NATIONAL GUIDELINES FOR THE MANAGEMENT OF MULTI DRUG RESISTANT TUBERCULOSIS

SECOND EDITION, 2015

NATIONAL TUBERCULOSIS CONTROL PROGRAMME
HEALTH PROTECTION AGENCY
MALDIVES

CONTENTS

ABBREVIATIONS and ACRONYMS

AFB	Acid Fast Bacilli
ART	Antiretroviral therapy
AIDS	Acquired immunodeficiency syndrome
CPT	Cotrimoxazole Preventive Therapy
CTX	Cotrimoxazole
CXR	Chest X-ray
DOTS	Directly observed treatment short course
DST	Drug Sensitivity Testing
DRTB	Drug Resistant Tuberculosis
EPTB	Extra Pulmonary Tuberculosis
EQA	External Quality Assessment
FQ	fluoroquinolone
HIV	Human immunodeficiency virus
IC	Infection Control
IEC	information Education and Communication
IGMH	Indira Gandhi Memorial Hospital
LFT	Liver function test
MoH	Ministry of Health
MDR-TB	Multidrug-resistant Tuberculosis
NTP	National TB Control Programme
NSAID	Non steroidal anti inflammatory drug
OPD	Out Patient Department
PTB	Pulmonary Tuberculosis
PPI	Proton pump inhibitor
RFT	Renal function test
RMC	Respiratory Medicine Clinic
TB	Tuberculosis
TBM	Tuberculous Meningitis
WHO	World Health Organization
XDR-TB	Extensive Drug Resistant TB

Drug abbreviations

Amikacin	Am
Amoxicillin/Clavulanate	Amx/Clv
Bedaquiline	Bdq
Capreomycin	Cm
Clarithromycin	Clr
Clofazimine	Cfz
Cycloserine	CS
Ethambutol	E
Ethionamide	Eto
Gatifloxacin	Gtx
Isoniazid	H
Kanamycin	Km
Levofloxacin	Lfx
Moxifloxacin	Mfx
Para-aminosalicylic Acid	PAS
Prothionamide	Pto
Pyrazinamide	Z
Rifampin	R
Streptomycin	S
thioacetazone	T

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Technical working group

Fathimath Nadhiya: Consultant in Internal Medicine at Medica Hospital, Maldives, facilitated group discussions

Mohamed Ismail: Pulmonologist and In Charge of the Respiratory Medicine Clinic IGMH and Technical focal point for the National TB Programme, Maldives

Moosa Hussain: Pulmonologist, Indira Gandhi Memorial Hospital,Maldives

Ahmed Saeed: Consultant in Paediatrics, Indira Gandhi Memorial Hospital and Technical focal point for NTP Maldives for management of childhood TB

Ali Abdullah Latheef: Senior Consultant in Internal Medicine/Head of Department of Medicine IGMH

Abdul Malik: Senior Medical Officer, Health Protection Agency

Review group

Niyasha Ibrahim Mohamed: Senior Consultant in Paediatrics and Head of Department of Paediatrics, IGMH

Mohamed Faisham ; Senior Registrar in Internal Medicine / Hulhumale Hospital ,Maldives

Aishath Aroona Abdulla: Senior Medical Officer, Health Protection Agency

Moosa Murad: Consultant Physician, Indira Gandhi Memorial Hospital

Zubair Mohamed: Senior Registrar in Internal Medicine, IGM Hospital

Shina Ahmed: Public Health Programme Officer, Maldives National TB Programme

Aminath Aroosha: Public Health Programme Officer, Maldives National TB Programme

Mariyam Waheeda, Assistant Public Health Programme Officer, HPA

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Chapter 1

INTRODUCTION

Tuberculosis remains a leading cause of morbidity and mortality worldwide and the development of resistance to Anti-tuberculosis drugs, particularly MDRTB has become a major challenge for effective Tuberculosis care and control globally. Drug resistance arises due to many factors, from improper use of anti tuberculosis drugs, poor quality of drugs administered, irregular or incomplete treatment and poor adherence to treatment by patients.

MDR-TB strains with additional resistance to second-line drugs, described as extensively drug-resistant TB (XDR-TB) has been seen since 2006 further compromising treatment options available to patients infected with these strains. Since then, clinicians in some settings have reported patients infected with strains in which virtually all treatment options have been exhausted.
The introduction of new diagnostic and treatment tools for the management of drug-resistant TB has made a significant contribution to enable earlier diagnosis of MDR-TB, leading to more effective treatment

National Guidelines for the management of Multi Drug Resistant Tuberculosis (MDRTB) in the Maldives was first written down in 2010 and since then several important new developments have occurred in regard to Tuberculosis care and control both in diagnostics and treatment. The 2010 guideline required revision in areas of patient registration, diagnostic facilities, definitions of treatment outcomes and the treatment regimen for MDR and mono and poly resistant TB.

This revision of the existing guideline provides updated recommendations and guidelines in alignment with the latest policy recommendations from World Health Organization for the management of multidrug resistant TB including XDR-TB. This Guideline is intended to be used by the National Tuberculosis programme managers, clinicians, nurses, DOT providers, community and family health workers and other stakeholders committed and involved in the prevention and management of drug resistant TB.

1.1 MAGNITUDE OF THE PROBLEM

Globally, 3.6% (2.1–5.1%) of new cases and 20% (13–27%) of previously treated cases are estimated to have MDR-TB. Each year, about 450 000 (range 300 000–600 000) MDR-TB cases are estimated to emerge, and 170 000 persons with MDR-TB die.
Patients infected with XDRTB strains are considered at a greater risk of dying and less likely to complete their treatment successfully. According to the WHO Global Report 2014, XDRTB has been reported from 100 countries and on average estimated 9% of MDRTB patients have XDRTB.
Drug resistance is strongly associated with previous treatment and in previously treated patients, the probability of any resistance is over 4-fold higher, and of MDR-TB over 10-fold higher, than for untreated patients.

Maldives has no representative data on levels of drug resistance. Case detection and treatment success rates of over 90% have consistently been achieved for tuberculosis over several years. WHO listed Maldives, among the 5 countries that were announced in 44th World Health Assembly, for achieving the targets TB control well ahead of 2005. Maldives was the first country in the SAARC Region to reach global targets and receive an award from Stop TB Partners Forum in 2004.

But since 2006, a worsening of treatment outcome has been observed: the treatment success rate, which was above 85% until 2006, has been 80-81 percent for the last 5 years. The death rate of 9 percent in 2010 was the highest ever reported, and a default rate of 13 percent was recorded in 2009. Number of patients started on retreatment (Cat II regimen) is very low, on average 3-5 per year and entire treatment is given under direct observation.

Few MDR-TB cases have been identified and so far 7 cases of MDR-TB have been registered and treated between 1995 and 2012. However there is a risk that this trend may change as the country employs a large expatriate workforce from neighbouring countries with high MDR prevalence.

Tuberculosis has a high risk of spread in Male' the capital, due to overcrowding and poor housing conditions. The increasing prevalence of substance abuse among the youth and an influx of a large number of migrant workers from nearby high TB burden countries are among the leading challenges to the NTP at present.
The migrant work force is almost one third of the Maldivian population and though a medical checkup is required to be eligible for work visa however, this screening is often not strictly

enforced and does not specifically target symptoms of TB. In addition, a large proportion of migrant workers are illegal immigrants, and currently efforts are being made by the NTP to raise awareness and undertaken active screening for TB in this population group.
A system for TB screening is not yet established at penitentiary institutions in the Maldives, although prisoners undergo general health screening upon entry to a prison.

The stigma associated with TB in the Maldives remains high and some are very scared about receiving a diagnosis of TB, and about having other members of the community know about the diagnosis. As a result of this along with a general mistrust in the health system, some of these patients travel to neighbouring countries to obtain TB treatment usually from private practitioners. Such treatments may consist of inadequate drug combinations, given for insufficient time periods, thereby increasing the risk for the development of MDR TB.

Maldives remains among low prevalent countries for HIV in the region. However, risk factors that may contribute to spread HIV are high and are increasing at an alarming rate. So far among the locals, only 19 HIV positives have been reported. HIV positives among TB patient also remain low and 2 cases of TB-HIV co infection have been reported. Screening of all HIV positives for TB infection and TB patient for HIV infection started as a collaborative effort of both the programme since 2008 which still needs strengthening.

Laboratory capacity needs to be strengthened especially in regard to diagnostics and quality assurance. Drug susceptibility testing is currently not available in the country and when deemed clinically necessary, is undertaken by the NTP by shipment of samples to Bangalore/ India for conventional DST which takes about 2 ½ to 3 months. In addition samples are also sent to a well-established private tertiary level laboratory facility in Mumbai/India in collaboration with IGMH Laboratory for Xpert MTB/Rif and conventional DST.

It is vital that rapid DST techniques be introduced in line with comprehensive, laboratory capacity strengthening by the NTP for earlier diagnosis of Multi drug resistance. Availability of these techniques would ensure that patients with a likelihood of MDR TB would not be put on the 8 month retreatment regimen as this would not be effective in a patient with MDR and in addition may lead to amplification of resistance.

