH test can be done on all patients.
- Audiometry.
- Chest radiograph.

- ECG.
- Baseline psychosocial assessment.

Patients placed on second-line anti-TB medications usually belong to one of the following groups:

- Confirmed RR-TB or MDR-TB.
- Presumptive RR-TB or MDR-TB. Patients may be registered and started on second-line anti-TB treatment on the basis of significant risk for drug resistance and before laboratory confirmation of resistance. In such cases, all attempts should be made to confirm microbiologically the status of resistance as soon as possible.
- 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.

Treatment regimen for MDR-TB

Standardized Treatment Regimen will be used for the treatment of MDR-TB. The regimen can be individualized after receiving reports of the SL-DST.

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

In all cases diagnosed as RR-TB by rapid DST (Xpert MTB/RIF) Isoniazid (H) will be added to the regimen after receiving DST results to H, if the mycobacterium is found susceptible to H.

The injectable (Ka) will be administered 6 times a week during the intensive phase while for the entire duration oral drugs will be administered daily under observation.

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. This, however, will only be done in consultation with the PMDT committee or experts at JDWNRH.

In most cases the total treatment duration will not be less than 20 months. A decision to prolong treatment will also be undertaken in consultation with the experts.

Cm and PAS will be made available as reserve drugs for about 10% of cases. These cases may have significant adverse effects in response to any of the drugs in the standard treatment or in special conditions.

The treatment of MDR-TB in paediatric population is similar to that of adults. The dosages will be given according to the weight and adjusted regularly as weight increases during treatment (annexure 3)

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). Standardised regimen to be used for such cases would be:

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

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

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

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

Treatment regimens for mono- and poly-resistant TB

Table No.14: Pattern of resistance and recommended regimen

PATTERN OF DRUG RESISTANCE	REGIMEN	MINIMUM DURATION OF TREATMENT (MONTHS)	COMMENTS
H (± S)	R, Z,E & FQ	6–9	Use Xpert 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 injectable 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 Xpert 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

Use of shorter regimen for MDR-TB

The WHO has recently (in May 2016) approved the use of a shorter regimen for the treatment of RR and MDR-TB. At the time of writing these guidelines, however, the country is not prepared at present to launch the shorter regimen, mainly because:

1. DOT needs to be further strengthened for both drug susceptible and drug-resistant cases.
2. There is a need to rule out resistance to fluoroquinolones and second-line injectable before the start of this regimen. This means SL-DST should be performed in all cases being initiated on treatment.

While strengthening DOT is an ongoing process, it is expected that SL-DST will be established in the country in a few years. After this is established, Bhutan will review the guideline learning from experiences of other countries.

Adverse effects management

Table No.15: Common side effects and ancillary medicines used

INDICATION	DRUG/S
Nausea and vomiting	Metoclopramide, dimenhydrinate, prochlorperazine, promethazine, ondansetron (and other serotonin 5-HT3 receptor antagonist)
Heartburn and acid indigestion	H2-blockers (ranitidine), proton pump inhibitors (omeprazole, pantoprazole 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 antidepressants (amitriptyline)
Severe anxiety	Lorazepam, diazepam

INDICATION	DRUG/S
Insomnia	Dimenhydrinate
Psychosis	Haloperidol, thorazine, risperidone (Also include stocks of benzotropine or biperiden to prevent extrapyramidal effects). Consult psychiatrist.
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
Musculoskeletal pain, arthralgia, headaches	Ibuprofen, paracetamol, codeine
Cutaneous reactions, itching	Hydrocortisone cream, calamine, caladryl lotions

Systemic hypersensitivity reactions	Antihistamines (diphenhydramine, chlorpheniramine, dimenhydrinate), corticosteroids (prednisolone, dexamethasone)
Bronchospasm	Inhaled beta-agonists (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)

CHAPTER 11

Latent Tuberculosis Infection

Latent tuberculosis infection (LTBI) is defined as a state of persistent immune response to stimulation caused by Mycobacterium tuberculosis antigens without evidence of clinically manifested active TB. A direct measurement tool for M. tuberculosis infection in humans is currently unavailable. The vast majority of infected individuals have no signs or symptoms of TB but are at risk for developing active tuberculosis (TB) disease. This can be averted through preventive treatment.

It is recommended that resource-limited and other middle-income countries implement the existing WHO guidelines for people living with HIV and child contacts below the age of 5 years.

Systematic testing for LTBI is not recommended in people with diabetes, people with harmful alcohol use, tobacco smokers and underweight people. Individuals should be asked about symptoms of TB before being tested for LTBI. Chest radiography can be done if efforts are also intended for active TB case finding. Individuals with TB symptoms or any radiological abnormality should be investigated further for active TB and other conditions.

In Bhutan, LTBI detection will focus mainly on the HIV positives and child contacts of active TB disease. The Tuberculin skin test (TST) or the Mantoux test will be used to diagnose LTBI after ruling out active TB as already explained in earlier section. Isoniazid preventive therapy will also be provided to adults who are severely immunocompromised such as those after solid organ transplant, chronic kidney disease on dialysis, those who are immunosupressed with high dose steroids or anti-TNF as these people are at increased risk of progression to active TB disease.

Induration of diameter ≥5 mm is considered positive in:

- HIV-positive individuals including children.
- Severely malnourished children.
- Severely immunocompromised individuals (chronic kidney disease on dialysis, post organ transplant, immunosupressed individuals).

Induration of diameter ≥10 mm is considered positive in:

- All other children (whether or not they have received BCG vaccination) and adults.

All positive cases will be administered IPT for 6 months. The availability of the Mantoux test, however, will not be a limiting factor in deciding whether or not to start IPT. Treating physician can start IPT based on clinical history after ruling out active TB.

Isoniazid preventative treatment (IPT)

In the case of HIV infection without active TB, IPT is recommended in the following:

- All HIV infected adult/children who are close contacts of smear positive TB patients.
- HIV infected Adults/children with a tuberculin test > 5mm.

IPT is not recommended for HIV infected individuals who do not belong to the above categories. They should be monitored closely and if symptoms develop at any time after the initial screening, they should be reinvestigated to exclude active TB.

Dose:

Isoniazid 5mg/kg in adults and 10 mg/kg in children with a maximum of 300mg per day for 6 months is recommended for preventive TB treatment. This should be commenced after carefully excluding active TB.

CHAPTER 12

Infection Control

From the public health point of view, the best way to prevent TB is by interrupting the chain of transmission. This is achieved by identifying the infectious cases as early as possible and providing effective treatment to cure them. Generally the patients become quickly non-infectious after starting the appropriate treatment. However until the patients become non-infectious, it is important to protect the contacts from TB infection. This includes health care providers.

Overview

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

Airborne infection control

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

- **Administrative controls:**
  Administrative controls refer to policies and practices which identify individuals with respiratory symptoms, separate them into an appropriate environment, fast-track them through the health care facility to reduce exposure time to others and diagnose/treat them with minimal delay. To the greatest extent possible, hospitalization should be reduced or avoided. At the facility level, administrative controls play a major role in reducing the risk of TB transmission and are essential for the implementation of other controls (i.e. environmental controls and personal protective equipment).

- **Environmental Controls:**
  These controls refer to interventions which minimise the infectious TB particles in the environment. The choice of environmental controls is largely determined by local factors and resources. Ventilation should be prioritized to reduce the number of infectious particles in the air. Effective ventilation can be achieved by natural ventilation wherever possible. It can be assisted by use of exhaust fans. Properly designed, placed and maintained shielded ultraviolet germicidal irradiation devices should be considered as a complementary control in high-risk settings, where optimal ventilation cannot be achieved through natural or mechanically-aided means.

- **Personal protective equipment:**
  Personal protective equipment (e.g. particulate respirators certified as N95) should be available as required in high-risk situation, especially for drug-resistant tuberculosis and during high-risk aerosol-generating procedures such as bronchoscopy or sputum induction. These should be applied only after addressing the administrative and environmental controls.

Managerial activities for National, Dzongkhag and health facility level:
Managerial activities should ensure political commitment and leadership at all levels (national, dzongkhag and facility level). Airborne infection control committees should supervise, monitor and ensure that all health facilities follow the guidelines. These committees are required to play a supportive role and facilitate the implementations of the guidelines.

Role of Health Care Facility
Hospital administration plays a key role in creating the necessary conditions to prevent spread of health care associated pathogens at the institutional level. The physical separation of TB patients or people suspected of having TB requires rational design, construction, renovation and use of buildings. Controls aimed at reducing TB transmission in health-care settings include triage, physical separation or isolation of TB patients or people suspected of having TB, cough etiquette, respiratory hygiene and minimizing the time spent in health care facilities. Facility Infection Control Committee should have a facility infection control/bio-medical waste management plan in place. The airborne infection control plan should be an integral part of this facility plan.

Following are the specific activities for health care facility administration:

- Conduct a facility-risk assessment and develop a facility plan for airborne infection control:
  - Risk assessments help identify strengths, weaknesses and opportunities for improvement.
  - should strengthen facility infection control committees to incorporate airborne and TB infection control as a core responsibility.
  - The committees should develop a facility plan for implementation of airborne (including TB) infection control.
  - The facility infection control plan should ensure proper implementation of all recommended controls and should complement and be aligned with the national guidelines.

- Design the use of available spaces and consider renovation and/or construction to optimize implementation of controls:
  - Consider renovation and/or new construction of physical infrastructure to optimize the implementation of infection control measures.
  - Adequate space for screening of patients should be available.
  - Waiting areas should be moved out of poorly ventilated corridors.
  - Separate, well-ventilated waiting area for respiratory symptomatic should be made available wherever possible.
  - Consider developing outdoors waiting areas for high-risk settings like chest OPD, ART centres, microscopy, DOT centres and MDR TB management sites .
  - Ventilation in all areas, especially registration, waiting areas, OPD should meet standards for health care settings.
  - Great care should be taken to ensuring adequate air exchange regardless of the climate control solution.

- Designate focal points for the facility-level activities and support training of frontline health care workers:
  - Facilities should have focal points designated to ensure activities are properly implemented.
  - These focal points should play a key role in sensitizing the front-line health care staff in all aspects of infection control, including standard precautions, patient risk assessments and airborne infection control considerations .
  - Regular sensitization and reinforcement of policies and practices should be conducted by infection control focal points.

- Supervise and monitor infection control activities:
  - Facility-level infection control activities frequently involve changes in work practices that tend to weaken over time, hence ongoing supervision and monitoring is essential.
  - Facility administrators are responsible for ensuring that administrative and environmental controls outlined in the facility plan are successfully and consistently implemented.

Administrative control strategies for health-care facilities

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

Summary of key recommendations on administrative controls:
Outpatient Settings:

- Screen for respiratory symptoms as early as possible upon patient's arrival at the health care facility.
- Provide patient education on cough hygiene and sputum disposal.
- Segregate patients with respiratory symptoms without stigmatising.
- Fast-track patients with respiratory symptoms.
- Well ventilated waiting area - preferably through an open corridor/s.

Inpatient settings:

- Minimize or no hospitalization of TB patients.
- Establish separate rooms, wards or areas within wards for patients with infectious respiratory diseases. Such areas should promote minimum mixing with other patients.
- Educate inpatients on cough hygiene and provide adequate sputum disposal facilities.
- Establish safe radiology procedures for patients with infectious respiratory disease including smear-positive TB cases or TB suspects.

The implementation of the key administrative interventions (screening, education, segregation and fast tracking) might vary from facility to facility.

- Screening:
  Screening for respiratory symptoms should occur as early as possible upon patient's arrival at the health care facility. Patients can be effectively screened at the registration counter itself. By asking simple questions related to chronic respiratory symptoms those likely to have tuberculosis can be given special cards or priority slips. The services of existing staff at the registration counter can be used for this purpose or

a special screening counter can be established prior to the registration process. This screening can be performed by physicians, nurses, paramedical staff and/or volunteers specially deputed for this purpose. Even if screening at registration is not possible, screening can occur when patients are in waiting areas.

- Education on cough etiquette and respiratory hygiene:
  The education can easily be imparted to patients through posters and other means in the waiting area, as well as through discussions with paramedical staff or volunteers while patients are waiting for their turn. Whenever poor cough etiquette is observed, good cough etiquette should be reinforced by all staff members. It is recommended that disposable medical masks are distributed to patients attending these facilities along with instructions on how and when to use them.

- Patient segregation:
  Segregation of patients with respiratory symptoms can be achieved by having a separate waiting area for chest symptomatics within the overall outpatient area. This is particularly important in larger institutions that have heavy OPD loads. So that these patients do not mix with other patients waiting in the outpatient area, if feasible, a separate doctor can be deputed to assess these patients in the segregated waiting areas. Another alternative is to implement a patient flow control mechanism at the entry point of the waiting area, so that chest symptomatics are diverted to this special area rather than to the common waiting area. The outpatient area, and even more so the segregated area, should be well ventilated to reduce overall risk of airborne transmission.

- Fast tracking of patients with respiratory symptoms:
  Those identified as patients with respiratory symptoms can be further fast-tracked in both their clinical and laboratory evaluations. One option could be to directly send these patients for sputum smear examination before they see a doctor. The other options are to allow these patients to bypass the routine queue and be seen earlier than other patients. There could also be a totally segregated physician area. These patients can also be given priority while chest radiography is being performed.