1.2 THE FRAMEWORK APPROACH FOR DR-TB MANAGEMENT

The five essential components of the framework approach for DR-TB management are:

1. Sustained political commitment

- Addressing the factors leading to the emergence of MDR-TB
- Long term investment of staff and resources
- Coordination of efforts between community, local governments and international agencies
- A well-functioning DOTS programme

2. **Appropriate case-finding strategy including quality-assured culture and DST**

- Rational triage of patients into DST and the MDR-TB control programme
- Relationship with supranational TB reference laboratory

3**. Appropriate treatment strategies that use second-line drugs under proper case management conditions**

- Rational treatment design (evidence-based)
- DOT
- Monitoring and management of adverse effects
- Properly trained human resources

4. **Uninterrupted supply of quality-assured second-line anti-TB drugs**

5. **Recording and reporting system that enables performance monitoring and evaluation of treatment outcomes**

1.3 PREVENTION OF DRUG RESISTANT TB

Prevention is the key to effective control of drug resistant TB. MDR-TB arises as a result of poor management of TB patients and most cases of XDR-TB arise as a result of poor MDR-TB management.

Interventions to prevent drug resistant TB include:

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

- Availability of diagnostic methods to ensure early detection of TB
- Contact screening,
- Effective treatment with follow up
- Minimizing barriers to healthcare access
- Adherence to treatment
- Uninterrupted supply of drugs

- Compliance with management guidelines
- DOT

2. **Early detection and high quality treatment of drug-resistant TB**
    - Early diagnosis
    - Effective Management of DRTB
    - Contact tracing
    - Uninterrupted supply of drugs
    - Adherence to treatment
    - DOT

3. **Effective implementation of infection control measures**
    - Establish and implement Infection control policies at all levels of health delivery
    - Increase Community awareness and societal level infection control measures

4. **Strengthening and regulation of health systems**: Poorly functioning general health systems contribute to poor TB diagnosis and treatment outcomes
    - Establish well developed health-care infrastructure
    - Well-trained and motivated workforce
    - Uninterrupted supply and good management of medicines
    - Availability of diagnostics and other commodities
    - A well functioning health information system

5. **Addressing underlying risk factors and social determinants**

Chapter 2

NATIONAL TB PROGRAMME

The public sector conforms to the largest share of the health system in Maldives and the Ministry of Health is responsible for the provision of health and health related services in the country and formulates the overall health policy, planning, monitoring and evaluation of health services.

Health service delivery in the public sector is currently delivered by a four tier referral system comprising of island, atoll, regional and central level services. The Indira Gandhi memorial Hospital in Male' serves as the tertiary level hospital at the central level of the referral system.
The Health Protection Agency under the Ministry of Health is responsible for delivering public health related programmes across the country through atoll and island based public health units in addition to running of specialized national programmes such as the National TB control programme

The NTP under the Health protection Agency, at the central level is responsible for overall program coordination including planning, awareness, IEC and training. NTP is also responsible for DOTs implementation, registration, reporting, monitoring and evaluation of the programme. NTP has achieved and sustained full coverage with DOTS in the country since 1996. It is the policy of NTP that all TB patients will receive treatment as DOT.

The Respiratory Medicine Clinic at Indira Gandhi Memorial Hospital is the main referral center for management of TB and where all MDR and XDRTB cases will be initially evaluated and treatment initiated under the guidance of the DOTS plus Committee.

The NTP activities are well integrated in to the general health care system. At present mainly passive case finding is followed with a clear policy that all TB suspects reporting to the various health facilities will have three sputum samples examined and cases confirmed where smears are negative, by radiology and/or other tests as indicated clinically.

Laboratory

Mycobacteriology is a key component in management of Drug resistant TB. Strengthening laboratory capacity along with Quality control and Quality assurance of the laboratory network is of critical importance for the effective TB care and control.

Facilities for sputum Smear examination are available at the Central, Regional level and at some of the Atoll Hospital and Health centers.

At present culture and DST are not available at IGMH lab but samples are packed at IGMH laboratory and send to Bangalore/India by NTP for conventional culture and DST. In addition samples are also send for culture, DST and Xpert/MTB Rif through IGMH Laboratory to a well established laboratory facility in Mumbai/ India.

Hematological and biochemical tests that are required at baseline and for treatment monitoring of MDRTB are available at IGMH laboratory.

XpertMTB/Rif will be available only at the central level (IGMH laboratory) and samples from the peripheries are to be send to IGMH in accordance with the national guidelines for transfer of biological samples

Anti Tuberculosis Drugs

Anti Tuberculosis Drugs are available only through the NTP as the Government had prohibited the sale of anti TB drugs throughout the country in 2001. Fixed-dose combinations were introduced in 2005 through a grant from the Global Drug Facility and Support from GDF continues for procurement of first line drugs.

Tuberculosis treatment under NTP is free of charge for all patients. This applies to all TB patients, local and expatriates diagnosed with TB and it includes diagnostic and monitoring tests for TB in addition to anti TB medications. NTP has to ensure that there is uninterrupted supply of anti TB medications.

Recording and Reporting

NTP maintains a national register of TB patients which is updated by input of monthly reports form RMC, Regional and Atoll Health Facilities. TB is a notifiable disease in Maldives and it is required to notify every patient to NTP as soon as the diagnosis is established.

RMC, regional and atoll hospitals maintain treatment registers for all patients receiving treatment from that facility. Each patient is allotted a standard treatment card at the time of initiation of treatment.

Standard sputum request forms are available All sputum samples for smear microscopy is send to the lab along with the sputum request form which is filled by the DOT provider or health care worker and all microscopy centres and laboratories maintain sputum registers for all the patients undergoing sputum examinations

A Separate treatment register should be available at RMC for registering MDR and XDR TB patients as well as separate standard patient treatment cards for these patients should also be available.

Contact tracing

The policy of contact tracing is actively followed where lists of contacts at home and at work are entered on the treatment cards and advice given to undergo Mantoux testing and if mantoux is positive to do CXR and sputum examinations and this is largely accepted by the contacts. Children under 5 years are provided treatment for latent infection with TB after screening to rule out active disease.

Intensification of case finding through regular targeted screening of populations potentially at higher risk of developing TB such as those in accommodation setups for laborers, factories and reprimand facilities is being considered by the NTP at present and need to be strengthened.

ACSM activities

Information Education and Communication activities to address the long-standing stigma attached to TB and awareness programs are on going to encourage early self referrals and to reduce the proportion of nationals seeking care abroad. Sessions on TB have been introduced into school health programs. However, the need to develop well formulated plan for a comprehensive nation-wide communications campaign and IEC activities is recognized

Supervision and monitoring

The system of monitoring and supervision needs strengthening at the peripheral levels. On site supervision visits to the peripheries are not optimum due to limitations in resources and staff. Strengthening of monitoring is vital to the program because a weak monitoring system may result in serious quality deficiencies remaining unnoticed and this may contribute to a weak TB programme adding to increase in resistant TB.

2.1 ORGANIZATION OF MDRTB SERVICES

RMC at IGMH will be the designated treatment center for MDR and XDR TB.

All patients with suspected DRTB should be referred to RMC for establishing the diagnosis and commencement of treatment

National TB programme at HPA

- Over all program coordination and planning
- Develop guidelines and SOPs
- Providing ongoing training, support and supervision for all the health facilities

- Ensuring availability of drugs and monitoring rational usage of second-line drugs
- Providing technical assistance and capacity building to health facilities
- Coordinating IEC preparation and awareness
- DOTS coordination
- Facilitate referral of patients with MDR and XDR-TB, severe ADRs, and complicated disease to RMC
- Ensure mechanism of transport of sputum for culiure and Xpert/MTBRif to IGMH Laboratory
- Ensure QA of the sputum microscopy network
- Mass contact screening and arranging follow up
- Collaboration with the HIV programme
- Collaboration with private sector and NGOs
- Compiling monthly, quarterly, six monthly and annual reports of DR-TB patients started on treatment, culture conversion and outcomes
- Establishing and maintaining functional clinical management teams
- National Reporting and Registration
- Monitoring and evaluation DR-TB programme performance

Function of RMC at IGMH (central level)

- Diagnostic workup of all suspected DRTB patients
- Functioning DOTS plus Committee for decision making on MDR and XDRTB management
- Admit patients in IGMH for initial 4 weeks for counseling and adherence promotion
- Initiating DR-TB treatment
- Monitoring the initial response to treatment and possibly adjusting medication
- Educating and counseling the patient, family or care giver on MDR-TB and HIV
- Assessing the household in preparation for discharge including household infection control
- Communicate with peripheral health facility and ensure effective down referrals
- Ensure effective infection control measures in place for transfer of patient
- Monitoring DR-TB patients post discharge until completion of treatment and two years post treatment completion
- Monitoring rational usage of second-line drugs and ancillary drugs for side effects management
- Establishing and maintaining functional DOTS PLUS Committee
- Providing technical assistance and capacity building to NTP and peripheral health facilities on management of DR-TB

- Providing DOT to all DR-TB patients taking treatment in Male
- Conduct contact screening programmes for all close contacts of confirmed DR-TB patients six monthly for two years
- Monthly Recording and reporting to the NTP