Administrative interventions in the inpatient areas are:

- Minimize hospitalization of TB patients:
  One of the most effective means to reduce the risk of transmission of airborne pathogens, such as M. tuberculosis, in hospital settings is to manage such patients in the outpatient setting whenever possible.

- Establish isolation rooms, wards or areas within wards for patients with infectious respiratory diseases:
  When hospitalization is required, patients with infectious respiratory diseases should be physically separated from other patients so that other's exposure to infectious droplet nuclei can be minimized. Policies on patient separation inevitably generate concern about stigma, but with appropriate measures, such as training and publicly displaying of separation rules, stigma can be minimized. Administrative procedures should ensure that separation happens promptly and automatically, similar to the automatic separation of men and women during inpatient admission.

- Educate inpatients on cough hygiene and provide adequate sputum disposal facilities:
  Wards housing infectious patients should display sign boards in the ward demonstrating cough hygiene. All patients admitted in the ward/ area should be issued surgical masks and counselled on how they can be used properly. Adequate measures should be taken to ensure the safe collection and disposal of sputum.

Environmental controls

Environmental control measures are the second line of defence for preventing the spread of TB in health care settings. Environmental controls include ventilation (natural and mechanical), ultraviolet germicidal irradiation (UVGI), filtration and other methods of air cleaning. It is important to recognize that if administrative controls (policies and work practices) are inadequate, environmental controls may not eliminate all the risk. Some environmental control measures are simple and inexpensive while many others are technically complex and expensive.

Environmental controls work on the same basic principle: dilution of infectious particles through real or 'effective' air exchange. In the case of ventilation, dilution occurs through the introduction of fresh, uninfected air and the removal of infected air. In the case of UVGI or filtration, dilution is 'effective' through the creation and re-circulation of 'cleaned' air, in which

infectious particles have been removed by irradiation or physical extraction. So that air containing infectious particles is not introduced into clean air where staff or other patients are located, certain circumstances may require directional control of airflow.

Key recommendations on environmental controls are:

- Health-care facilities should seek to achieve minimum standards for air exchange. High-risk settings should be prioritized for immediate assessment and implementation of an improved ventilation system.
- Natural ventilation is the preferred method for ensuring adequate air exchange in most settings.
- In existing health-care facilities that rely on natural ventilation, ensure that there is effective ventilation at all times and in all climatic conditions. This is achieved through proper operation and maintenance and by performing regular checks to ensure fixed, unrestricted openings. If mechanical ventilation is used, the system should be well designed, maintained and operated so as to achieve adequate airflow rates and air exchange.
- In high-risk settings where it is not possible to achieve adequate air exchange using natural ventilation, a complementary option is to use an upper room, exhaust fans or shielded ultraviolet germicidal irradiation (UVGI) devices.
- Optimal arrangement of patients and staff should be implemented in all outpatient departments, TB units, microscopy centres and radiology departments.
- Directional control of air flow is recommended in specific high-risk settings where infectious patients with drug-resistant TB or other acute respiratory diseases of potential concern are likely to be managed – i.e. airborne isolation rooms, MDR-TB wards and clinics and bronchoscopy units.

Ventilation

Ventilation can reduce the risk of infection through diluting and removing infectious particles. When clean or fresh air enters a room, by either natural or mechanical ventilation, it dilutes the concentration of airborne particles, such as droplet nuclei, in the room. This is similar to the opening of windows or doors to remove foul odours. Dilution reduces the likelihood that a person in the room will breathe air that contains infectious droplet nuclei. As room air exchange doubles, the concentration of airborne particles in the room is halved.

Improved ventilation in health-care facilities is essential in preventing transmission of airborne infections and is strongly recommended. Better ventilation lowers the risk of transmission of TB and other airborne infections.

- Natural ventilation
  This refers to the fresh dilution air that enters and leaves a room or other area though openings such as windows or doors. Natural ventilation is "controlled" when openings are fixed, unrestricted and maintain air flow at all times. Unrestricted openings (i.e. those that cannot be closed) on opposite sides of a room provide the most effective natural ventilation. In existing health-care facilities that have natural ventilation, when possible, effective ventilation should be achieved by proper operation and maintenance of openings and by regular checks to see that openings remain free of obstruction at all times.

  Simple natural ventilation may be optimized by maximizing the size of the windows, opening up fixed window panes, by locating windows on opposing walls and by the use of propeller "mixing fans". Types of mixing fans include ceiling fans, stand/desk mounted fans, or window/ exhaust fans located in open windows. Mixing of air can disperse pockets of high concentrations, such as in the vicinity of patients. The total number of infectious particles in the room will not change with mixing. However, the concentration of particles near the source will be reduced while the concentration in other parts of the room may increase. In other words, unless adequate ventilation is present, the mixing fan will not be useful in reducing infectious particles nor the risk of transmission.

  A common problem with reliance on natural ventilation is the need to close windows during cold weather or at night. Further, varying weather is likely to produce variable airflow patterns. In colder climates, where rooms are closed to keep an adequate temperature, natural ventilation can be implemented by airing via windows at frequent intervals. If natural ventilation is inadequate, additional mechanical ventilation or other measures may be needed, especially in areas where risk of M. tuberculosis transmission is high.

- Mechanical ventilation
  Mechanical ventilation uses fans to drive the air flow through a building. Mechanical ventilation can be fully-controlled and combined

with air conditioning and filtration systems as is normally done in some office buildings. Mechanical ventilation also includes "Mixed Mode ventilation", in which exhaust and/or supply fans are used in combination with natural ventilation to obtain adequate dilution. This is done when a sufficient ventilation rate cannot be achieved by natural ventilation alone.

Mechanical ventilation with or without climate control may be appropriate wherever natural ventilation cannot be implemented effectively or where ever such systems are inadequate given local conditions (e.g. building structure, climate, regulations, culture, cost and outdoor air quality). If mechanical ventilation is used, the system should be well designed, maintained, and operated so as to achieve adequate airflow rates and air exchange.

The simplest form of mechanical ventilation is the use of exhaust fans, placed for instance in windows, that move air from inside a room to the outdoors. Exhaust fans may also be more acceptable for staff and patients than keeping windows constantly open. If exhaust fans are used, it is important to ensure that airflow is adequate, that air flows across the room (not in and out the same window or vent) and that exhaust fans and air intake (windows or vents) are not located in such a way that short-circuiting will occur.

Ultra-Violet Germicidal Irradiation (UVGI)

Achieving adequate air exchange using ventilation (natural or mechanical) should be the priority. However, in some settings it is not possible to achieve adequate ventilation because of climatic changes (e.g. in cold climates or during the night) or building structure. In addition, in settings such as MDR-TB wards and HIV wards, transmission of TB poses a high risk of morbidity and mortality. In high-risk settings where adequate ventilation is not possible, a complementary option is to use an upper room or shielded ultraviolet germicidal irradiation devices. However, maintenance is critical and has a lot of limitations. If UVGI is not installed and maintained properly, it may be ineffective at inactivating M. tuberculosis.

Filtration (HEPA Filters)

Filtration is another option to remove infectious particles from the air. It may be considered where sustainable resources for membrane replacement

and maintenance are assured, where natural ventilation is not possible and where the risk of TB transmission and morbidity are high. Filtration devices perform poorly in high-dust conditions because air exchange effectiveness can rapidly diminish.

Situations where it could be considered include small room volume settings such as bronchoscopy units, laboratories or individual TB patient rooms. Careful attention should be given to the number of air exchanges the filter requires per hour; most filters clean very little air per hour and only marginally add to the dilution of potentially infectious air with clean air.
If filters are chosen, then only true-HEPA membrane filters (rated to remove 99.97% of 1 micron particles) should be entertained. Other filtration mechanisms, such as ionizers, have not been adequately studied.

Personal Protective Equipment
These include the following:

- Protective clothing.
- Gloves – usually not necessary but should be worn when likely to be in contact with respiratory secretions or contaminated articles.
- Plastic aprons and gowns – should be worn at the time of contact with the patients and their environment to avoid contamination of clothing.
- Masks –
  - Ordinary surgical masks reduce aerosol generation by patients but are not useful for protecting healthcare workers. To reduce aerosol spread, surgical masks could be given to patients with uncontrolled cough.
  - N-95 Respirators for healthcare workers in special situations like:
    - during high risk aerosol generating procedures associated with high risk of TB transmission especially in laboratory where sputum needs to be manipulated
    - Providing care to infectious or presumptive MDR-TB/ XDR-TB patients
  - TB wound care too requires the wearing of particulate respirators and gloves.
  - Masks should be close fitting and filter particles of 1-5 microns. N95 particulate respirators have a filter efficiency of 95% and are usually used. These masks can be reused a few times, provided they are not damaged and the elastic bands are working well. Careful labelling is required for a single staff member's use and the masks should be stored without getting contaminated.
  - Training is essential on proper use and disposal.

Infectious waste disposal

All infectious waste should be discarded in the bio-safety disposal bin. All infectious solid waste-wipes, swabs, plastic, paper towels, gauze pads, gloves, etc., should be placed inside the double autoclave bags, sealed with autoclave tape and sterilized in the autoclave for 15 minutes at 121ºc. Liquid waste, kept in the steel discarding bins should be disinfected in 5% phenol for at least 1 hour, before the caps are sealed and it is autoclaved at 121ºC for 15 minutes.

All reusable material such as glassware should be autoclaved in autoclave steel trays for 15 minutes at 121°C before being washed and repacked for sterilization.

Colour coded bins/bags are recommended for the disposal of various types of bio-medical waste and the National Guidelines for solid waste management should be followed as well.

CHAPTER 13

Non-Governmental Organization and Partner involvement in TB control

Currently there are not many NGOs working in the field of Tuberculosis in Bhutan. In future they could be involved in the following roles:

- awareness-raising specifically among unreached populations, monastic bodies and migrant workers.
- reducing stigma and discrimination through behaviour change communication and community mobilization.
- screening for TB and TB-related morbidity (e.g. HIV counselling and testing; diabetes screening) through home visits.
- facilitating access to diagnostic services (e.g. sputum or specimen collection and transport).
- referral of community members for diagnosis of TB and related diseases.
- treatment observation (DOT) for TB and co-morbidities.
- treatment adherence support through peer support and education and individual follow-up.
- social and livelihood support (e.g. food supplementation, income-generation activities).
- home-based palliative care for TB and related diseases.
- community-led local advocacy activities.

The programme will also take initiatives for involvement of other departments within the ministry of health and other ministries to support TB case finding. In-country partners include:

- Ministry of health, its departments and sub-national counterparts.
- Other ministries, such as MoLHR, MoHCA and MoE.
- Drug regulatory authority.
- Academic institutions.
- Monastic body.

Their engagement in TB control will be in form of:

- HIV programmes and projects: Encouraging people living with HIV to be screened for TB and vice versa
- Maternal and child health programmes and projects: Encouraging all pregnant women to test for HIV and to be screened for TB symptoms at the nearest facility.

- Education programmes and projects: Incorporating messages of TB prevention and care into curricula and classroom learning.
- Agriculture and income-generation programmes and projects: Raising awareness about TB symptoms and signs among organized groups, identifying symptomatics, diagnosis and treatment as per the National Programme.
- Academic institutions can undertake operational research.

Operational Research

Operational research (OR) aims to develop interventions that result in improved policies, better design and implementation of health systems and more efficient methods of service delivery. The OR is therefore critical for reaching the unreached people who need TB care. It produces evidence that lays the groundwork for improving current strategies and introduces new tools and new partners. Fostering better and more relevant operational research and ensuring careful evaluations of local experiences will not only help in better implementation, but it will also greatly assist further development of the national policy. Some of the broad areas for OR in the country include:

1. Understanding the barriers and improving access, screening and diagnosis of TB.
2. Sustainable collaboration with all care providers for TB control.
3. Prevention of TB in people living with HIV, and joint treatment of HIV and TB.
4. Access to and delivery of treatment for drug-susceptible and M/XDR-TB.
5. Capacity-building for operational research.

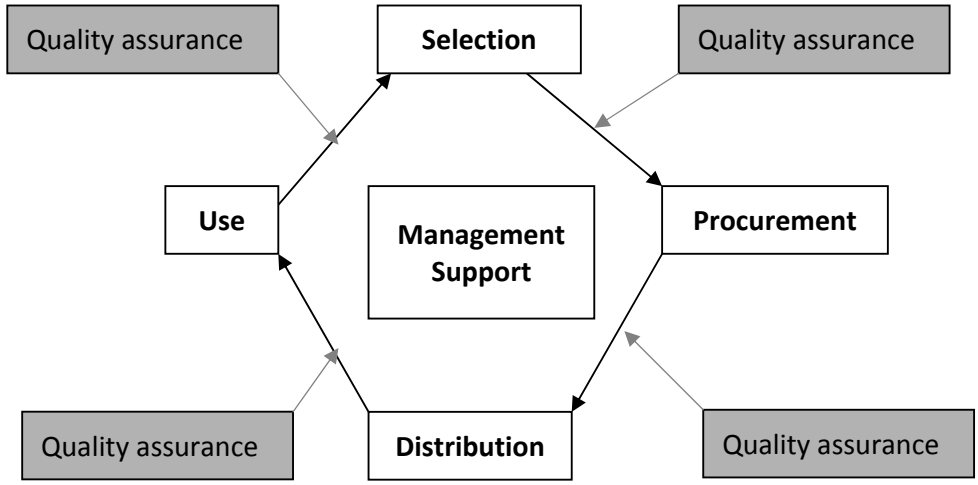
The national programme plans to collaborate with international and national academic institutions for building capacity for OR as well as undertaking the operational research.