Functions at peripheral Hospitals including Regional and Atoll Hospitals

- Ensure continuum of care for patients post discharge from RMC
- Providing DOT to all DR-TB patients taking treatment
- Ensure sputum monitoring including culture
- Transfer sputum samples for MTB/Rif and culture/DST to IGMH laboratory in accordance with national guidelines on transfer of biological samples in communication with RMC
- Trace all suspected DR-TB patients and refers to RMC at IGMH for confirmation
- Discuss with clinician in RMC prior to sending sample or patient
- Discuss with clinician at RMC if serious adverse reaction or complication requiring referral to central level
- Ensure effective infection control measures in place for transfer of patient
- Ensure availability of drugs for the patient at the hospital
- Establish an efficient patient retrieval system for patients who default DR-TB treatment
- Arrange transportation for patient evaluation and follow up at RMC
- Conduct contact screening programmes for all close contacts of confirmed DR-TB patients six monthly for two years
- HIV counseling and testing for contacts
- Conduct household assessments prior to receiving patients discharged from RMC
- Ensure on-going psychosocial support for patients
- Ensure effective infection control measures in the health facility
- Education of patient and family regarding household infection control
- Increase awareness and education about DR-TB among community
- Monthly Recording and reporting to the NTP

Health centers and health posts

- Identifying high risk groups
- Providing counseling and education of the patient and family
- Coordinating referrals to the Atoll/ Regional Hospital for monitoring tests (not available at health center)

- Ensure sputum monitoring including culture
- Providing DOT to all DR-TB patients
- Ensure availability of drugs including ancillary medicines for management of side effects
- Conducting contact screening of close contacts
- HIV counseling and testing for contacts
- Following up patients initiated on DRTB treatment who are post discharge from RMC
- Tracing treatment interrupters
- Monitoring treatment side effects
- Ensuring referral of patients with severe ADRs, and complicated disease to the RMC
- Ensure communication with clinician at RMC prior to transfer of patients
- Ensure effective infection control measures in place for transfer of patient
- Ensure effective infection control measures in the health facility
- Education of patient and family regarding household infection control
- Increase awareness and education about DR-TB among community
- Monthly Recording and reporting to the NTP

Programme performance

NTP will be using an indicator based monitoring system which will allow the programme manager to compare detection, enrollment on treatment and outcomes.

Indicators used by NTP for monitoring DRTB management include:

- Six monthly report on detection of TB cases with RR-TB and MDR-TB
- Six monthly report on enrolment of TB cases with RR-TB and MDR-TB on second-line TB treatment
- Quarterly report on interim results of TB cases with RR-TB and MDR-TB and XDR TB on second-line TB treatment
- Annual report of final outcomes of TB cases with RR-TB, MDR-TB and XDR-TB on second line TB treatment

Chapter 3

DRUG RESISTANCE

There are two types of drug resistance: 1) Primary drug resistance
2) Acquired (secondary) resistance

Primary drug resistance

Primary drug resistance means that the person has been infected with a drug resistant TB strain.
High prevalence of drug-resistant TB in the community and conducive environments for TB transmission such as crowding, poor ventilation and poor infection control practices contribute to transmission of drug-resistant TB in the community

Acquired drug resistance

Acquired drug resistance is the result of inadequate or incomplete treatment quality that allows the selection of mutant resistant strains.
Simultaneous natural mutations in Mycobacterium tuberculosis resulting in r**e**sistance 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 of resistant strains.

The exact causative nature of drug resistance in a patient is not always possible to assess. Patients may be erroneously labeled as having primary resistance, if they do not disclose previous treatment for TB (taken treatment outside the program), while patients who fail treatment (and are therefore labeled to have acquired resistance) may have been infected with a resistant strain from the beginning.

3.1 Causes of drug-resistant tuberculosis

Health care provider	**Drugs**	**Patients**
Inadequate regimens	Inadequate Supply/unavailability	Inadequate Drug intake/ Poor adherence
Inappropriate guidelines	Poor Quality	Lack of information
Noncompliance with guidelines	Poor storage conditions	Lack of money
Absence of guidelines	Poor regulation of medicines	Lack of means to adhere to treatment (transportation}
Poor patient education	Wrong dose or combination	HIV
Poor management of adverse reactions		Psychiatric conditions
Poor training of health staff		Adverse Effects
No monitoring of treatment		Social barriers eg: Substance dependence
Poorly organized or funded TB Control programs		Mal-absorption

Chapter 4

STRATEGIES FOR CASE FINDING, DIAGNOSIS AND REGISTRATION

Cases of TB are classified based on the:-

- Anatomical site of disease
- Bacteriology
- History of previous treatment
- HIV status
- Drug susceptibility testing

1. CLASSIFICATION BASED ON THE SITE OF TUBERCULOSIS DISEASE

- Pulmonary
- Extra pulmonary

Pulmonary tuberculosis: Tuberculosis involving the lung parenchyma. (A patient with both pulmonary and extra pulmonary TB is classified as a pulmonary case)

Extra pulmonary tuberculosis: Tuberculosis of organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints, bones and meninges.
The definition of an extra pulmonary case with several sites affected depends on the site representing the most severe form of disease

2. CLASSIFICATION BASED ON BACTERIOLOGY

Bacteriological examinations used in patients with drug-resistant TB will include sputum smear microscopy and culture and Xpert MTB/RIF
Examinations are required at the start of treatment to confirm the diagnosis of TB, and to determine the infectiousness of the patient. Patients with positive sputum smear are the most infectious.
Xpert MTB/RIF is recommended for diagnostic testing for the presence of MTB and detection of mutations associated with rifampicin resistance. It is not recommended for treatment monitoring.
The mainstay for testing patient response to treatment is sputum smear microscopy and culture

For a patient to be considered bacteriologically confirmed at the start of treatment, the following criteria must be met:

- At least one pre-treatment specimen is positive on sputum smear microscopy, Xpert MTB/RIF or culture.
- The collection date of the sample on which the laboratory examination was performed is less than 30 days before or seven days after the initiation of second-line treatment

3. CLASSIFICATION BASED ON HISTORY OF PREVIOUS ANTI TUBERCULOSIS TREATMENT

Before enrolling a patient in a regimen with second-line drugs, the following history of treatment should be taken and recorded:

- Previous history of ATT
- Outcome of previous treatment
- Previous history of treatment with second line drugs

New patients: - Never received anti tuberculosis treatment or who have received anti tuberculosis treatment for less than one month

Relapse: - A patient who was previously treated for TB and whose most recent treatment outcome was Cured or Treatment completed, and who is subsequently diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection)

Treatment after loss to follow-up:- A patient who had previously been treated for TB and was declared lost to follow-up at the end of the most recent course of treatment

After failure of first treatment with first-line drugs: - A patient who has received first-line drug treatment for TB and in whom treatment has failed.

After failure of retreatment regimen with first-line drugs:-A previously treated TB patient who has received a retreatment regimen with first-line drugs and in whom the retreatment has failed

Other previously treated patients:- A previously treated TB patient whose outcome after the most recent course of treatment is unknown or undocumented

Patients with unknown previous TB treatment history do not fit into any of the groups listed above.

For the purposes of registration on second-line treatment for MDR-TB, patients are considered New if DST was performed within one month of the start of treatment, even if they had

received more than one month of first-line drug treatment for TB by the time that the DST results returned and they were registered for second-line TB treatment

4. CLASSIFICATION BASED ON HIV STATUS

HIV positive TB patient: refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a positive result from HIV testing conducted at the time of TB diagnosis or other documented evidence of enrolment in HIV care once ART has to be started.

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

HIV status unknown TB patient: refers to any bacteriologically confirmed or clinically diagnosed case of TB who has no result of HIV testing and no other documented evidence of enrolment in HIV care. If the patient's HIV status is subsequently determined, he or she should be reclassified accordingly

5. CLASSIFICATION BASED ON DRUG SUSCEPTIBILITY TESTING

Different patterns of drug resistance carry different implications for treatment and management and drug-resistant cases are classified in categories based on DST in clinical isolates confirmed to be M. Tuberculosis

Mono-resistance: - Tuberculosis in patients who's infecting isolates of M. tuberculosis are confirmed to be resistant in vitro to one first-line anti tuberculosis drug only

P**oly-resistance:-** Tuberculosis in patients who's infecting isolates are resistant in vitro to more than one first-line anti tuberculosis drug, other than both isoniazid and rifampicin

MDR-TB: - Tuberculosis in patients who's infecting isolates are resistant in vitro to at least isoniazid and rifampicin

XDR-TB:- (Extensive drug resistant): In addition to multi drug resistance; resistance to any one of the FQs and one of the three second line injectable drugs(Cm, Am, Km)

Rifampicin resistance (RR): resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, in the form of mono-resistance, poly-resistance, MDR or XDR

4.1 CASE DEFINITIONS

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 MDRTB:** 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, or on the basis of a rapid molecular result
- **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

4.2 TREATMENT OUTCOME DEFINITIONS

The revised treatment outcome definitions make a distinction between two types of patient groups

1. Patients treated for rifampicin susceptible TB
2. Patients treated for RR/MDRTB using combination second line drug treatment

The two groups are mutually exclusive. Any patient found to have RR/MDRTB and placed on second-line treatment is removed from the rifampicin susceptible TB treatment cohort.
RR/MDRTB patients who were not started on a MDRTB regimen are assigned an outcome from those for rifampicin susceptible TB.
The Basic TB register and the Second line TB treatment register need to be coordinated to ensure proper accounting of treatment outcomes

Cured: Treatment completed as recommended by the national guideline without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase

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

Treatment Failed: Treatment terminated or need for permanent regimen change of at least two anti TB drugs because of:

- Lack of conversion by the end of the intensive phase
- Bacteriological reversion in the continuation phase after conversion to negative
- Evidence of additional acquired resistance to FQ or second line injectable drugs

- Adverse drug reactions

Died: A patient who dies for any reason during the course of DR-TB treatment

Lost to follow up: A patient whose treatment was interrupted for 2 consecutive months or more

Not evaluated: A patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown)

Treatment success: The sum of cured and Treatment completed

Note:

- The outcome 'Cured' is restricted to pulmonary bacteriologically confirmed cases only.