CHAPTER 14

Drugs and Consumables Management

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

Figure 7: Drug management cycle



Selection of drugs and consumables

Usually the selection of drugs and consumables are carried out using a tender procedure and should be based on the quality, efficacy, safety and cost of the items. First and second line drugs are procured through the Global Drug Facility (GDF) after introducing the Fixed Dose Combination (FDCs) of Anti TB drugs.

Process of quantification

Quantification of anti-TB drugs is usually done annually according to the number of patients diagnosed during the previous one year. Local health authorities will calculate the quantity of drugs required and fill in the requisition form for drugs at the end of every year. The form will be signed by the Dzongkhag unit level head and forwarded to the central level once in a year. The DoMSHI/MSD shall arrange for the supply of drugs to the indenting authority. During the quantification a buffer stock of 25% should be calculated for each year.

The information about drug consumption and stock is monitored on quarterly bases along with the quarterly TB report.

This estimation of the quantity of drugs required is adjusted annually and based on the number of TB cases treated during the previous year; treatment regimen adopted, buffer stock (including amount of drugs required during lead time to supply) and stock-in-hand at the time of the drug order.

Laboratory Consumables

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

Documentation materials

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

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

Referral/Transfer forms:
Referral/Transfer forms are needed for about 3 in 10 TB patients. Calculate 30% of the expected patients and then add 20% for reserve minus stock in hand.

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

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

Inspection and Storage of Drugs and Supplies
Upon receipt, all drugs and supplies shall be inspected by a 'Quality Assurance &Standardization Division'. The committee will physically inspect the supplies with the 'Invoice' and the specifications as per the purchase order awarded. The committee will then report any discrepancies or damages, if any.
Drugs and supplies should be stored in optimal conditions in a secured room. The drugs and laboratory reagents should be monitored regularly for the expiry date. The drugs with shorter expiry dates should be placed in the front and those with later expiration dates should be placed behind (FEFO or first expiry-first out). A stock ledger must be maintained and updated whenever drugs and other materials are received or dispensed. The drugs and other supplies will also need to be recorded in our software system at the dzongkhag hospital level, MSD, Phuentsholing and at DoMSHI.

The Store In-charge (Pharmacy Technician) of the store will ensure the inspection of supplies, its optimum storage and its proper recording as detailed in the "Good Store Management for Managing Drugs and Supplies".

Issuance of Drugs and Supplies
Considering the number of indenting centers and the consequent workload, DoMSHI has worked out a 'schedule of distribution cycle & procurement cycle' outlining the month to start and for which districts the supplies will be issued. 'The distribution cycle & procurement cycle' has been approved and signed by Director General, DMS.

The Sr. Procurement Officer, MSD, Phuentsholing is designated to supervise the Central Store and should be responsible for following the distribution schedule as detailed in the "Standard Operating Procedures for Managing Drugs and Supplies".

Monitoring and Supervision of Stores

The monitoring and supervision of drugs/supplies management must be done at all levels. The raw material used for monitoring should be the reports of casefinding and drug stock status from the dzongkhag that are received through the indent form as well as the six monthly drugs report, stock status from the Central Store. Drug/supply management (especially GDF drugs) should be included at all levels in the agenda of monitoring meetings. It is essential that all drugs are stored in proper conditions, away from heat, direct sunlight and moisture.

Supervisory visits, including drug/supply management, should be done by using a checklist as revised and included in the general supervisory checklist. Reports of the supervisory visits should be analyzed for monitoring and feedback.

CHAPTER 15

Recording and Reporting

Collection of TB data forms part of the general health information system, which aims to:

- Ensure high-quality patient care, a continuum of care, information-sharing with patients, and transfer of information between health facilities.
- Aid staff in providing adequate services to individual patients.
- Allow managers at different levels in the national TB control programme (NTCP) to monitor programme performance in a standardized and internationally comparable way.
- Provide the basis for programmatic and policy development.

Recording and Reporting is an essential part of the National Tuberculosis Programme. Careful recording of information helps to monitor the treatment and the progress of each patient. Periodic reporting on NTCP activities helps to evaluate the performance of the control programme and facilitate proper planning.

While as of now most of the recording and reporting in Bhutan is paper based, there is a gradual move towards electronic recording and reporting. TB Information & Surveillance System (TBISS) is online software that was initially introduced to monitor the laboratory and diagnostic investigations for presumptive TB cases and their follow-up investigations. However, the program's use is now being expanded to all aspects of patient management and its access is being gradually expanded to all reporting centres. Internet connectivity, however, is still an issue but is expected to be resolved in near future.

Registration and notification process

- Once diagnosed, the patient should be classified depending on:
  - the site of the disease.
  - bacteriological examination and.
  - history of previous TB treatment.

- The patient should be registered in the District TB Register and allotted a District TB Number irrespective of the patient's district of residence. The TB Treatment Card should be filled in duplicate for ambulatory

treatment. One copy should be kept at the health facility and the second copy should be sent to the DOT Provider or to the referring centre.

- To ensure that all bacteriologically confirmed cases have been initiated on treatment, the laboratory register should regularly be cross-checked with the district TB register.

Following recording and reporting formats are used in the NTCP:

Presumptive Tuberculosis Register (Refer Annexure I)

The Presumptive Tuberculosis Register is maintained at all Health Institutions in the district which are involved in detecting TB symptomatic. This register is useful to ensure that TB symptomatic receives proper investigation and management. In addition, the register helps to monitor the performance of health facilities in screening symptoms of TB among patients reporting to the health facility. The concerned physician who sees/came across the TB suspects will maintain the register and send the patient to the Lab Unit for investigation.

Request form for Bacteriological Examination by Microscopy and GeneXpert MTB/RIF (Refer Annexure IV)

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

This form consists of two parts:

- the upper part of the form should be filled up by the requesting medical health worker. The request can also be done on the OPD slip along with request form.
- the laboratory technician of the GeneXpert center should fill the lower part of the form and the report must be sent to the referring center or the treating physician of the GeneXpert center for necessary action as soon as the results are available.

Sputum Request and Shipment Form for Culture and DST (Refer Annexure V)

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

This form consists of two parts:

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

District Tuberculosis Laboratory Register for smear microscopy and Xpert MTB/RIF (Refer Annexure VI)

The Tuberculosis Laboratory Register is maintained at all laboratories and microscopy centres where sputum smear examination or GeneXpert test for TB is carried out. The laboratory technician is responsible for maintaining and timely updating the register. The register includes results from both types of tests – samples for diagnosis and for follow-up.

The register gives information on the number of suspects examined, the number of smear-positive cases detected and the number and results of smear examination for follow-up of treatment. The TB registration number is the serial number and should be started with 1 at the beginning of each month. At the end of each quarter a line should be drawn beneath the last patient entered in the register. After each quarter, the number of suspects and number of total smears of suspects examined, number of smear-positive patients, number of follow-up examinations and number of positive follow-up examinations should be entered. Source of referral can also be tallied. The next quarter can start on a new page but the serial number will continue throughout the year. The following are the instructions related to the use of this register.

Serial No: Write the serial number of patients for the sputum sample received for undergoing tests. This is the serial number that should be allotted to each patient for particular date for each day.

Laboratory Reference No: Write the laboratory reference number of the particular date for each month. This is the number that is allotted to the patient from the 1st day of new starting calendar year from 1st January to 31st December of the particular calendar year. This is the number that the laboratory technician must report with the result of the examination. E.g. if the given Lab. Ref. Number for a patient is 50 and his report is positive (1+) then the report should be written as "1+/50". The figure 1+ is the sputum

report and 50 is the laboratory reference number. This should always be reported as it would facilitate crosschecking of results from the TB Register with Laboratory Register when necessary.

Name of Patient: Write the full name of the patient clearly.

Age/Sex: Write the completed number of years for each patient. Write 'M' for male and 'F' for female patient.

CID Number: Write the Citizenship Identity Card Number of the individual patient during the time of initial registration. By writing this number will help the TB in-charge to avoid duplication of registration and help to trace the patient when necessary.

Telephone Number: Ask for the patient's mobile number and write in the given column of the register. By writing this number will help the TB in-charge to monitor and follow up the patients when necessary.

Patient address: The address of the patient must be clearly written with their contact number. The address must be the one where the patient is likely to be staying during the next six to eight months.

Hospital OPD Registration Number: This is the number given to the patient during registration in the OPD. It is not to be confused with the District TB Control Number.

Treatment Unit: This space is kept in the event that sputum or other specimen is received from other treatment centres for examination. For example if a hospital receives sputum samples from BHU, then the name of that BHU should be written. Also, if the Clinical Laboratory in JDWNRH and RCDC in Thimphu receive samples from other hospitals for examination, then the name of that hospital will be noted under this space.

HIV Infection: The information on whether TB patient has HIV infection or not has to be mentioned in the given column after undergoing the VCT and HIV test. Write Y for Yes, N for No and Unk for Unknown.

Patient previously treated for TB: In this column, the information of the patient whether he or she had been treated for TB before or not should be written. Write Y for Yes, N for No and Unk for Unknown.

Date of specimen received: Put the date on which the patient brought the first sputum specimen for examination.

Type of specimen: Write the type of specimen received by the laboratory technicians. Need to specify clearly the specimen whether it is for pulmonary or EPTB. (Write P for pulmonary and EP for EPTB).

Specimen quality: Write the quality of sputum sample received for the test to be performed, such as saliva, blood stained, mucous pleurulent etc.

Reason for specimen: Write the reason of the specimen received for examination.

Diagnosis Specimen examination results: Under this, there are two separate columns. One for sputum smear microscopy examination and another for GeneXpert MTB/RIF test results. Enter the Day 1 to Day 3 (spot - morning - spot) reports in the column with date above and report below for smear examination performed during initial diagnosis of the patient. Enter the day 1 report in the column with date above and report below for the Xpert test result. If the report is positive for AFB, write in red or highlight in red colour. For the GeneXpert test result, write T for MTB detected, rifampicin resistance not detected. RR for MTB not detected, rifampicin resistance detected. TI for MTB detected, rifampicin resistance indeterminate. N for MTB not detected. I for invalid/no result/error. If Xpert MTB/RIF is indeterminate result, indicate error code or "invalid".

Follow up specimens examination results: Similarly for the follow up sputum examination results at defined intervals (2, 4 and 6 months for bacteriologically confirmed pulmonary cases and 3, 5 and 8 months for retreatment cases, enter the Day 1 to Day 2 (spot – morning) reports in the column with date above. and report below. For the sputum non-converters, GeneXpert test results to be recorded in the given column.

Date of sample sent for Culture and DST: Write the date on which the sample was sent to RCDC for culture and DST.

Remarks: Any information of the patient which is not covered in the above should be mentioned in the remarks column.

District Tuberculosis Register (Refer Annexure VII)

This register is maintained by the district TB in-charge. All tuberculosis patients receiving treatment in the district are entered in this register. It contains the patient's name, age, sex, contact details, disease type, disease site, treatment category, date of commencing the treatment, the DOT centre, results of sputum examination and treatment outcome. This register should be updated regularly according to the TB Treatment Card of the patient. The district TB in-charge is responsible for maintaining and updating the TB Register. The information in this register is used to prepare the Quarterly Reports on Case Finding, Sputum conversion and Treatment Outcome including TB/HIV collaborative activities.

This register is kept at the TB treatment unit of the hospital or BHU grade I. The Tuberculosis Register contains all the important general information of the patient, classification of the disease, type of patient, date of start of treatment, smear microscopy results and outcome of the treatment. The date of registration is the date the patient is registered in the Tuberculosis Register and may be different from the date the patient was diagnosed in the laboratory or started treatment. At the end of each quarter a line should be drawn beneath the last patient registered during that quarter to highlight the end of the quarterly cohort. This will facilitate preparation of the quarterly reports and cohort analysis of treatment outcome. At the end of the quarter, a tally can be made per sex (males and female patients), disease classification, type of patient or treatment outcome. A new page should be used for starting a new quarter.

This register should be updated regularly according to the TB Treatment Card of the patient. The district TB in-charge is responsible for maintaining and updating the TB Register. The information in this register is used to prepare the Quarterly Reports on Case Finding, Sputum conversion and Treatment Outcome.

Year: At the top right hand corner is marked "year _____". Please put the calendar year for which the register is being filled.

Date of Registration: Enter the date in this column on the day TB patient reports to you.

TB Control Number (No.): The TB Control Number is unique for each patient. It comprises of abbreviated name of the diagnosing centre, the month, the

year and the patient serial number (e.g. THI/10/15/125). The above code would mean a patient registered at Thimphu (JDWNRH), in the month of October 2015 and the patient registered at serial No. 125 in their TB register. All the hospitals in the country have been given a three letter code to identify the diagnosing and treating centre.