- If the clinician changes two or more anti-TB drugs during the intensive phase because of lack of response or adverse drug reactions, then the case is not considered a Treatment failure and the same treatment episode needs to be monitored for outcomes.

- **Culture Conversion:** culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. The specimen collection date of the first negative culture is used as the date of conversion

- **Reversion of culture** : culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining Treatment failure, reversion is considered only when it occurs in the continuation phase

- The sum total of Cured and Treatment completed is commonly used as an indicator of favorable outcome or Treatment success.

4.3 CASE-FINDING STRATEGIES FOR MDRTB

Strategies for case finding and diagnosis of patients with suspected MDR-TB are needed for:

- Timely identification and prompt initiation of treatment
- prevent the patient from spreading the disease to others
- prevent acquiring further resistance and progressing to a state of permanent lung damage

In all individuals suspected of having TB (adults and children), Xpert MTB/RIF will be used as an initial diagnostic test for TB. This can result in more bacteriologically confirmed patients and shortened time to treatment

In all individuals (both adults and children) suspected of having TB who are considered to be at risk of harboring drug resistant TB bacilli, Xpert MTB/RIF will be used as an initial diagnostic test to rapidly detect MTB and Rifampicin resistance

High risk groups for MDRTB (people more likely to have drug resistant TB**):**

1. Failure of treatment regimen with first line drugs
2. Exposure to a known MDR-TB case
3. Relapse and return after lost to follow up

4.4 ESSENTIAL LABORATORY SERVICES

Optimal management of drug-resistant TB requires both mycobacteriology and clinical laboratory services.

Culture capacity is essential for monitoring drug resistant TB patients' response to therapy.

Capacity to reliably identify M. tuberculosis and detect resistance to rifampicin and isoniazid remains a minimum requirement in any drug resistant TB programme

Clinical laboratory services should also provide basic haematology, biochemistry, serology and urine analysis, required for adequate evaluation of patients and treatment monitoring.

Capacity to perform DST against specific second line agents can be established once the laboratory competence has been established.

Laboratory-acquired TB infection, including MDR-TB and XDR-TB, is a well-recognized risk for laboratory and specific precautions, good microbiological practices, engineering controls, proper training and containment measures are needed to ensure safe handling of
M. tuberculosis at all levels of the laboratory network

In order to ensure quality and reliability of laboratory results as well as safe working conditions in the TB laboratory, it is necessary for laboratories to implement a quality management system to ensure that all aspects of laboratory diagnostic services are performed properly and allow for the detection of any laboratory errors.

These systems must include standard operating procedures and both internal quality control and external quality assessment protocols for all performed laboratory techniques, which are necessary to ensure accurate detection of drug resistance for subsequent treatment decisions and avoid false diagnoses.

Smear Microscopy

Smear microscopy is a low cost, frontline tool for TB but not for diagnosis of drug resistant TB. Microscopy cannot distinguish viable from non viable organisms nor differentiate between drug susceptible and drug resistant M. tuberculosis bacteria, or between different species of mycobacteria

The LED fluorescence microscopy is recommended for use by WHO as it has increased test sensitivity and reduced turnaround time required allowing the screening of a larger number of slides
The main purposes of microscopy for drug-resistant TB:

- assess initial bacterial load (infectiousness)
- triage to different diagnostic algorithms ie sputum positive TB
- monitor response to therapy

Its usefulness in drug-resistant TB treatment monitoring is also limited as samples showing AFB by smear microscopy but negative to culture suggest that bacilli are not viable (caution is nonetheless warranted for these patients to be considered as possibly Infectious)

Samples showing AFB by smear microscopy but negative by molecular tests may likely harbour non tuberculous mycobacteria

Culture of MTB

Culture in liquid media is the current reference method for bacteriological confirmation of TB. However, good quality specimens, prompt transport to the laboratory and quality of laboratory processing, as well as good quality culture media and incubation conditions are essential to optimize the yield of culture

In general, the recovery of tubercle bacilli is higher and the time to detection is shorter with liquid culture than with solid culture methods. However, liquid culture media being a more sensitive culture system has higher contamination rates than solid media.
NTM are more frequently isolated with liquid media than with solid media. It is therefore essential to differentiate M. tuberculosis isolates from other mycobacteria

Laboratory errors, such as mislabelling or cross-contamination between specimens during aerosol-producing procedures, may lead to false-negative or false-positive results. Therefore, laboratory findings should be always correlated with the patient's clinical condition and any diagnostic test should be repeated if necessary.

Drug susceptibility testing

DST plays an important role to identify and treat patients with drug resistant TB. NTP should develop the capacity to provide access to DST for any patient for whom resistance is considered likely.
The reliability of DST (performed under optimal circumstances) varies with the drug tested
First line DST is most reliable for rifampicin and isoniazid and less reliable and reproducible for streptomycin, ethambutol and pyrazinamide.

Second line DST has good reliability and reproducibility for second-line injectable drugs (amikacin, kanamycin, capreomycin) and fluoroquinolones. Data on the reproducibility and reliability of DST for the other second-line drugs are limited, and for several of them methods have not been established or standardized
For rifampicin resistance there is not complete concordance between phenotypic and genotypic detection methods.
Emerging evidence suggests that DNA sequencing of the rpoB gene (the gold standard method for genotypic DST) may be a better although not perfect reference method than the phenotypic DST.

XPERT MTB/RIF

The assay has similar sensitivity, specificity and accuracy as culture on solid media and has been recommended by WHO as the initial diagnostic test among persons at risk of MDR-TB

- Will be the Initial diagnostic test in all adults suspected with TB as well as MDRTB for increased case detection and rapid rifampicin testing for earlier identification of patients on inappropriate first line regimens, and allow for early interruption of MDRTB transmission.

- Results are available within 2 hours to guide the choice of regimen for the patient and detection of rifampicin resistance serves as a reliable (though not complete) proxy for MDR-TB

- Detects mutations in the rpoB region of M. tuberculosis DNA, which are responsible for >95% of rifampicin resistant strains. Given the high sensitivity, a negative result generally excludes rifampicin resistance and no further testing to confirm negative results is required.

- In rare instances, when a patient is strongly presumed to have RR-TB even after a negative test, follow-up testing using phenotypic culture-based DST may be used to test for rifampicin resistance resulting from a small number of mutations occurring outside the rpoB region

- XpertMTB/Rif has a very high specificity for detection of rifampicin resistance but when used in a population with a low prevalence of the condition can result in a lower positive predictive value (number of false-positive results are present)

- Increasing evidence, however, is showing that the occurrence of false-positive R resistance detected by Xpert MTB/RIF compared to phenotypic DST methods may be linked to the detection of strains that are truly resistant to rifampicin, yet are not detected by culture based DST.

INTERPRETING RESULTS FROM XPERT MTB/RIF

An Xpert MTB/RIF result can indicate that

- MTB was not detected
- MTB was detected and was not resistant to rifampicin (rifampicin susceptible)
- MTB was detected and it was resistant to rifampicin.
- A small proportion of tests may result in an error or invalid result; these tests need to be repeated.

When Xpert MTB/Rif does not detect MTB:

- The disease can be ruled out in most cases unless there is still a strong suspicion of TB (special attention is required in people living with HIV who have signs and symptoms of TB) that may warrant further investigation (such as a chest X-ray, culture, another Xpert MTB/RIF test, or a trial of antibiotics)

  Note: The ability of any diagnostic test to detect TB depends on the quality of the specimen collected.

When Xpert MTB/RIF detects MTB without rifampicin resistance:-

- Patient should be started on first line regimen and registered as a case with susceptible bacteriologically confirmed TB.

When Xpert MTB/Rif detects MTB with rifampicin resistance:-

In patients considered to be at high risk of MDR-TB:

- A regimen for MDR-TB with the addition of isoniazid should be initiated and the patient should be registered as having bacteriologically confirmed rifampicin resistant TB (RR-TB)

- Another sputum sample should be taken immediately to be sent for phenotypic DST for at least isoniazid, fluoroquinolones and second-line injectables and when the DST results are available, treatment can be modified if necessary and the patient's registration can be updated accordingly.

- Treatment modifications may include stopping isoniazid if resistance has been found, changing the quinolone and/or second-line injectable, or, in the case of XDRTB, placing the patient on an appropriately designed regimen that includes group 5 drugs.