Always give a new TB Control Number for each course of treatment. For example if a patient is still sputum positive after 5 months of treatment, re-register the patient as a Treatment Failure and give a new TB Control Number. The reason for entering the same control number when a patient comes on transfer is to prevent the duplication of reports.

Also, the reason why both month and year is noted is to ensure that the patient completed the treatment as planned. We are following six months Short Course Chemotherapy. Therefore, the due date for completion of treatment is easily predictable. And if a patient comes to a treating physician with a date of registration long past the expected 8 months, this should alert the doctor/TB in-charge to some possible problem with this patient. For example, if in October 2005, a doctor sees a patient with a TB Card on which the Control No. is THI/2/04/231, it should immediately be clear that this patient should have completed treatment by October 2004 and the obvious question that should arise is, why the patient is still taking ATT one year after it should have been completed.

Three letter code for hospital or reporting centre in Bhutan. (Note: The hospitals have been divided into three regions).

Reporting centers		Reporting centers	
Western Regions	**Code**	**Central Region**	**Code**
1. JDWNR hospital	THI	1. Bumthang	BUM
2. L/phu RBA hospital	LPU	2. Trongsa	TON
3. Gidakom hospital	GID	3. Yebileptsa	YEB
4. Paro hospital	PAR	4. Gelephu RRH	GAY
5. Bajo BHU I	BAJ	5. Sarpang	SAR
6. Bali BHU I	BAL	6. Damphu	DAM
7. Punakha hospital	PUN	7. L/zingkha BHU I	LHZ
8. Tsimalakha hospital	TSI	8. Dagapela	DGP
9. Gedu hospital	GED	9. Panbang BHU I	PBG
10. Phuntsholing	PHU	**Eastern Region**	**Code**
11. Samtse hospital	SAM	1. Lhuentse	LHU
12. Sipsoo hospital	SIB	2. Mongar RRH	MON
13. Gomtu hospital	GOM	3. Trashigang	TGA
14. Gasa BHU I	GSA	4. Reserboo	RIS
		5. Trashiyangtse	TYZ
		6. Pemagatshel	PGA
		7. Nanglam BHU I	NLM
		8. Deothang	DEO
		9. S/jongkhar	SJG

Name: Write the name in full and clearly under this column.

Age: Put the completed number of years of the patient's age.

Sex: Put 'M' for male and 'F' for female patient.

Occupation: Mention the occupation of the patients. CID No: Citizenship Identity card Number of the patients should be written.

Complete Address: Put the actual place of residence, i.e. the place the patient is likely to stay for next six to eight months period. Often when you ask patient where they are from, they tend to give the name of their village, but this same person may not be staying there currently. For example, in

Thimphu, when a patient is asked where he is from, he may say, Trashigang. But actually this person may be living in Thimphu either with relatives or is doing some business or government service and, therefore, is living in Thimphu rather than in Trashigang. So the address of interest for us is where the patient is likely to be found in the next 6 to 8 months. Also record their telephone number (if available) so that we can trace him or her in case such a need arises. The contact details of the patients must also be mentioned along with the address.

Name of health facility where treatment started: Enter the name of health facility where the treatment has been started.

Date of Start of Treatment and Regimen: Write the date and regimen on which the treatment was started.

Type of Patients: Record N for the new case and R for relapse, TF for treatment after failure, LF for treatment after loss to follow up and O for others previously treated cases (default cases) and UK for previous treatment history unknown. Record T for transfer cases from other reporting centers. For every patient, there will be only one type or classification of case; for example the same patient cannot be 'New' and 'Transfer' or both 'New' and 'Other'.

Disease Classification: In this column, classify the disease whether it is bacteriologically confirmed PTB, clinically diagnosed TB case or EPTB put 'P' if the patient is a pulmonary positive tuberculosis case and 'EP' if extra pulmonary. Put P+ve for sputum positive and Neg. to elaborate the type of pulmonary case.

Treatment category: Tick appropriate treatment category of initial regimen with First line drugs, retreatment regimen with first line drugs and second treatment regimen.

TB-HIV activities: Offer VCT to all TB patients and record TB-HIV activities such as ART, CPT and IPT for HIV positive patients.

Result of Sputum smear examination and Xpert test: Record Y for Yes, N for No and U for unknown for the HIV test result at the time of TB diagnosis. Similarly, record RR/MDR for drug resistance TB and None/Unknown for

unknown drug resistance at the time of TB diagnosis. Also record the date and results for smear microscopy, culture and GeneXpert test results with letter S, C and X respectively at the time of TB diagnosis and during the follow up schedule of the patients.

Treatment outcome and date: Under this heading, there are 6 columns starting from 'cured (bact. negative)' to 'outcome not evaluated' with additional column for moved to second line treatment register for the MDR-TB cases.

Cured: This column should be filled for a pulmonary TB patient with bacteriologically confirmed TB who has completed treatment with a proof of sputum or culture negativity at the end of treatment and on least one previous occasion for a patient to be declared cured.

Treatment completed: This column should be filled when a TB patient who completed full course of treatment without proof of cure or treatment failure, but with now record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative.

Treatment Failure (smear positive): If a patient is to be declared Treatment Failure (please see definition) then the date when the treatment was stopped and patient labeled as "Failure" should be entered in this column. This same patient should be re-registered, i.e. given a new TB Control number and now this patient will become Treatment Failure (in the Type of patient) and will be put on retreatment regimen.

Died: If the patient dies during the course of treatment, it should be noted in this column with the date of death (if known). However, patient may die due to TB, or due to some other causes. If patient dies due to some other causes, then the actual cause of death should be mentioned in the 'Remarks' column.

Lost to follow up: This should be assigned to a TB patient who did not start treatment or whose treatment was interrupted for two consecutive months or more. Enter the date on which the treatment was stopped.

Treatment outcome not evaluated: A Patient for whom no treatment outcome is assigned. This includes cases transferred out to another treatment center as well as cases for whom the treatment outcome is unknown to the treatment unit.

Move to second line treatment register: Patient who was registered to SLD during the course of FLD treatment after drug resistance result from GeneXpert or Culture and DST.

Moved to Second Line TB Treatment register: All types of TB patients who failed treatment during the course of first line TB treatment and started on MDR-TB treatment based on the laboratory confirmed results should be mentioned in the column.

Remarks: The 'Remarks' column is provided for the TB in-charge to note any relevant information about the treatment etc.

Tuberculosis Treatment Card (Refer Annexure VIII)

The medical officer or TB in-charge fills the Tuberculosis treatment card as soon as patient is diagnosed with TB. The card is kept at the health facility where the patient is treated. In the front page of the treatment card, the details of patients such as name, age/sex, address and contact number, name, address and contact number of the community treatment supporter, TB control number, date of registration, date of treatment started, treatment category, disease site, type of patient, sputum smear microscopy, culture and DST weight of patient etc. need to be filled up properly. Date of X-rayperformed and the result should also be mentioned. Date of VCT offered and ART eligibility also need to be mentioned.

In the front page of the treatment card, the details of patients such as name, age/sex, address and contact number, name, address and contact number of DOT provider, TB control number, date of registration, date of treatment started, category, disease classification, type of patient, prescribed treatment regimen for both intensive and continuation phases, sputum smear microscopy, GeneXpert, culture and DST results including weight of the patient need to be filled up properly. The date of X-ray performed and the result should also be mentioned. Similarly, date of VCT offered and other TB HIV collaborative interventions like ART, CPT and IPT provisions should be mentioned.

Intensive Phase: On the back page of the treatment card, record to be maintained for the treatment provided for this phase.

Since the initial intensive phase will be carried out under supervision in the hospital, the card should be filled and kept in the TB unit. Please mark 'v' for

directly observed treatment, 'S' for drug supply given for self administration and '0' for treatment interruption.

The information that is on both the 'Patient's Card' and Tuberculosis Treatment Card' is identical. However, there is slight variation on the Tuberculosis Treatment card. This card must be updated along with the Patients' card and the District TB register as we monitor the patients.

Continuation phase: In the continuation phase, Enter 'V' on day of observed drug administration and if the medications are given to the patient for self medication, then draw a horizontal line (--------) to indicate the number of days supply given for self administration from the date on which drugs are issued to the date up to which the drugs were issued.

Remarks: Similar to the 'Patient's Card', the 'Remarks' space is provided for the treating physician/TB in-charge to note any relevant information about the treatment etc.

Treatment outcome: At the end of the treatment, select and tick the appropriate outcome of the patient and write the date of decision taken.

Tuberculosis Patients Card (Refer Annexure IX)

The medical officer or TB in-charge fills this card as soon as the diagnosis of tuberculosis is made and the patient keeps the card. The most important parts of this card are the date on which treatment was started, and categorization of the patient. The patient should be instructed to bring this card each time (s)he attends for anti-TB treatment, but (s)he should also bring and show it if (s)he attends for any complaint at a health facility, as the complaint might be caused by the anti-TB drugs.

Name: Write the full name clearly in the space provided.

Age: Put the completed number of years.

Sex: Write M for Male and F for Female.

District TB Control No: In this space, the full District TB Control number must be written.

Date of registration: Write the date on which the patient has been registered.

Date of start of Treatment: Write the date on which the patient was started on TB treatment.

Address and contact number: (put the actual place of residence): Enquire and put the patient's address and contact number. Address has to be the place where he/she is likely to be in the next six to eight months; it does not refer to his place of origin.

Name and address of DOT provider: Discuss with patient and identify a community DOT provider and write the name, address and contact number of a DOT provider.

Treatment centre: Write the name of the hospital or BHU grade I where the treatment had been initiated.

Type of patient: Please tick the appropriate classification and category of the case for which this card is being filled. It is better to put a tick mark clearly against each.

Treatment category: Select and tick the appropriate category.

Intensive phase: Select the appropriate treatment regimen according to category and write the dosages for this phase. Please mark 'v' for directly observed treatment, 'S' for drug supply given for self administration and '0' for treatment interruption.

Every day, after the patient receives the injection/medicines, the date should be entered in the grid sequentially. This is required as sometimes the patient will come to take the injection from the out patient's unit during holidays when the TB Unit may not be operating. However, the health worker should be able to see the injection record and make appropriate entry after each injection. Below the grid is the space for the dose of Streptomycin.

Result of sputum examination: The months are marked 0, 2, 5, 6 and 8. It is to emphasize the need to get sputum checked for all pulmonary tuberculosis patients at the time of initiating the treatment (month 0), end of 2nd, 3rd, 5th and 6th/8th months of treatment.

The 'date' is the date on which the sputum was examined; under 'Lab.#' the

lab. number has to be written and under the 'result' the result of the sputum examination is to be entered as “Neg” or “1+ or 2+” etc. in red if positive. The ‘Lab No’. refers to the number given by the examining laboratory to this sputum specimen in the laboratory register.

It is important to note the ‘weight’ of the patient at the time of starting the treatment, then at the time as and when the sputum is being examined and record under the ‘weight’ column. The weight record is a good indicator of the patient’s response to the treatment; it will be seen that even if the patient does not report any significant symptomatic relief, the weight record may show progressive improvement after the treatment was started. On the other hand, if a patient was put on adequate anti-tuberculosis treatment, but you notice that the weight is progressively declining, then the diagnosis of tuberculosis should be re-considered.

Continuation phase: Select and tick the appropriate treatment regimen for continuation phase. In the continuation phase, Enter ‘√’ on day of observed drug administration and if the medications are given to the patient for self medication, then draw a horizontal line (--------) to indicate the number of days supply given for self administration from the date on which drugs are issued to the date up to which the drugs were issued.

Treatment completed: Write the date on which the patient has completed the full course of treatment.

Remarks: Similar to the ‘Treatment Card’ the ‘Remarks’ space is provided for the treating physician/TB in-charge to note any relevant information about the treatment etc.

Drug Regimen: For practical purpose the continuation drug regimen is 6HR. However, in some cases, there may be slight difference. It should be clearly written in the space provided.

Dose (of each drug): The dose of each drug administered to the patient should be entered here next to the appropriate drug in the space provided.
Drug Collection Record: The ‘dates’ on which the drug was issued, ‘from’ which period ‘to’ which, and the ‘next due’ date should be entered every time the patient is issued drug. The ‘remarks’ column may remain empty most of the time.

However, occasionally a patient may turn up at a health centre for medication although this patient is not receiving treatment from this particular centre. If he is going to stay till the end of treatment, you must inform the center where patient was being treated by writing a letter with the patient's TB Control No. If, on the other hand, the patient is going to be there only for a short while, then estimate an appropriate requirement of the drugs and issue it to the patient without the need to enter this patient in your TB register, but mention under 'Remarks' that the drugs for the duration mentioned on the card was issued from your centre. This way, when the treating unit sees the patient again, they will know that this patient had not interrupted his treatment.

This Patient Card contains similar information to the Tuberculosis Treatment Card. It belongs to the patient and includes a drug collection record and appointment record.

Patient referral/acknowledgement Form (Refer Annexure X) Transfer from hospital to BHU (Between districts)

This form is used when referring/transferring a TB patient from one treating centre to another. This form consists of two pages, an original/white and duplicate/ pink. This form has two parts, the upper part contains the patient information and the lower part 1 is the referral acknowledgement slip. The referring/transfer centre fills up the upper part of this form and send them as follows.

- The upper part of the duplicate/pink acknowledgement slip should be sent to BHU where the patient is transferred to.

- The entire original/white referral form and the pink acknowledgement slip should be sent to BHU where the patient is transferred.
- BHU, which receives these forms in turn, returns the original/white acknowledgement slip to the transferring centre and the duplicate pink acknowledgement slip to his/her DMO duly filled after the patient report.

- The patient information on the original /white forms should be copied to the treatment card and stapled.

- Patient should be registered in the hospital TB register as "transfer in" highlighted in blue.

Hospital to hospital Transfer/refer and hospital to BHU Transfer. (Within the same District)

- Only the original/white form should be filled and sent to the centre where the patient is transferred/referred along with the acknowledgement slip.

- The receiving centre in turn fills up the acknowledgement slip after the patient reports and sends it back to the transferring/referring centre.

- The patient information on the original/white form should be copied to the treatment card and stapled.

- Patient should be registered as "transferred in" and highlighted in blue (Applicable to Hospital to Hospital transfer)

In case the patient does not report to the referred centre, it is the responsibility of the receiving centre to make efforts to trace the patient.

Monthly TB Report Form from BHU to District Hospital (Refer annexure XI)
At the end of each month, staff at the BHU must fill in the monthly report on tuberculosis patients, and send it to the district hospital. This information will be used to update the Tuberculosis Register and prepare the quarterly reports.

There are two sections on the form:
Section 1 (a) Cases referred from the district hospital. Write in the details of all patients who were referred for treatment from the district hospital during the previous month.

Section 1 (b) Cases referred/transferred from other district is for patients who started their treatment in other district, and have now come to your BHU to continue their treatment.

Section 2 is for cases having an outcome of treatment during the month. You must report all patients who were cured, completed treatment, died, failed, interrupted treatment or were transferred out during the previous month. To help you fill up this section, definitions of the outcomes are given at the bottom of the form.

For all Transferred cases, the feedback on sputum conversion, regular intake of treatment by the patient, supply of drugs and treatment outcome result at the end of treatment has to be intimated to the initial referring centre as soon as the patient arrives at an outcome. From the BHUs the treatment outcome must be sent to the Dzongkhag Hospital which has the master TB register and the TB in-charge further intimates to the initial treating centre after updating the TB register. This is to avoid duplication of reporting to the Programme.

Quarterly TB report on TB case registration in the reporting centre (Refer Annexure XII)

The TB in-charge fills this report every three months. They have to prepare this report at the end of each quarter from the Tuberculosis Register. We use this report to monitor laboratory performance, case finding, type of cases by age and gender, cases registered by treatment category, sputum conversion at 2/3 months for the previous quarter and treatment outcomes and quarterly monitoring of TB drugs. This report has seven sections.

Section I: Laboratory Diagnostic activity report: You fill this in from the Tuberculosis Laboratory Register for Patients who had under gone bacteriological sputum examination for each quarter. Report all patients with presumptive TB who had undergone bacteriological examination and patients with presumptive TB with positive bacteriological examination results by gender for the particular quarter.

Section II: All TB cases registered during the quarter: Under this section, report all bacteriologically confirmed pulmonary cases, clinically diagnosed pulmonary and bacteriologically and clinically diagnosed extra-pulmonary TB cases by types (new, relapse, previously treated excluding relapse and history of previous treatment unknown).

Section III: All new and relapse cases (bacteriologically confirmed of clinically diagnosed): Report all forms of new and relapse cases by age group and gender break down.

Section IV: TB-HIV collaborative activities (all TB cases registered during the quarter) Report all the TB patients who had undergone HIV test during the quarter. HIV test results, HIV positive TB patients on ART, HIV positive TB patients, HIV patients on IPT and CPT by gender need to be reported.

Section V: Sputum conversion report at 2/3 months for the previous quarter:

This report is prepared on new bacteriologically confirmed patients and retreatment registered during the quarter that ended three months ago (previous quarter). Sputum results are collected in the following manner in this report:

- At the end of second month for all bacteriologically confirmed new patients;
- At the end of third month for the bacteriologically confirmed new patients if sputum smear is not available at the end of second month or if the sputum is positive at 2 months and.
- all re-treatment TB patients.

The sputum conversion at the end of 3rd month is cumulative for all new bacteriologically confirmed cases i.e. those who converted at 2 months as well as those who converted at 3 months. The details for this should be available from the TB register for patients registered during the previous quarter.

Section VI: Treatment Outcome Report for the past one year:

All TB cases registered during the same quarter of the previous year should be reported in the treatment outcome of the current reporting period (for the quarter) by gender. The details for this should be available from the TB Register for those patients registered during same quarter of the past one year.

Submission of Quarterly TB report: The quarterly report should be submitted manually or electronically to the National TB Control Programme as per the following schedule. Once the electronic reporting system becomes fully functional in all 32 reporting centres, the manual reporting will be phased out.

The reports should be submitted as follows:

Quarter	**Date of completion.**
1st Quarter (January-March)	- By 14th of July of the same year.
2nd Quarter (April-June)	- By 14th of October of the same year.
3rd Quarter(July-September)	- By 14th of January of the succeeding year.
4th Quarter(October-December)	- By 14th of April of the succeeding year.

This quarterly TB report should be completed by respective TB in-charges

counter signed by Medical Officer and should be submitted to the NTCP before the end of the third week with a copy to the concerned District Health Officer (DHO). The report should be completed in all respect. This report provides information laboratory activities, case finding, sputum conversion, TB/HIV collaborative activities and treatment outcome of the patients. Along with this report, TB drugs stock monitoring and TB mortality report should also be submitted as per the template provided in the annexure. The correctness, consistency and timeliness of the report are very crucial by all the 32 reporting centres.

Compilation and analysis: The quarterly reports are compiled at the district level during the first two weeks of the next quarter and sent to the central level. The district TB in-charge, in consultation with DHO, CMO, medical officers and all concerned staff, should initiate remedial actions if technical and managerial indicators have not been met or if any other deficiencies are identified. Actions taken and further remedial actions proposed should be communicated to the NTCP. Whatever the data is gathered should be compiled, analyzed and need to put into action and planning by the reporting centers and district health officials.

At the central level, the NTCP compiles and analyses reports received from all the reporting centres and should also provide feedback to the districts within 6 weeks of receiving the reports. The NTCP also shares this information with other relevant departments within the Ministry of Health and uses them for publication in an annual report.

Quarterly Stock Monitoring of TB Drugs (Refer annexure XIII):
This form has to be completed and submitted to the NTCP along with the quarterly TB report by the TB reporting centers on a quarterly basis. In this report, the name of all TB drugs with opening balance, quantity received, quantity issued and closing balance with their expiry dates need to be reported. The quantities of drugs that have been date expired during the quarter with their expiry dates including the action taken also need reflected in the report.

National TB Reference Laboratory (NTRL) Register for Culture, Xpert MTB/ RIF and Drug Susceptibility testing (Refer annexure (Refer annexure XIV)

This Register is to be maintained at National TB Reference Laboratory at Royal Center for Disease Control, Sertbithang. The laboratory technician/ technologist is responsible for maintaining and updating the register on a timely manner. The register includes results from both types of tests – samples for initial diagnosis and for follow-up cultures for MDR-TB.

Serial No: Write the serial number of patients for the sputum sample received for undergoing tests. This is the serial number that should be allotted to each patient for particular date for each day.

Laboratory Identification No: Write the laboratory identification number of the particular date for each month. This is the number that is allotted to the patient from the 1st day of new starting calendar year from 1st January to 31st December of the particular calendar year. (to be reviewed by RCDC)
Name of Patient: Write the full name of the patient clearly.

Age/Sex: Write the complete number of years for each patient. Write 'M' for male and 'F' for female patient.

CID Number: Write the Citizenship Identity Card Number of the individual patient during the time of initial registration for the culture and DST.

Telephone Number: Write the patient's mobile number in the given column of the register and other contact details of the patient for informing and providing the culture and DST results.

Name of Referring Hospital: Mention the name of the health center/facility that has shipped the sample for culture and DST.

Reason for examination: Mention the reason for examination such as, bacteriologically confirmed pulmonary TB (NSP cases), clinically diagnosed pulmonary TB (NSN cases), previously treated cases, non-converters or MDR-TB culture follow up or other reasons if any.

Date of specimen received: Mention the date of the specimen received in the given column at National TB Reference Laboratory.

Specimen quality: Write the quality of sputum sample received for the test to be performed, such as saliva, blood stained, mucous pleurulent or contaminated etc. In case if the sample is contaminated, communicate with the referring center and take appropriate actions as required.

Microscopy and GeneXpert results: Mention the district lab result for the smear microscopy, GeneXpert results for the initial diagnosis, and NTRL concentrated smear results in the space provided.

Culture results: Record date of inoculation, type of culture done (solid or liquid), cultures results and date of the culture results in the register.

Culture identification: Record colony morphology, culture growth rate, rapid identification on test results and ZN confirmation in the culture identification column.

Results on Drug Susceptibility testing (DST): In this column, record the date of the DST processed, DST type (solid, liquid or LPA) and resistance pattern for each drugs. Further mention the date of the DST result.

Reporting: Under this, record and upload the reports of the culture and DST in Tuberculosis Information and Surveillance System (TbISS). At the same time share the culture and DST report to the respective referring centers and communicate accordingly for early initiation of the treatment.

Remarks: Any information of the patient which is not covered in the above should be mentioned in the remarks column.

Quarterly TB/MDR-TB Mortality Report (Refer Annexure XV):
All TB reporting centers in consultation with treating physician should report the death of TB patients who were on TB treatment. The actual cause of the death of TB patients should be ruled out and clearly mentioned in the reporting form and this report needs to be reported on a quarterly basis.

Contract Tracing Form (Refer Annexure XVI)

This form has to be used to conduct the contact tracing of those close contacts of bacteriologically confirmed PTB and MDR-TB patients. The questions as mentioned in the form should be asked to all those close contacts of the patients as per schedule of months at 0, 3, 6, 9 and 12 months. Those close contacts who may have TB symptomatic during the time of performing contact tracing need to be further investigated.

Supervisory Checklist (Refer Annexure XVII).

This checklist is to be used by the NTCP staff for the conduct of monitoring and supervision visits to the TB reporting centers. It can also be used by the district health officials who are responsible for monitoring and supervision activities. The findings and recommendations of the visit should be provided as a feedback to the reporting centers for follow up action as required.

Annual TB drugs Quantification Form (Refer Annexure XVIII)

This form has to be completed and submitted to the concerned division/NTCP by the TB reporting centers on an annual basis. In this reporting form, the total requirement of each TB drugs has to be reported taking into consideration of the physical stock balance with expiry dates. The quantification has to be worked out as per the case factor already mentioned in the form based on the average number of tablets to be taken by each patient, the number of days in each month and duration of treatment months for both intensive and continuation phases of treatment. The total number of TB patients that was treated in the previous year has to be considered while quantifying the total requirement of each drug for both new and retreatment TB cases. Buffer stock of 20-30% need to be considered in addition to the actual requirement quantity of each drug.

Annexure XIX: Combined annual treatment outcomes report for TB and for RR-TB/MDR-TB

The outcome report of both TB and MDR-TB should be reported at the end every calendar year as per the template provided in annexure XXI. While the outcome for TB patients are for the particular calendar year of the previous year, the outcome for MDR-TB patients should be for the previous two years cohort.

CHAPTER 16

Supervision and Monitoring TB Control Programme

Supervision can be considered a systematic process that increases the efficiency of health workers. It develops their knowledge, perfects their skills, improves their attitudes towards their work and increases their motivation. It is thus an extension of training. Supervision is carried out in direct contact with the health workers. Supervision is an essential part of any programme. Supervision can be defined as a relationship between different levels of the staff which is evaluative, serving to enhance the skills of the staff and to monitor the quality of the services provided by them at various levels of health facilities. Supervision is not a one-time activity but instead it is a continuous process that extends over time.

Supervisory visits

Supervisory visits give an opportunity to assess the performance of the health staff and to provide technical advice and guidance so that they can correctly perform their activities as stipulated in the programme. The objective of the supervisory visits should be to educate and guide the staff so that they can perform as per the guidelines.

Supervisory visits should be carried out on a regular basis at all levels.

- Supervision from the Central level to the Regional and District level: This includes supervisory visits by the National Programme in-charge and his team. It also includes a chest specialist, a medical expert, a Microbiologist, and/or a Pharmacist. Efforts should be made to visit each district at least once a year. Under performing districts should be visited more frequently.
- Supervision is also conducted by Regional and District level officers. This includes supervisory visits by the DHO, Medical superintendent, TB In-charge and/or medical officer at the regional level to health institutions, reporting centres and microscopy centres in their respective districts.

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

For the supervisory visit to be productive and effective it should be planned well in advance, preferably at least a quarter earlier. Adequate preparation should be made as well.

A supervisory check list should be used. Check list should include activities in relation to

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

The concerned staff should be informed about the visit in advance so that they can be prepared and are available at the time of the visit.