In patients considered to be at low risk of MDR-TB:

- Rifampicin resistance may be unexpected and clinicians may be hesitant to enrol patients on a treatment regimen requiring second-line drugs (mostly because of the treatment length and concerns about toxicity)

- An unexpected Xpert MTB/ RIF result may be attributed to the PPV for rifampicin resistance due to low underlying prevalence, or may also result from nonsystematic or random errors at the preanalytical or postanalytical stages of testing (clerical errors made when information about specimens or test results is recorded, or administrative errors that result in specimens being mixed up, etc)

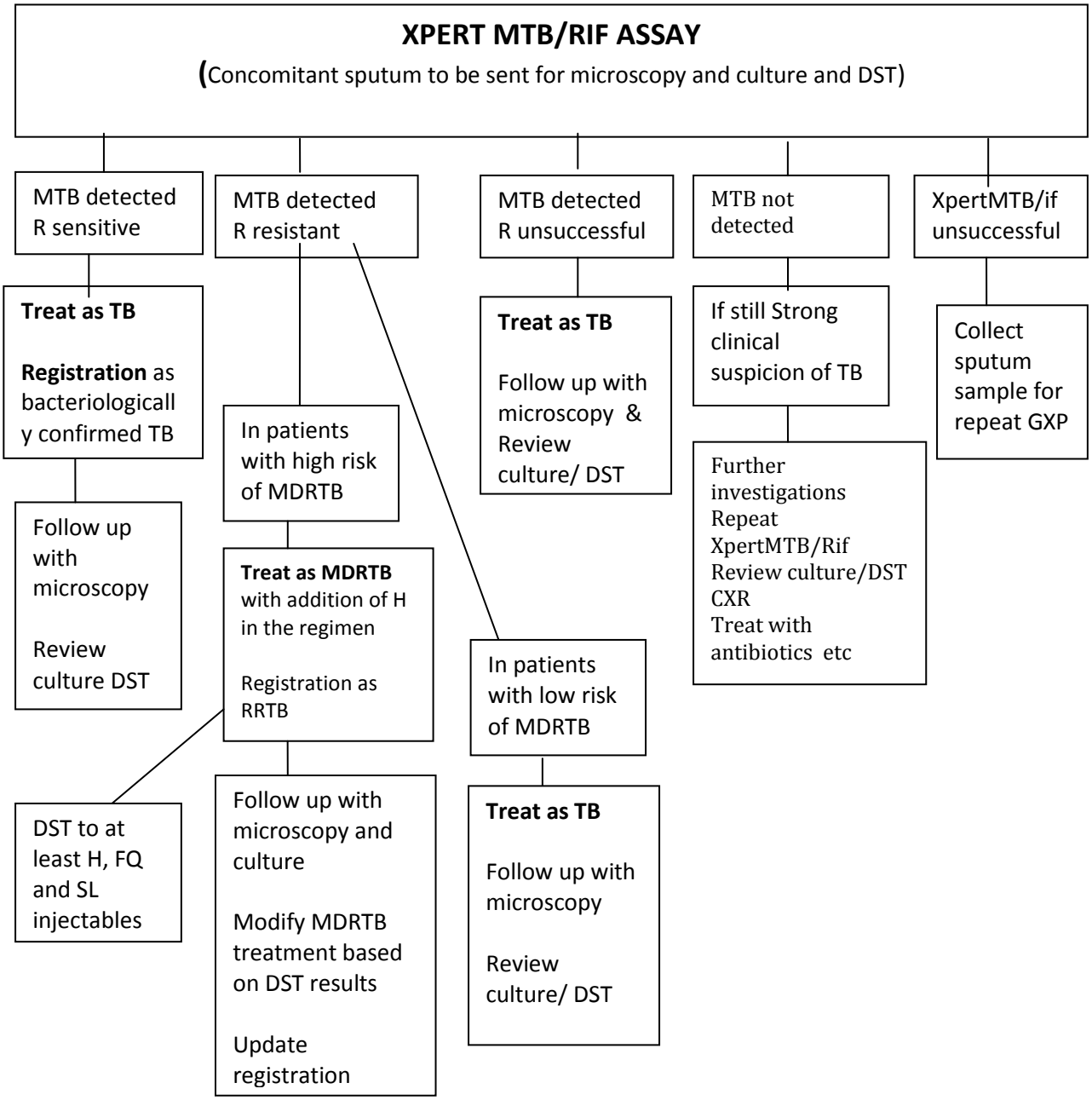
- Recommended regimen for TB with first line drugs should be started and the patient should be registered as having bacteriologically susceptible TB

- Additional specimen should be taken for phenotypic DST to reconfirm resistance to rifampicin and also to test for susceptibility to isoniazid, fluoroquinolones and second line injectables. When DST results are available, the treatment regimen and patient registration should be adjusted as appropriate

- **Use of XpertMTB/Rif does not eliminate the need for microscopy, conventional culture and DST. Microscopy and culture, both, remain necessary for monitoring MDRTB treatment**

- **Conventional culture and DST will be required to detect resistance to anti TB agents other than rifampicin and for performing second line DST (Xpert MTB/RIF detects resistance only to rifampicin**

4.5 Algorithm using XpertMTB/Rif for diagnosis of TB and Rifampicin resistance



4.6 DIAGNOSING XDR-TB

- **XDR TB is diagnosed through conventional phenotypic DST**
- **All individuals presumed to have XDR-TB should have DST to isoniazid, rifampicin, the three second-line injectable agents (kanamycin, amikacin, and capreomycin) and levofloxacin**

All patients diagnosed with MDR-TB and all patients with risk factors for XDR-TB should be tested for XDR-TB. The risk factors for XDRTB are:

- failure of an MDR-TB treatment regimen, which contains second-line drugs including an injectable agent and a FQ
- close contact with an individual with documented XDR-TB
- Close contact with an individual for whom treatment with a regimen including second-line drugs is failing or has failed.

DRUG-RESISTANT TB CASE FINDING IN PAEDIATRIC PATIENTS

- Most young children will not be able to produce adequate sputum specimens for examination
- Sputum induction with nebulized hypertonic saline may facilitate collection of tracheobronchial secretions, especially in children who have a dry cough or no cough
- Where nebulization is unsuccessful, gastric lavage is the most common procedure for collecting specimens for Xpert MTB/RIF or culture and DST. Children swallow their tracheobronchial secretions so gastric lavage specimens may contain respiratory secretions, especially early in the morning before the child has had anything to eat or drink.
- If gastric aspirate fails, fibre-optic bronchoscopy may be the best next step.

- In cases where the anatomic location of disease includes sites outside the pulmonary parenchyma, fine needle aspiration or biopsy should be considered. Specimens obtained by aspiration or biopsy may also need to be sent to the pathology laboratory for examination, in addition to the microbiological testing to rule out other diseases

DRUG-RESISTANT TB CASE FINDING AMONG EXTRA PULMONARY TB PATIENTS

- Drug-resistant extra pulmonary TB can be detected using Xpert MTB/RIF or conventional culture and DST

- Xpert MTB/RIF will be used in as the initial diagnostic test in testing cerebrospinal fluid specimens from patients presumed to have TB meningitis

- Xpert MTB/RIF will be used for testing of specific non respiratory specimens (lymph nodes and other tissues from patients presumed to have extra pulmonary TB

DRUG-RESISTANT TB CASE FINDING IN HIV-INFECTED PATIENTS

- HIV-infected persons are more likely to have smear-negative TB or extra pulmonary TB and unrecognized drug-resistant TB are associated with very high mortality in HIV-infected patients

- Xpert MTB/RIF would be used as a primary diagnostic test in all living with HIV who have signs or symptoms of TB and those seriously ill and suspected of having TB regardless of HIV status, and those with unknown HIV status presenting with strong clinical evidence of HIV infection

- HIV-infected patients with MDR-TB or rifampicin resistance should be tested for second-line anti-TB drug resistance

4.7 Specimen collection and transport

Good quality specimens are very essential for laboratory diagnosis of TB and drug resistant TB. Sputum is the most frequent specimen collected for testing and represents a significant hazard as coughing produces potentially infectious aerosols.

The quality of sputum specimens submitted to the laboratory is vital in obtaining reliable results for XpertMTB/Rif, as with other tests, although contamination of specimens due to inappropriate storage and long transport times of specimens to the laboratory is less of a concern than for conventional culture

Wherever possible, sputum should be collected in open air where infectious droplets are rapidly diluted and UV rays can rapidly inactivate TB bacilli.

Sputum specimens should not be collected in laboratories, toilets, waiting rooms, reception rooms, or any other enclosed space not specifically conceived and organized as a sputum collection area.

Collecting a good specimen in a safe manner also requires trained staff to provide the patient with effective instructions and procedures, using wide-mouthed containers that are sterile, clear and leak-proof with screw caps

Specimen containers should be promptly transported to the laboratory using appropriate packaging for safe transport of infectious materials i.e. surrounded by absorbent material, protected by a secondary packaging and then placed in a shock resistant outer packaging labeled according to national protocol

.

If transport delays are anticipated, specimens should be kept refrigerated at 4°C and transported to the laboratory in a cool box.

A reliable specimen transport system will ensure that full benefit is gained from use of a rapid assay, by reducing diagnostic delay times.

4.8 INFORMATION REGISTRATION ON MDRTB PATIENTS

Four main forms will be used for registration of patients and other information related to the patients

1. Second line Treatment Register

- All patients, once diagnosed will be registered on a separate second line register for MDRTB patients located at RMC of IGM Hospital

- The Second-line TB treatment register is primarily intended to keep a record of those data that are important for generating indicators and reports among patients placed on second line regimens

- Patients on treatment for MDRTB, RR TB and XDR TB would be entered in the register consecutively by their date of registration

- Patients bearing strains resistant to first-line drugs and who are not on a full MDR-TB regimen should be kept in the TB register and any modified regimen can be noted in the Comments section

- Those patients who are registered and started on treatment based on the presumption of RR-TB or MDR-TB, if later are found not to be RR-TB/MDR-TB based on DST, the entry would be crossed out and the follow-up recorded in the TB register

- This register is updated by the DOT provider at RMC, and includes the bio data of the patient, site of disease; treatment received in the past if any, DST results, treatment regimen and sputum smear, culture or Xpert MTB/Rif results.

- The patient is assigned an outcome at the end of treatment according to the standard treatment outcome categories. The date that the outcome is also recorded

- The Second line TB treatment register should be updated regularly from individual Second line TB treatment cards and from the laboratory registers.

2. Second line TB treatment card

- The second line treatment card is usually opened when the decision is taken to start a patient on treatment and is registered in the Second line TB treatment register.

- All Information that is relevant to treatment including patients demographic data, clinical details, weight of the patient, site of disease are to be entered on the patient's Treatment card in addition to the patients registration number and date of registration in the second line register

- Sputum results including smear, culture and DST along with the date of testing are entered on the treatment card in addition to weight, laboratory and X-Ray monitoring

- Patients are assigned to a registration group based on the most recent treatment history. For the purposes of registration, patients are considered 'New', if DST was performed within one month of the start of treatment, even if they had received more than one month of first-line ATT by the time that the DST results returned

- If the patient has received any TB regimen received in the past, whether first- or second-line, the previous TB register number and the respective date of registration as well as the outcome of treatment should be recorded

- HIV information will not be included on the treatment card for patient confidentiality

- A daily record of the drugs administered will be maintained on the Treatment card by the DOT provider. Daily treatment administration is indicated by tick marks under the date. If split doses are used, the upper left half is used to mark the morning dose and the lower right for the evening dose

- At the end of treatment, the final outcome should be recorded on the treatment card. Lost to follow up is recorded after two consecutive months of interruption and the date when the interruption started is recorded

- A copy of the treatment card must always accompany the patient whenever a patient is referred to another health care facility

3. Laboratory register

A laboratory register will also be maintained at the microbiology section of the laboratory for maintaining records of sputum smear, culture/DST examinations and the laboratory technologist will enter the relevant data in to this register including date of receiving the sample and the result of testing. XpertMTB/Rif results are recorded in the register alongside culture

4. Form for examination of sputum

This standard request form accompanies the sputum specimen to the laboratory. The form being used for TB patients is to be used for DRTB cases

Chapter 5

TREATMENT OF MDR AND XDRTB

MDRTB TREATMENT

Any patient in whom multi drug-resistant TB is diagnosed requires treatment with second line drugs and will need specialized regimens for treatment. This chapter describes the standardized approach to treat patients with MDR-TB, the rationale and the role of counseling in ensuring patient compliance while on the regimen

All drug resistant suspects would be evaluated at the Respiratory Clinic (RMC) at IGMH. These patients will be further examined and investigated by the Consultant at RMC. Each patient should give two sputum samples for smear and DST at the IGMH laboratory and all should be registered in the Register kept at the lab, IGMH.

5.1 PRE-TREATMENT EVALUATION

All MDR TB patients will be subjected to pretreatment evaluation prior to start of treatment since the drugs used for the treatment of MDRTB are known to produce adverse effects, a proper pretreatment evaluation is essential to identify patients who are at increased risk of developing such adverse effects.

In addition to a thorough clinical evaluation , a chest radiograph, Audiometry and relevant hematological and bio-chemical tests including screening for diabetes mellitus, liver disease, drug or alcohol use, mental illness, renal insufficiency, thyroid function, pregnancy and lactation.

CONDITIONS TO BE SCREENED FOR AT INITIAL MEDICAL EVALUATION

-LIVER DISEASE	- MENTAL ILLNESS	-DIABETES	- PREGNANCY
- THYROID DISEASE	- HYPERTENSION	- RENAL INSUFFICIENCY	- BREAST FEEDING
-SEIZURE DISORDER	- MALNUTRITION	- DRUG/ALCOHOL DEPENDENCE	- HIV
_HEARING			

5.2 DOTS PLUS COMMITTEE

The hospital based DOTS plus committee at RMC will review the patient details, including previous history, sputum results and concurrent illnesses, and make a decision in relation to treatment with MDRTB regimen.
The committee will also decide on all issues pertaining to these cases including changes in treatment regimen, treatment failures, suspension of treatment and surgical intervention

The DOTS plus committee would consist of 5 members:

- technical focal point for the NTP
- respiratory consultant
- physician
- pediatrician
- surgeon/cardiothoracic surgeon

Decisions regarding MDRTB /XDRTB patients will be made by the DOTS PLUS COMMITTEE at IGM Hospital

This committee advises and recommends:

- Appropriate clinical management of individual MDR- and XDR-TB patients
- Use of salvage regimens in individual patients with high grade resistance
- Management of drug resistant TB regarding termination of treatment and palliative Care
- Management of patients who refuse treatment
- Management of infectious patients who do not cooperate with the health professionals and
- those who abscond from hospital or refuse to be admitted
- Identification and resolutions to health systems issues contributing to poor service delivery such as delays in culture results or shortages of medication
- Surgical intervention

All MDRTB patients will be admitted in the isolation ward at IGM Hospital for the initial 4 weeks of treatment as this will help in counseling and other necessary tasks needed for adherence.

All MDRTB patients will be admitted at the time of diagnosis for the initial 4 weeks of treatment

The patient and the family will be counseled in regard to treatment, the drugs, length of treatment, monitoring requirements during treatment, the need for adherence, possible adverse effects of treatment and DOTS
Counseling should also include information on TB transmission and household infection control

All patients would be offered HIV counseling and testing and if found to be HIV+ve, then the patient will be managed in collaboration with the national HIV programme.

5.3 CLASSES OF ANTI TUBERCULOSIS DRUGS

Group 1 First line Anti tuberculosis agents	Isoniazid (H) Rifampicin (R) Ethambutol (E) Pyrazinamide (Z) Rifabutin(Rfb) (Rifabutin added here as routinely used in patients on protease inhibitors in many settings) Rifapentine(Rpt) (rifapentine is part of latent TB and active TB in some areas but is not part of any WHO endorsed regimens)
Group 2 Injectable anti tuberculosis agents	Streptomycin (S) (high rates of streptomycin resistance in MDRTB strains, so not considered as a 2nd line agent) Kanamycin (Km) Amikacin (Am) Capreomycin (Cm)
Group3 Fluroquinolones	Levofloxacin (Lfx) Moxifloxacin (Mfx) Gatifloxacin:
Group4 Oral bacteriostatic second line ATT	Ethionamide (Eto) Prothionamide (Pto) Cycloserine (Cs) Terizidone (Trd): (limited program & effectiveness data than Cs) P-aminosalicylic acid (PAS)
Group5: Anti tuberculosis agents with limited data on efficacy and/or long term safety in the treatment of DR-TB. (includes new anti-TB drugs)	Bedaquiline (Bdq) Delamanid(Dlm) Clofazimine (Cfz) Amoxicillin/Clavulanate (Amx/Clv): (As adjuvant to Imp and Mpm) Linezolid(Lzd) Thioacetazone(Thz); Clarithromycin(Clr): (limited data) Imipenem(Imp);Meropenem(Mpm) High dose INH(H) : (defined as 16-20mg/kg per day)

5.4 TREATMENT REGIMEN

In the absence of representative national DRS data for Maldives and given the low use of second line drugs in Maldives the National TB Control Programme, Maldives will be using a standardized regimen based on recommendations provided by the WHO for the programmatic management of drug resistant tuberculosis.

Hence for the treatment of MDR-TB cases, the NTP of Maldives will be using a Standardized Treatment Regimen that would be changed to Individualized treatment once individual DST results are obtained

Standardized regimens are simpler to operate/ order drugs, and easier to train healthcare providers where as Individualized treatment avoids placing patients on toxic and expensive drugs and identifies appropriate and specific regimens for each patient

Suspected MDRTB patients would be started on a Standardized Treatment Regimen that would be changed to Individualized treatment once individual DST results are obtained

Advantages of individualized and standardized treatment strategies

Standardized treatment regimen	Individualized treatment regimen
Simple operational aspect of implementation	Avoids placing patients on Toxic and expensive drugs to which the strain may be resistant
Simple drug ordering	Identifies appropriate and specific regimen for each patients
Easier training	
Less likelihood of mismanagement	
Less dependence on highly technical laboratory	

The regimen consists of two phases: the first phase is the one in which the injectable anti TB drugs are used and is referred to as the intensive phase of treatment. The intensive phase will last eight months.

The main indication of response to therapy is smear and culture conversion however; the overall clinical picture (weight gain, resolution or improvement of respiratory symptoms and/or lesions in pulmonary images) will be taken into consideration in deciding whether to continue an injectable agent for longer than eight months
Till date, there is no demonstrated benefit of injectable phases beyond eight months and, in general, failure of treatment should be started to be considered for those that have not culture converted by month eight.