Some ways to collect information during supervisory visits are:

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

In review of documents emphasis should be given on:

- **Accuracy:** Also known as validity. Accurate data is considered correct: the data measures what it is intended to measure.
- **Reliability:** The data generated by a programme's information system are based on protocols and procedures that do not change according to who is using them and when or how often they are used.
- **Precision:** This means that the data has sufficient detail. For example, an indicator requires the number of TB patients by sex who have received HIV counselling & testing and have received their test results. An information system lacks precision if it is not designed to record the sex of the individual who received counselling and testing.
- **Completeness:** Completeness means that an information system from which the results are derived is appropriately inclusive: it represents the complete list of eligible individuals or units and is not just a fraction of the list.

- **Timeliness:** The data is considered timely when it is up-to-date (current) and when the information is available on time.
- **Integrity:** Data has integrity when the system used to generate it is protected from deliberate bias or manipulation for political or personal reasons.
- **Confidentiality:** Confidentiality means that clients are assured that their data will be maintained according to national and/or international standards. This means that personal data is not disclosed inappropriately and that data in hard copy and electronic form are treated with appropriate levels of security.

Observation of staff and procedures may include:

- Interaction with patients.
- Personal safety and infection control.
- Quality of care.
- Accuracy of procedures.
- Measures to minimize wastage.
- Waste disposal.
- Cleanliness.
- Status/condition of buildings and other resources.

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

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

Supervising officer should verify:

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

Monitoring and Evaluation

Monitoring and evaluation are essential tools for identifying and measuring the results of any programme or project. While evaluation can only be done

after a certain time and requires more thorough investigations, monitoring provides regular information on how things are working.

- Monitoring can be defined as a continuous process of data collection and analysis used to assess a programme (or a project) and it's comparison with its expected performance.
- Evaluation is defined as a systematic and objective measurement of the results achieved by a programme, or a project, in order to assess its relevance, its coherence, the efficiency of its implementation, its effectiveness, its impact, and its sustainability.

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

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

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

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

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

Programme monitoring indicators
Case notification indicators

i) Notification rate of new and relapse TB cases

No of new and relapse TB cases notified during the year / Mid-year population for the same year	X 100,000 population

If all new and relapse cases were to be notified, this would be an indicator for incidence rates. Notification of new cases is indicator of spread of the disease

ii) Notification rate of new bacteriologically confirmed TB cases

No of new bacteriologically confirmed cases reported for a specified year / Mid-year population for the same year	X 100,000 population

Both these indicators are important for observing trends in case notification over several years. This is usually calculated annually. This should be analysed by age and sex at national level (age group/ sex specific rates per 100,000 population). It provides information on the trend of TB.

iii) Proportion of bacteriologically confirmed TB cases

Total number of bacteriologically confirmed cases reported for a specified year / Total number of TB cases reported for the same year	X 100%

This indicator is particularly helpful in determining the use of lab diagnostics in diagnosing TB cases. As the use of newer, sensitive diagnostics increases, this proportion should increase.

iv) Proportion of bacteriologically confirmed cases among TB symptomatics tested

No of bacteriologically confirmed cases detected / Total number of TB symptomatics examined	X 100

When the prevalence of TB decreases in the community this rate also decreases. However in certain instances, the rate may increase initially if there are intensified case finding activities and with introduction and greater use of highly sensitive molecular tests like Xpert MTB/RIF

v) Re treatment TB casestested

Number of re treatment TB cases registered during specified time period / Total number of TB cases registered in the same period	X 100

Generally retreatment cases are a small proportion of TB cases. A high proportion of retreatment cases could be due to cases not being given appropriate treatment in the first course of treatment, adherence problems or poor quality of drugs. This should decline with time with proper implementation of quality assured services. However a very low proportion of retreatment cases may also point to the fact that history of previous treatment is not being properly taken.

vi) New extra-pulmonary TB cases

No of new extra pulmonary TB cases registered during a specified time period / Total No of new TB cases registered in the same period	X 100

High proportions of EP-TB cases may indicate an improved access to diagnostics specifically WHO approved rapid diagnostics (like Xpert MTB/RIF), imaging diagnostics detecting occult TB or a higher proportion of HIV co-infection. The data needs to be analysed taking into account local epidemiology.

vii) Diagnosis of childhood TB

No of childhood TB cases registered during a specified time period / Total No of all TB cases registered in the same period	X 100%

viii) Detection rate of RR/MDR-TB cases

No of laboratory confirmed RR/MDR-TB cases registered during a specified time period / Estimated MDR-TB cases among notified TB cases in the same period	X 100%

ix) Proportion of HIV TB co-infected cases started on ART

No of HIV-TB co-infected cases started on ART / Number of TB cases found HIV positive in the same period	X 100

Programme outcome indicators

Indicators of case holding

i) Sputum conversion rate at the end of the intensive phase of treatment for new TB cases

No. of new bacteriologically confirmed pulmonary TB cases registered in a specified time period that are smear negative at the end of initial phase of treatment / Total No of new bacteriologically confirmed pulmonary TB cases registered for the treatment in the same period	X 100

The proportion of new cases showing negative sputum smear at the end of 2 months is at least 80%

ii) Cure rate of new bacteriologically confirmed TB cases

No of new bacteriologically confirmed TB cases registered in a specified time period that were declared cured / Total number of new bacteriologically confirmed TB cases registered in the same period	X 100%

iii) Treatment completion rate for new bacteriologically confirmed TB cases

No of new bacteriologically confirmed TB cases registered in a specified time period that completed treatment and did not meet the criteria for cure or failure / Total No of new bacteriologically confirmed TB cases registered in the same period	X 100%

iv) Treatment completion rate for all TB cases

No of TB cases registered in a specified time period that completed treatment and did not meet the criteria for cure or failure / Total No of TB cases registered in the same period	X 100

v) Cure rate of patients started on second line treatment

No of RR/MDR- TB cases registered in a specified time period that were declared cured / Total number of RR/MDR- TB cases registered in the same period	X 100%

vi) Treatment completion rate of RR/MDR-TB cases

No of RR/MDR-TB cases registered in a specified time period that completed treatment and did not meet the criteria for cure or failure / Total No of RR/MDR-TB cases registered in the same period	X 100

vii) Treatment Failure Rate

No of new bacteriologically confirmed pulmonary TB cases registered in a specified time period that are sputum positive at five months or later after initiating treatment	X 100
Total No of new bacteriologically confirmed pulmonary TB cases registered in the same period	

Ideally this should be less than 5%

viii) Loss to follow-up Rate

No of all TB cases registered in a specified time period that interrupted treatment for more than two consecutive months	X 100
Total No of TB cases registered in the same period	

Ideally this should be less than 5%

x) Death rate

No of deaths occurred among TB cases registered in a specified time period, due to any reason during course of treatment	X 100
Total No of TB cases registered in the same period	

This is usually between 3-5%. All deaths among TB patients that occurred due to any cause are accounted here.

xi) Treatment Success Rate*

Treatment Success Rate = Cure rate + Treatment Completion rate

The target for treatment success rate is at least 90% for all TB cases.

* Can be used to measure treatment success rate of RR/MDR-TB cases as well. The country target of success rate among RR/MDR-TB cases is 75% Cohort analysis of re-treatment cases, clinically diagnosed cases and extra pulmonary cases also should be done in the same way as of the analysis carried out for bacteriologically confirmed TB cases.

The NTCP will give feed back to the District regarding the performance of their district for the quarter and suggest corrective actions, if any.

In addition, review meetings are conducted annually with the participation of all stakeholders.

Annexure I:

Presumptive TB Referral Register

Right Side of the Register

Sl.No.	Date of referral for sputum microscopy	Name of Patient	Age	Sex	Address	Telephone No.	CID No.	Patient History				
								Cough for 2 weeks or more	Unexplained fever	Blood in the sputum	Weight loss	Others

Left Side of the Register

HIV Status			History of previous TB treatment	Family History of TB	Result of sputum smear microscopy	Action Taken/Remarks
+ve	-ve	Unknown				

Annexure II: Weight based dosing in adults

Weight-based oral anti-TB drug daily dosing in adults ≥30 kg						
DRUGS	**DAILY DOSE**	**30–35 KG**	**36–45 KG**	**46–55 KG**	**56–70 KG**	**>70 KG**
Isoniazid	4–6 mg/kg once daily	150 mg	200 mg	300 mg	300 mg	300 mg
Rifampicin	8–12 mg/kg once daily	300 mg	450 mg	450 mg	600 mg	600 mg
Pyrazinamide	20–30 mg/kg once daily	800 mg	1000 mg	1200 mg	1600 mg	2000 mg
Ethambutol	15–25 mg/kg once daily	600 mg	800 mg	1000 mg	1200 mg	1200 mg
Rifabutin	5–10 mg/kg once daily	300 mg	300 mg	300 mg	300 mg	300 mg
Levofloxacin	750–1000 mg once daily	750 mg	750 mg	1000 mg	1000 mg	1000 mg
Moxifloxacin*	400 mg once daily	400 mg	400 mg	400 mg	400 mg	400 mg
Ethionamide	500–750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750 mg	1000 mg
Prothionamide	500–750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750 mg	1000 mg
Cycloserine	500–750 mg/day in 2 divided doses	500 mg	500 mg	500 mg	750 mg	750 mg
p-aminosalicylic acid[a]	8 g/day in 2 divided doses	8 g	8 g	8 g	8 g	8–12 g
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	600 mg	600 mg	600 mg	600 mg	600 mg
Amoxicillin/clavulanic acid7/1	80 mg/kg/day in 2 divided doses	2600 mg	2600 mg	2600 mg	2600 mg	2600 mg
Amoxicillin/clavulanic acid8/1	80 mg/kg/day in 2 divided doses	3000 mg	3000 mg	3000 mg	3000 mg	3000 mg

*for shorter MDR-TB regimen, 800 mg once a day is used

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

Annexure III: Weight-based dosing of ATT 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

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

Annexure IV:

Request for Mycobacterium tuberculosis examination by Microscopy and GeneXpert MTB/RIF

Name of Hospital: _____Date of request _____ / _____ / _____

Name of Patient: _____ Age: _____Sex M/F: _____

Patient Address: _____Patient occupation:_____

Patient's Telephone No.: _____Patient's CID no_____

Specimen type : [Sputum] [EP]

Test requested : [Microscopy] [Xpert MTB/RIF]

Reason for Examination(mark√):

- [ ] Diagnosis: if diagnosis presumptive RR-TB/MDR-TB: [ ] Yes [ ] No
- [ ] Follow up: if follow up months of treatment_____
- High risk group*: [ ] Yes [ ] No [ ] Unknown
- Previously treated for TB? [ ] Yes [ ] No [ ] Unknown
- Others, please specify:_____

Date sample sent for direct Xpert test (If no Xpert MTB/RIF test available,)_____/_____/_____

Sample shipped by & Contact no.:_____

Microscopy and GeneXpert MTB/RIF Result (to be completed in Laboratory)

Lab serial No./Lab ID	Date of specimen collection	Date specimen received at laboratory	Visual appearance (blood stained, Mucopurulent, saliva)	Microscopy result					Xperts result*
				No AFB seen (0 AFB/100 HPF)	**scanty** (1-9AFB/HPF, record the exact count)	**1+** (10-99 AFB/ HPF)	**2+** (1-10 AFB/ HPF)	**3+** (>10 AFB/ HPF)	

* Select one of the following for the xpert MTB/RIF result:

(T) - MTB detected, Rifampicin not detected
(RR)- MTB detected, Rifampicin detected
(TI) - MTB detected, Rifampicin indeterminate
(N) - MTB not detected
(I) - Invalid/no result/error

Examined by (Name & Signature): _____ Date of result:_____/_____/_____

- High risk group as per National TB guideline

Annexure V:

Tuberculosis Drug Resistance Surveillance

National Tuberculosis Reference Laboratory, RCDC
Version 1. 4

Request form for Culture & DST of Mycobacterium tuberculosis complex

Name of Hospital: _____Date of request _____ / _____ / _____

Name of Patient: _____Age: _____Sex M/F: _____

Patient Address: _____Patient occupation:_____

Patient's Telephone No.: _____Patient's CID no_____

Reason for examination/TB case: [ ] New Smear positive [ ] New Smear Negative [ ] Retreatment

[ ] MDR culture follow-up, Month of follow-up & DS No.: .....

[ ] Others, specify the reason.....

.....

SAMPLE INFORMATION

Date sample collected	Specimen type(mark √ or circle & specify if Extra Pulmonary TB (EP))	Microscopy Smear result (specify the grading)	GeneXpert MTB/RIF result
_____/_____/_____	[Sputum][EP].....		
_____/_____/_____	[Sputum][EP].....		

If EP sample, Direct inoculation in solid media: [ ] Yes [ ] No

Shipment prepared by & contact no.: ……..... Date Sample shipped to RCDC:.....

Rejection Criteria

Sample will be rejected under following conditions:

- Sample leakage during transportation
- Incomplete label on sputum container (label container with name, age, sex, CID no.& hospital address)
- Cold chain not maintained
- Presence of food particles & sample less than accepted quantity
- Incomplete Sputum shipment form

RCDC, NTRL Use Only

Shipment received by: ……..…….. Date samples received: ……. / ……. / …….