Intermittent therapy with the injectable agent (thrice a week) can also be considered in patients who have been on the injectable for a prolonged period of time (ideally after sputum conversion) and when toxicity becomes a greater risk to the patient. (This is based on expert opinion, as no direct comparisons of thrice a week versus daily doses exist).

General principles when making a MDRTB regimen

- The intensive phase of MDRTB treatment should consist of at least four second line anti TB drugs that are likely to be effective including an injectable anti TB drug as well as PZA

- MDR regimens should include at least pyrazinamide, a fluoroquinolone, an injectable antiTB drug, ethionamide (or prothionamide) and either cycloserine or PAS if cycloserine cannot be used

- The drugs in the regimen should be judged to be "likely effective". An anti-TB drug is considered "likely to be effective" when:
  - The drug has not been used in a regimen that failed to cure the individual patient
  - DST performed indicates that it is susceptible to the drug (DST for isoniazid, rifampicin, Groups 2 and 3 drugs is considered reliable; DST for all other drugs is considered not reliable enough for individual patient management)
  - No known resistance to drugs with high cross resistance
  - No known close contacts with resistance to the drug
  - DRS demonstrate that resistance is rare to the drug in patients with similar TB history

Note: It is not always possible that information of all five criteria can be ascertained. Therefore, clinical judgment is often necessary on whether to count a drug as "likely effective"

- There are conditions when more than five drugs are used. These conditions would be applicable when the effectiveness for a drug is unlikely or questionable such as in the treatment of XDR-TB

- A later-generation fluoroquinolone rather than an earlier generation fluoroquinolone should be used

- Drugs that the patient is known to have a strong contraindication due to drug interactions, toxicities, co-morbidities, history of severe allergy or other adverse reactions, and/or pregnancy should not be used

- PZA can be used for the entire treatment. Many drug resistant TB patients have chronically inflammed lungs, which theoretically produce the acidic environment in which pyrazinamide is more effective

- Kanamycin is to be given 6 days a week and all other drugs are given seven days a week and when possible, pyrazinamide and FQs will be given once per day.

- Once a day dosing is permitted for other second-line drugs, depending on patient tolerance. Ethionamide/prothionamide, cycloserine and PAS have traditionally been given in split doses to reduce adverse effects

- If four second line drugs are not likely to be effective, addition of 2 or more drugs from group 5 will be considered

Standardized treatment regimen

Intensive phase: **8 Km + Lfx + Eto + Cs +Z**
Continuation phase: **12 Lfx + Eto + Cs +Z**

Kanamycin is to be given 6 days a week and all other drugs are given seven days a week

Duration of treatment

The duration of administration of the intensive phase for MDRTB is for a minimum of 8 months and a minimal treatment length of not less than 20 months. In those patients previously treated with MDR regimen (XDR TB) the total treatment duration would be at least 24 months

Drug doses

Weight based ATT in adults' ≥30 kg

DRUGS	**WEIGHT CLASS**				
	30-35 Kg	**36-45kg**	**46-55kg**	**56-70kg**	**>70kgkg**
ORAL ATT					
Isoniazid (4-6mg/kg once daily)	150mg	200mg	300 mg	300 mg	300mg
Rifampicin(8-12mg/kg once daily)	300 mg	450mg	450mg	600mg	600mg
Ethambutol(15-25mg/kg once daily)	600mg	800mg	1000mg	1200mg	1200mg
PZA (20-30mg/kg once daily)	800mg	1000mg	1200mg	1600mg	2000mg
Levofloxacin (750-1000mg daily)	750mg	750mg	1000mg	1000mg	1000mg
Moxifloxacin (400mg daily)	400mg	400mg	400mg	400mg	400mg
Ethionamide(500-750mg/day in 2 divided doses)	500mg	500mg	750mg	750mg	1000mg
Prothionamide(500-750mg/day in 2 divided doses)	500mg	500mg	750mg	750mg	1000mg
Cycloserine(500-750mg/day in 2 divided doses)	500mg	500mg	500mg	750mg	750mg
P-aminosalicylic acid(8g/day in 2 divided doses)	8g	8g	8g	8g	8-12g
Rifabutin(5-10mg/kg once daily)	300 mg	300 mg	300 mg	300 mg	300 mg
High dose INH(16-20mg /kg daily	600-1000mg	1000-1500mg	1500mg	1500mg	1500mg
Clofazimine	200-300mg daily (first 2 months) then 100mg				
Imipenem/cilastatin	1000mg twice daily				
Meropenem	1000mg three times daily (alternative twice daily)				
Linezolid	600 mg once daily.				

Weight based Group 2 injectable agents

DRUG	30-33kg	34-40kg	41-45kg	46-50kg	51-70kg	>70kg
Streptomycin(12-18mg/kg daily)	500mg	600mg	700mg	800mg	900mg	1000mg
Kanamycin(15-20mg/kg daily)	500mg	625mg	750mg	875mg	1000mg	1000mg
Amikacin(15-20mg/kg daily)	500mg	625mg	750mg	875mg	1000mg	1000mg
Capreomycin(15-20mg/kg daily)	500mg	600mg	750mg	800mg	1000mg	1000mg

5.5 EXTRAPULMONARY AND CENTRAL NERVOUS SYSTEM DRUG RESISTANT TB

Extra pulmonary drug-resistant TB is treated with the same strategy and duration as pulmonary drug-resistant TB; the one exception is central nervous system involvement.

If the patient has central nervous system involvement with drug-resistant TB, then the regimen should use drugs, which have adequate penetration into the central nervous system.
Isoniazid, pyrazinamide, prothionamide/ethionamide and cycloserine, all have good penetration into the cerebrospinal fluid, whereas kanamycin, amikacin and streptomycin do so only in the presence of meningeal inflammation. PAS and ethambutol have poor or no penetration.

The FQs have variable cerebrospinal fluid penetration, with better penetration of moxifloxacin based on animal studies.
Imipenem has good central nervous system penetration, but children with meningitis treated with imipenem, had high rates of seizures so meropenem is preferred for meningitis cases and children

The use of corticosteroids in MDR-TB patients with central nervous system involvement is be beneficial.

Prednisone will be used, starting the dose at approximately 1 mg/kg, with gradual decrease in the daily dose by 10 mg per week when a longer course is indicated and injectable corticosteroids when a more immediate response is needed.

5.6 ROLE OF SURGERY

- Surgical intervention for MDR/XDRTB would be undertaken once decided by the DOTS PLUS COMMITTEE

- The most common surgical procedure in patients with pulmonary drug resistant TB is resection surgery by taking out part or all of a lung but it is not indicated in patients with extensive bilateral disease

- Patients that may be considered for surgery include patients that remain smear-positive, with resistance to a large number of drugs; and localized pulmonary disease

- Computerized tomography, pulmonary function testing and quantitative lung perfusion/ ventilation is recommended as part of the preoperative work-up

- Resection surgery should be timed such that the patient has the best possible chance of cure with the least morbidity. Thus, the timing of surgery may be earlier in the course of the disease when the patient's risk of morbidity and mortality are lower.

- At least two months of therapy will be given prior to resection surgery to decrease the bacterial infection in the surrounding lung tissue and stringent infection control measures is to be followed during the surgical procedure

5.7 ADJUVANT THERAPIES IN DRUG RESISTANT TB TREATMENT

Corticosteroids

Corticosteroids should only be used if clearly indicated and if the patient is on an adequate effective regimen. If corticosteroids are used in an inadequate regimen, this could accelerate the deterioration of the patient.

Corticosteroids can be beneficial in conditions like severe central nervous system or pericardial involvement. Corticosteroids may also help in respiratory insufficiency and miliary TB with a tapering of dosage over several weeks

Corticosteroids may also alleviate symptoms in patients with an exacerbation of obstructive pulmonary disease.

Vitamin B6:

Tab Pyridoxine (100mg) should be given to all the patients especially MDR-TB patients receiving cycloserine and a high dosage of isoniazid or linezolid to prevent neurological side effects

5.8 MANAGEMENT OF XDR TB

Likelihood of cure has proven to be much lower in XDRTB than in MDRTB cases and deaths are higher, especially in HIV-infected patients. There is very limited data on the different clinical approaches to XDR-TB and it is observed that that success in XDR-TB patients is highest if at least six drugs are used in the intensive phase and four in the continuation phase.

The use of later-generation FQs, significantly improved treatment outcomes, even though DST demonstrated resistance to a representative fluoroquinolone

- Use PZA and any group1 agents that may be effective
- Use an injectable to which the strain is susceptible and consider an extended duration of use (12 months) or possibly entire treatment. If resistant to all, use an injectable the patient has not used before or consider regimen without an injectable agent
- Use a later generation quinolone such as moxifloxacin/gatifloxacin
- Use all group 4 agents that have not been used extensively in a previous regimen or any that are likely to be effective
- Use 2 or more agents from group 5
- Consider adding a new investigational drug eligible for use if WHO policy endorses its use for XDR-TB
- Consider high dose INH
- Consider adjuvant surgery if localized disease
- Consider the option of treatment in a hospital if the clinical condition of the patient is poor or major comorbidities coexist
- Manage HIV coinfection
- Provide comprehensive monitoring and full social support to enable adherence to treatment
- Ensure that all patients have full access to palliative and end-of-life care services, with a patient-centred approach to relieve the suffering of the disease and its treatment
- Ensure rigorous respiratory infection control measures at the site where the patient is being treated

Chapter 6

MONO AND POLY RESISTANT STRAINS

- Mono and poly resistance cases are more common than MDRTB in new cases and many of these cases contribute towards amplification of resistance and can eventually lead to MDR if not properly treated.