Sample shipment packaging: Satisfactory |___| Unsatisfactory |___|

Condition of sample received: Intact |___| Leakage |___| Container broken & leakage |___|

Specimen Type: SP 1: Mucopurulent |___| Saliva |___| Bloody |___| Contaminated |___|

SP 2 Mucopurulent |___| Saliva |___| Bloody |___| Contaminated |___|

Quantity of specimen received: Satisfactory (more than 5ml) |___| Unsatisfactory (> 5 ml) |___|

NTRL sample code: **DS/EP-** …… Year: ……. If rejected, reason.....

Royal centre for Disease Control, National Tuberculosis Reference Laboratory.

Contact details :(+975) 02-323317 EPABX: (+975) 02-350577/350578 Fax: (+975) 02-332464

Annexure VI: District TB Laboratory register for smear microscopy and Xpert MTB/RIF (1 of 2)

Serial no.	Lab. serial no.	Name of Patients	Age	Sex	CID Number	Telephone Number	Patient address	Treatment unit	HIV infection (Yes/No/ Unknown)	Patient previously treated for TB (Yes/No/ Unknown)	Date of specimen received	Type of specimen (P or EP)	Quality of specimen (Mucopurulent/ Saliva/ blood stained/ contaminated

District TB Laboratory register for smear microscopy and Xpert MTB/RIF (2 of 2)

	Diagnosis Specimen Results				Follow up sputum examination results							Date of sample sent for Culture and DST	Remarks
		Smear microscopy results.											
Specimen quality(MP ,SAL,BLD, Contam)	GeneXpert MTB/RIF result	Spot	Morning	Spot	2/3 months		GeneXpert MTB/RIF result for Non-converters	4/5 months		6/8 Months			
					Morning	Spot		Morning	Spot	Morning	Spot		
	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date	Date		

Smear results reported as: 0 = No AFB 1-9 = exact number if 1-9 AFB/100 HPF (Scanty) + = 10-99 AFB/100 HPF ++ = 1-10 AFB/HPF +++ = >10 AFB/HPF
Xpert MTB/RIF test result 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
**If Xpert MTB/RIF indeterminate result, indicate error code or "invalid".

Annexure VII: District TB register (page 1 of 2)

Sl.No.	Date of registration	District TB Control No.	Name	Age	Sex	CID No.	Resident address	Health facility where treatment is started	Date of treatment started	History of previous treatment						Transfer in	Site
										New	Previously treated patients				Previous treatment history unknown		PTB/EPTB
											Relapse	TAF	TA loss to follow up	Other previously treated patients			

District TB register (page 2 of 2)

Treatment Category		TB/HIV activities		Smear (S), culture (C) or Xpert MTB/RIF (X) results and other examinations**										Treatment outcome and date outcome determined							Remarks
				At the time of TB diagnosis					Month 2 or 3		Month 4 or 5		Rx (6 or 8)		Outcomes						
Initial regimen with FLDs	Retreatment regimen with FLDs	ART Yes/ No	CPT Yes/ No	HIV infection (Y/N/ unknown)	Drug resistance (RR/MDR/None/ unknown)	S	C	X	S	C	S	C	S	C	Cured	T.compl.	T.Failure	Died	Lost to follow-up	Not evaluated	Moved to second-line treatment regimen	
						Date			Date		Date		Date									

Annexure VIII: TUBERCULOSIS TREATMENT CARD Name of Treatment Centre:.....

Name of Patient: .....Date of Birth: .....Age: ..... Sex: ☐ M ☐ F C ID No.: .....

Occupation:..... Telephone No. ..... **District TB Control No:** ..... Date of registration: .....

Local address: .....Permanent address: .....

Date of treatment started: ..... Name/Designation of DOT Provider (with Tel No):.....

Name and address of contact person (with Tel No.):.....

Category
New ☐
Re treatment ☐

Disease Classification	
Pulmonary Bact. Confirmed ☐	EPTB ☐
Pulmonary Clinically Diagnosed ☐	Site.....

Type of Patient			
New	☐	Treatment after Loss to Follow Up	☐
Relapse	☐	Other Previously Treated	☐
Treatment after Failure	☐	Unknown Previous TB Treatment History	☐

PRESCRIBED TREATMENT REGIMEN	
Intensive Phase	Continuation Phase

TB/HIV	
Date of VCT offered	
VCT Status	
Date of ART started	
Date of CPT started	
Date of IPT started	

Month	**Results of Sputum/ other specimen examination**									Weight (Kg)
	Smear			GeneXpert			Culture/DST			
	Date	Lab. No.	Result	Date	Lab.No.	Result	Date	DS No.	Result	
0										
2										
3										
4										
5										
6										
8										

Referral by: ☐ Self referral ☐ MCH Unit ☐ VCT Unit ☐ VHW ☐ Indigenous Unit ☐ Others, specify:.....

Duration of IP (in months): .....

Day / Month	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

Intensive Phase (Mark '√' for directly observed administration, '**S**' for supply for self-administration and '**0**' for treatment interruption)

Continuation Phase Duration of CP in months: .....

Enter '√' on day of observed drug administration and draw a horizontal line (----------) to indicate the number of days supply given for self administration

Day / Month	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

Treatment Outcome	Date of Decision
Cured	
Treatment Completed	
Treatment Failure	
Died	
Lost to Follow up	
Not Evaluated	

Remarks: (Include co morbidities and adverse drug reactions if any)

_____

_____

_____

Contact investigations activities undertaken and IPT started

_____

_____

_____

Annexure IX: TB PATIENTS CARD

Treatment Center:

Name: _____

CID No. _____

TB Control Number: _____

Date of registration_____

Date of Treatment started _____

Did you know?

- TB is curable! Directly Observed Treatment (DOT) ensures Cure!
- TB is caused by a germ and is spread by coughing and sneezing
- Cough for 2 weeks or more could be due to TB.
- Take TB medicines regularly and get re-examined as advised by health worker
- Treatment is for only 6 to 8 months
- Take your medicines on time daily to ensure cure

Age/Sex _____

Address: _____

_____ Phone No: _____

Name of DOT provider: _____

Address of DOT provider: _____

Contact Number of DOT provider:_____

Treatment Regimen:_____

Date of treatment started:_____

Disease Classification:

☐ Bacteriologically confirmed TB ☐ clinically diagnosed TB

☐ Retreatment ☐ EPTB Site:_____

Type of Patient:

☐ New ☐ Relapse ☐Treatment after failuPre ☐ Treatment after loss to follow up

☐ Other previously treated patients. ☐ Patients with unknown previous treatment history

☐ Others specify_____

Treatment Category: New **Retreatment**

Chest X-Ray: Date: Result:

VCT Offered: ☐ Yes ☐ No. If Yes, Date of VCT offered: _____

INTENSIVE PHASE

Prescribed Treatment Regimen:	(RHZE)	Streptomycin

Date/ month	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

Result of sputum examination, GeneXpert test, Culture & DST

Sputum smear microscopy				GeneXpert test result		Culture and DST				Weight (kg)
Month	Date	Lab No.	Result	Initial test result	Repeat test if any	S	H	R	E	
0										
2										
3										
4										
5										
6										
8										

TB CAN BE CURED BY ENSURING REGULAR INTAKE OF MEDICINES AS ADVISED BY HEALTH WORKERS!

CONTINUATION PHASE

Prescribed Treatment Regimen:

(RH)	(HRE)

Date/ month	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

Date of Treatment outcome:

Treatment Outcome: ☐ **Cured** ☐ **Treatment completed** ☐ **Died**

☐ **Treatment after failure** ☐ **Lost to follow up Not evaluated**

Remarks:

If you find this card, send it to your nearest Health centre

Annexure X: Patient referral/acknowledgement form

Original

1. To be filled in the referring centre and sent to the health centre where the patient is referred / transferred (duplicate to be sent to DMO/ Superintendent, by the referring health centre)

Name of the referring health centre: _____ Date referred/transferred _____

TB control Number _____

Name of the health centre where referred: _____

Patient's Name: _____ Age: _____ Sex: M/F

Address: _____ Contact No.: _____

Disease Classification:

☐ Bacteriologically confirmed PTB
☐ Clinically diagnosed TB cases
☐ EPTB

Site: _____

Patient Type:

☐ New
☐ Relapse
☐ Treatment after failure
☐ Treatment after loss to follow up
☐ Other previously treated patients
☐ Patients with unknown previous TB treatment history

Date of starting treatment: _____

TB drugs given up to: _____ Signature: _____ Designation: _____

II. Referral acknowledgement: to be filled and sent back to the health centre that had referred the patient. *(Duplicate to sent to your DMO/Superintendent)*

Patient's name: _____Age: _____ Sex: M/F

TB Control Number: _____

The above named patient reported to this health centre on: _____ and the patient is now registered with us.

Name of the health centre: _____

Signature: _____

Designation: _____

Patient referral / acknowledgement form

Duplicate

2. To be filled in the referring centre and sent to the health centre where the patient is referred / transferred (duplicate to be sent to DMO/ Superintendent, by the referring health centre)

Name of the referring health centre: _____ Date referred/transferred _____

TB control Number _____

Name of the health centre where referred: _____

Patient's Name: _____ Age: _____ Sex: M/F

Address: _____ Contact No.: _____

Disease Classification:

☐ Bacteriologically confirmed PTB
☐ Clinically diagnosed TB
☐ EPTB

Site: _____

Patient Type:

☐ New
☐ Relapse
☐ Treatment after failure
☐ Treatment after loss to follow up
☐ Other previously treated patients
☐ Patients with unknown previous TB treatment history

Date of starting treatment: _____

TB drugs given up to: _____ Signature: _____ Designation: _____

II. Referral acknowledgement: to be filled and sent back to the health centre that had referred the patient. *(Duplicate to sent to your DMO/Superintendent)*

Patient's name: _____Age: _____ Sex: M/F

TB Control Number: _____

The above named patient reported to this health centre on: _____ and the patient is now registered with us.

Name of the health centre: _____

Signature: _____

Designation: _____

Annexure XI: TB monthly report form BHU to District Hospital

Name of Basic Health Unit: _____ District: _____

Month and year: _____

Name of reporter: _____Signature: _____

Date: _____

1. Cases added during the month

1. a. Cases referred from the district hospital

Sl. No.	TB Control No.	Patient name	Age	Sex	Disease classification	Type of patient	Date of start of treatment	Treatment Category (new/retreatment)
01								
02								
03								
04								
05								

1. b. Cases transferred from other districts

Sl. No.	TB Control No.	Transferred From	Patient name	Age	Sex	Disease classification	Type of patient	Date of start of treatment	Treatment Category (new/retreatment)
01									
02									
03									
04									
05									

Disease Classification: ☐ Bacteriologically confirmed PTB ☐ clinically diagnosed TB cases ☐ EPTB

Type of Patient: New. Relapse. Retreatment. Treatment after failure. Treatment after lost to follow up. Other previously treated patients Patients with unknown previous TB treatment history

2. Cases having an outcome of treatment during the month:

Sl. No.	TB Control No.	Patient name	Age	Sex	Treatment outcome	Date	Treatment Category (new/retreatment)
01							
02							
03							
04							
05							

Possible outcomes: Cured, treatment completed, treatment failed, died, lost to follow up, not evaluated, treatment success.

Annexure XII: Quarterly report on TB case registration in the reporting center

Name of Reporting Center: _____ Dzongkhag:_____	Patients registered during _____ quarter of year_____
Name of TB In-charge:_____ Signature: _____	Date of report submission: _____

Section 1: Laboratory diagnostic activity report:

Gender	Patients with presumptive TB undergoing bacteriological examination	Patients with presumptive TB with positive bacteriological examination result
Male		
Female		
Total		

Section 2: All TB cases registered during the quarter

TB Patient Type	New		Relapse		Previously treated (excluding relapse)		Previous treatment history unknown		Total	
	M	F	M	F	M	F	M	F	M	F
Pulmonary, bacteriologically confirmed										
Pulmonary, Clinically diagnosed										
Extra-pulmonary TB, bacteriologically confirmed or clinically diagnosed										
Total										

Section 3. All new and relapse cases (bacteriologically confirmed or clinically diagnosed) registered during the quarter by age group and sex

Gender	0–4	5–14	15–24	25–34	35–44	45–54	55–64	>65	Total
Male									
Female									
Total									

Section 4: TB/HIV activities (all TB cases registered during the quarter)

Gender	Patients tested for HIV at the time of TB diagnosis or with known HIV status[d] at the time of TB diagnosis	HIV-positive TB patients	HIV-positive TB patients on ART	HIV-positive TB patients on CPT	HIV-positive patients on IPT
Male					
Female					
Total					

[a] Registration period is based on date of registration of cases in the TB register, following the start of treatment. Q1: 1 January – 31 March; Q2:1 April – 30 June; Q3: 1 July – 30 September; Q4:1 October – 31 December.

[b] "Transferred in" cases are excluded.

[c] Data aggregated from the TB laboratory register based on *Date specimen received,* and **excluding** patients examined for follow-up.

[d] Include all TB patients previously known to be HIV-positive (e.g. documented evidence of enrolment in HIV care such as enrolment in the pre-ART register or in the ART register once started on ART) or with a documented negative HIV test conducted at the time of TB diagnosis.

Section 5: Sputum conversion report at 2/3 months for the previous quarter:

Reporting Center:_____ Patients registered during _____ quarter of year_____ Date of report submission: _____

Type of Patient	No. of new smear positive cases registered in the previous quarter		Negative		Positive		No result	
	M	F	M	F	M	F	M	F
Pulmonary, bacteriologically confirmed – New								
Relapse								
Previously treated for TB, excluding relapse								
Previously treated history Unknown								
Total								

Section 6: Treatment Outcome report of all TB cases registered for the same quarter of the previous year (except for TB cases moved to the second-line treatment register)

Reporting Center:_____ Patients registered during _____ quarter of year_____ Date of report submission: _____

TB patient type	Number of cases registered		Treatment outcomes											
			Cured		Treatment completed		Treatment failed		Died		Lost to follow-up		Not evaluated	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Bacteriologically confirmed, new and relapse														
Clinically diagnosed, new and relapse														
Retreatment (excluding relapse)														
HIV-positive, all types														
Total														

[a] Registration period is based on date of registration of cases in the TB register, following the start of treatment. Q1: 1 January – 31 March; Q2:1 April – 30 June; Q3: 1 July – 30 September; Q4:1 October – 31 December.

Section 7: Treatment Outcome Indicators (Treatment Success Rate)

Type	Cure Rate (B/A*100)	Treatment Completed rate(C/A*100)	Success Rate (B+C/A*100)	Mortality rate (D/A*100)	Failure Rate (E/A*100)	Lost to follow up (F/A*100)	Not Evaluated (G/A*100)
Bateriologically confirmed, new and relapse							
Clinically diagnosed, new and relapse							
Retreatment (excluding relapse)							
HIV -Positive, all types							
Total							

Annexure XIII: Quarterly Stock Monitoring of TB Drugs

Name of reporting Centre:_____ Report for the _____ quarter of year_____

Date of report submission: _____ Reported submitted by:_____ Signature_____

Name of TB Drugs	Opening Balance during the start of the quarter	Quantity received during the quarter	Quantity issued during the quarter	Closing Balance at the end of quarter	Expiry Date	Quantity of Expired drugs if any	Date of Expired drugs	Action taken on the expired drugs if any
HRZE (A)								
HR (A)								
HRZ (A)								
HRZ (P)								
HR (P)								
Streptomycin Inj.								
H 300mg (A)								
H 100mg (P)								
Z 400mg								
E 400mg								
E 100mg (P)								
Rifampicin 300mg								
Rifampicin 100mg								
Cycloserine 250mg								
Ethionamide 250mg								
Inj. Kanamycin								
Levofloxacin 250mg								
Pyrezinamide 400mg								
PAS								

Annexure XIV: NTRL Laboratory register for culture, Xpert MTB/RIF and drug susceptibility testing (page 1 of 2)

RCDC, NTRL Specimen Registration, Culture and DST Results Register Month_____Year_____

Sl. No.	Lab ID.No.	Patient Name	Age & Sex (M/F)	CID Number	Phone Number	Name of referring hospital	Reason for Examin-ation (NSP/NSN/Relapse/NC/retreatment	Specimen	Date of specimen collected	Date specimen received at NTRL	Specimen quality (MP, BLD, Sal, Contam)	Microscopy & GeneXpert Result			Culture Results			
												District lab result	Gene Xpert result **	NTRL Conc. Smear result	Date inoculated	Type of culture (solid/ liquid)	Culture results*	Date of culture result
								A										
								B										
								A										
								B										
								A										
								B										

MP- Mucopurulent, BLD-Bloody, Sal-Saliva, Contam-Contamination, NSP- New Smear Positive, NSN- New Smear Negative, NC- Non convertor

*Culture result reported as follows: Solid Culture: 0 =no growth reported Liquid Culture: +ve = Positive
-Ve = Negative

(1–9) = <10 colonies (report number of colonies)
\+ = 10–100 colonies
++ = >100 colonies
+++ = innumerable or confluent growth

**Xpert MTB/RIF test result 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
**If Xpert MTB/RIF indeterminate result, indicate error code or "invalid".

NTRL Laboratory register for culture, Xpert MTB/RIF and drug susceptibility testing (page 2 of 2)

Lab. ID. No.	Culture Identification				Result of Drug Susceptibility testing***															Reporting		Remarks
	Colony morphology	Solid culture Growth rate	Rapid Identification test result (MTBC/MOTT)	ZN confirmation	Date DST processed	DST type (Solid/ liquid/ LPA)	SM	INH	RIF	EMB	AMK	Km	Cm	FQ	Other _____	Other _____	Other _____	Other _____	Date of DST result	Report Available in TBISS (mark √/X)	If not available in TBISS, date result reported to TB Incharge	

MTBC- Mycobacterium Tuberculosis Complex, MOTT- Mycobacterium Other Than Tuberculosis

First-line drug abbreviations:
SM= streptomycin; INH= isoniazid ; RIF= rifampicin ; EMB=ethambutol; Z= pyrazinamide

Second-line drug abbreviations:

Amk=amikacin; Km= kanamycin; Cm=capreomycin; FQ=fluoroquinolone; Lfx= levofloxacin; Mfx= moxifloxacin; Ofx=Ofloxacin; Gfx=gatifloxacin; Eto=ethionamide;

Pto=prothionamide; Cs= cycloserine; PAS=*p*-aminosalicylic acid;Amx/Clv= amoxicillin/clavulanate; Clr= clarithromycin; Cfz= clofazimine; Ipm=imipenem;

Lzd= linezolid; T=thioacetazone

*** Report result as S= susceptible, R= resistance, C= Contaminated, ---- =Testing not done

Lzd= linezolid; T=thioacetazone

Annexure XV: Quarterly TB/MDR-TB Mortality Reporting Form

Name of TB Reporting Centre:		Dzongkhag:	
Name of Patient		Type of TB:	
Age/Sex		Date of diagnosis:	
Date of treatment started:		Address of the patients:	
Was the patient provided DOT while on treatment.		Was the patient on regular TB or MDR-TB treatment or not?	
Status of TB/HIV co-infection		Is there any one with TB or MDR-TB in the same household?	
Place of death:		Date of death:	
Cause of death (details to be provided)			
Signature of reporting health worker		Name of reporting health worker:	
Date of report submission:		Remarks:	

Annexure XVI: Contact Tracing Form

Name of Index case: Age/Sex:

Total number of people in the HH: Total male: Total female:

Write Yes or No in the table below for each of the close contact of Index patient against the schedule of months of contact tracing.

Details of close contacts of the Index case:

Name of contact	Age/ Sex	Do you have a current cough? (Yes or No)	Do you have fever? (Yes or No)	Have you lost weight? (Yes or No)	Do you have night sweats? (Yes or No)	Schedule of months to perform contact tracing (Date to be written in each column)					Remarks
						0	6	12	18	24	

SOPs for health care worker screening

1. All health care workers working in laboratories or health facilities providing TB care services or when the health care worker is considered at risk for other reasons will undergo regular screening for TB.

2. Symptomatic TB screening will be carried out every 6 months and a Chest X-ray screening done every year.

3. All health care workers found to have presumptive TB on screening or who have symptoms of TB will undergo GeneXpert testing as well as Culture and DST.

4. HIV positive health care workers would be offered relocation from laboratory jobs or patient care services where there is direct exposure to TB bacilli and risk of contracting TB is high.

Annexure XVII: Supervisory Checklist

Checklist for Supervisory Visits to the health facilities/TB Reporting Centers

Name of Health Facility: Name of TB in charge: Date of visit:

	Check TB Treatment Cards:	**Yes**	**No**	**Remarks**
1	Is the treatment card complete and up-to-date?			
2	Is each patient on the correct treatment regimen?			
3	Are all details of patient's information properly recorded and legible?			
4	Are sputum examination results recorded correctly?			
5	Are patient undergoing smear examination at 2 months (3 months in retreatment patients)			
6	Are patients undergoing smear examination at 4/5 months of treatment?			
7	Are patients undergoing smear examinations at the end of the treatment			
8	For each patient who has completed treatment, is the information on the TB treatment card sufficient to determine treatment outcome?			
9	Is there any record of contact investigations being done for the patient?			
10	Has the patient undergone DST (must for all retreatment cases at start of the treatment and all cases when found smear positive during follow-up)			
	Review of TB Register			
1	Does the facility have a district TB register?			
2	If yes, are the results of sputum smear microscopy written in the TB register?			
3	Is the color coding for NSP (bacteriologically confirmed) and transferred in and out cases highlighted as per the guideline?			
4	Is there delay between receiving microscopy results to initiating of treatment?			
5	Do sputum results recorded in the TB register match with that of treatment cards and laboratory register?			
6	No. of bacteriologically confirmed PTB cases that are converted into negative at 2 months that were registered in the previous quarter?			
7	No. of new bacteriologically confirmed cases that were cured and treatment completed that were registered in the previous year?			
	Review of other records			
1	Are the patient acknowledgement/feedback forms maintained for the transferred cases?			

2	Contact investigations of TB patients carried out?			
3	Are all TB patients offered HIV test?			
	Review of Lab Registers and Lab Supplies			
1	Does the facility have a Lab. TB register?			
2	If yes, are the results of smear microscopy written in the given column? (Red mark for positive cases)			
3	Is address and contact details of patient properly written?			
4	Do the sputum result in the Laboratory register match with that in the TB register?			
5	Have all the smear-positive patients started on treatment?			
6	A microscope in good working condition?			
7	An adequate supply of reagents?			
8	An adequate supply of micro-slides/markers?			
9	An adequate supply of sputum containers?			
Examine and ask about supplies. Is there:				
1	Any adequate supply of anti-TB drugs?			
2	Any TB drugs that are expired?			
3	Are the drugs stored properly?			
4	Any adequate supply of co-trimoxazole?			
5	Stock balance of HRZE (adults)			
6	Stock balance of HR (adults)			
7	Stock balance of HRE (adults)			
8	Stock balance of HRZ (Paediatric)			
9	Stock balance of HR (Paediatric)			
10	Stock balance of Isoniazid 300mg			
11	Stock balance of Isoniazid 100mg			
12	Stock balance of Pyrazinamide 400mg			
13	Stock balance of Ethambutol 400mg			
14	Stock balance of Ethambutol 100mg			
15	Stock balance of Rifampicin 300 and 150mg			
16	Stock balance of Second line drugs (if used)			
17	Stock balance of Inj. Streptomycin			
18	Does the physical stock balance of anti-TB drugs match with that of stock ledger?			
19	Any obvious change to the drugs – like damaged packing, colour change etc?			
	Others			
1	Adequate supply of TB treatment cards, patients cards, referral/transfer forms etc.			
2	Were there changes in TB in charges?			

Observations from this supervisory visit:
Actions and recommendations:

Annexure XVIII: Annual TB Drugs Quantification Form

Drugs	(New Cases) 2 HRZE/4 HR A Case Factor Total	Retreatment Cases 2HRZES/1HRZE /5HRE B	Total A+B = C	Running requirement D = (C from above)	Reserve requirement E = D	Currently in Stock F	Expiry Date	Total Order D+E-F
HRZE	X180=	X270=						
HR	X360=	X450=						
E 400mg								
S 1G		X60=						
HRZ (P)	X180=							
HR (P)	X360=							

Annexure XIX: Combined annual treatment outcomes report for TB and for RR-TB/MDR-TB

Name of Reporting Center: _____ Patients registered during ___ quarter of year_____ Date of report submission _____

Section 1. All TB cases (except for TB cases moved to the second-line treatment register) registered in calendar year _____

TB patient type	No. of cases registered		Treatment outcomes											
			Cured		Treatment completed		Treatment failed		Died		Lost to follow-up		Not evaluated	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
Bacteriologically confirmed, new and relapse														
Clinically diagnosed, new and relapse														
Retreatment (excluding relapse)														
HIV-positive, all types														

Section 2. TB cases started on a second-line TB drug regimen in calendar year: _____

TB patient type	No. of cases started on second-line TB treatment		Treatment outcomes											
			Cured		Treatment completed		Treatment failed		Died		Lost to follow-up		Not evaluated	
	M	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
All confirmed RR-TB/MDR-TB cases														
HIV-positive RR-TB/MDR-TB cases														
All confirmed XDR-TB cases														

[a] Patients to be assessed are all those registered in the current calendar year **minus two** (excluding those moved to a second-line treatment). Thus, if the current calendar year is 2013, the outcomes collated will be for the cohort registered in calendar year 2011.
[b] Patients on a second-line drug regimen to be assessed are those started on second-line drugs in the current calendar year **minus three**. Thus, if the current calendar year is 2013, the outcomes collated will be for the cohort started on second-line drugs in calendar year 2010.

References:

1. WHO treatment of tuberculosis guidelines - Fourth Edition.
2. Companion Handbook on the WHO guidelines for the PMDT - The End TB Strategy - WHO.
3. MDR-TB guidelines - Second Edition, 2016.
4. Definitions and reporting framework for tuberculosis - WHO 2013 revision.
5. WHO guidelines on the management of latent tuberculosis infection.
6. National guidelines for the management of TB - Fifth Edition.