- For patients with INH mono and poly resistance, treatment should be done with caution while monitoring for Rifampicin amplification and the regimen adapted to an MDRTB regimen if rifampicin resistance is detected

- The frequency of rifampicin mono and poly resistance is low and all patients with strains resistant to rifampicin should be treated using a full MDR-TB regimen, with isoniazid being added to the regimen until DST results to isoniazid are available and appropriate adjustments to the regimen can be made.

Regimens for mono and poly resistance

Pattern of resistance	**Suggested regimen**	**Minimum duration of treatment**	**Remarks**
H (+_ S)	R,Z and E (+/- FQ)	6-9 months	A FQ may strengthen the regimen for those with extensive disease Monitoring for R resistance at month 0,2,3
H and E(+/- S)	R,Z and FQ	9-12 months	Monitoring for R resistance at month 0,2,3 Second line injectable agent may be added for 1st 3 months (recommended by experts)
H,E,Z(+-S)	R, FQ, plus Eto plus a second line injectable agent for the first 2-3 months(+/-Z)	18 months	A longer course(6 months) of the second line injectable agent may strengthen the regimen in extensive disease Z to be added if resistance uncertain Monitor R resistance at month 0,2,3
R mono or poly drug resistance	MDR regimen plus H	20 months	

Chapter 7

TREATMENT DELIVERY AND ADHERENCE

Treatment delivery strategies are important in management of MDR-TB patients as it will improve patient adherence.
Patients with MDR-TB may be more likely to have problems with non-adherence due to prolonged duration of treatment, drug side effects and large number of drugs

7.1 Initial in-patient care

MDR-TB patient will be admitted in the hospital for initial patient care at least for a minimum of 4 weeks and the clinical team will visit the patient daily during this period. Patient will be admitted in the isolation room at IGM Hospital.

This time period will help in counseling the patient and family regarding treatment and other necessary tasks need for adherence. In addition all necessary investigations can be undertaken before Initiation of the Regimen for MDR TB and patient can be monitored for tolerance of the Regimen

Along with Motivation, counseling and providing health education to both the patient and their families, this period can also help in contact tracing and assessment.

And if the patient is from another island then linkages with the services in the respective island where the patient resides (including identification and training of the medical officer and local DOT provider can be undertaken)

Adherence promotion strategies for DOTS Plus include providing Patient and Family Counseling, Directly observed therapy and effective management of adverse drug reactions

7.2 Providing Patient and Family Counseling

Patients should receive counseling on the nature and duration of treatment, need for regular treatment and possible side effects of these drugs and the consequences of irregular treatment or pre-mature cessation of treatment.

Patients should be advised to report if he/she experiences any unusual problem. Female patients should receive special counseling on family planning.

Health education is carried on a continuous basis at all visits by the patient to a health facility. The counseling and motivation is required to be done not only of the patient but also of the family members since family support is an essential component in the management

7.3 Directly observed therapy

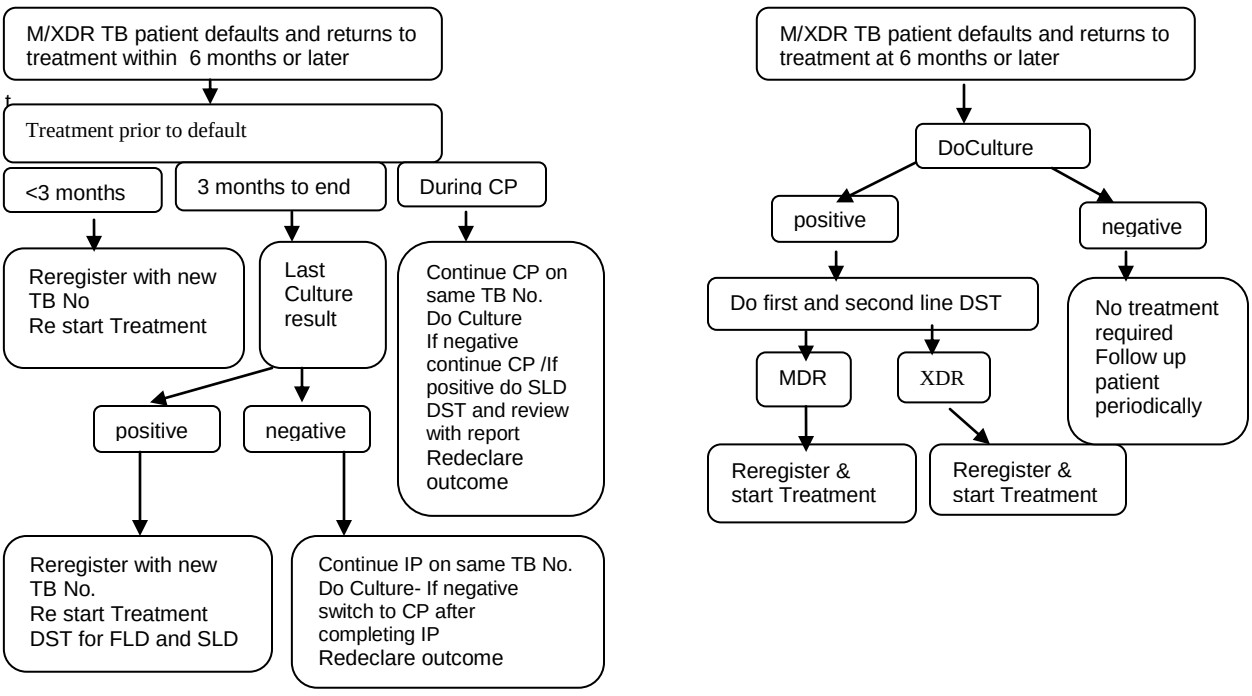
- **All patients receiving treatment for MDR and XDRTB should receive daily DOT**
- **Family members should not be used for delivering DOT in MDR and XDR TB**

Because MDR-TB treatment is the last therapeutic chance for patients for a cure and there is a high public health consequence if a patient with MDR-TB fails therapy, it is recommended that all patients receiving treatment for MDR-TB receive daily DOT
Family members should not be used for delivering DOT as they can be influenced by the patients.

Early and effective management of adverse drug reactions

Adverse drug reaction among patients on MDR-TB treatment may be one reason for non-adherence. So management of adverse drug reaction should be done in a simple and cost effective way without compromising the MDR-TB treatment regimen.

Management algorithm for patients who default and return to treatment



Chapter 8

MANAGEMENT OF MDR-TB IN SPECIAL CONDITIONS AND SITUATIONS

- Pregnancy and breastfeeding
- Children
- Diabetes mellitus
- Renal insufficiency
- Liver disorders
- Seizure
- Psychiatric disorders
- Substance dependence
- HIV

Pregnancy

- Female patients of childbearing age should be tested for pregnancy upon initial evaluation because of the great risks to the lives of both mother and fetus.

- Birth control is strongly recommended for all non pregnant women receiving therapy for drug-resistant TB because of the potential consequences for both mother and fetus resulting from frequent and severe adverse drug reactions.

- Most patients should be started on treatment as soon as diagnosis is made but treatment may be delayed till second trimester if patient stable with minimal disease as most teratogenic effects occur in first trimester

- Avoid injectable agents and ethionamide

- IF injectables.and Ethionamide were withheld because of pregnancy, they can be added post partum to make a more complete regimen

Breastfeeding

Breast feeding is not a contraindication to MDR-TB treatment and should receive a full course of anti tuberculosis treatment. However the effects on infants of such exposure during the full course of MDR-TB treatment have not been established.

Therefore, it is recommended to provide infant formula options as an alternative to breastfeeding.

Diabetes mellitus

Diabetic patients with MDRTB are at risk for poor outcomes as diabetes may potentiate the adverse effects of anti tuberculosis drugs, especially renal dysfunction and peripheral neuropathy. Diabetes must be managed closely throughout the treatment of drug resistant TB.
Oral hypoglycaemic agents are not contraindicated during the treatment of drug resistant TB but may require the patient to increase the dosage as use of ethionamide or prothionamide may make it more difficult to control insulin levels.
Creatinine and potassium levels should be monitored more frequently, often weekly for the first month and then at least monthly thereafter.

Children

Children with drug resistant TB generally have primary resistance transmitted from an index case with drug resistant TB. When DST is available it should be used to guide therapy, although children with paucibacillary TB are often culture negative.

The treatment of culture-negative children with clinical evidence of active TB disease and contact with a documented case of drug-resistant TB should be guided by the results of DST and the history of the contact's exposure to anti tuberculosis drugs.

MDRTB is life threatening and no anti tuberculosis drugs are absolutely contraindicated in children.
Anti TB drugs should be dosed according to body weight and monthly monitoring of body weight is therefore especially important, with adjustment of doses as children gain weight.

In addition microbiological monitoring of the response to treatment is often difficult in children and weight loss or, more commonly, failure to gain weight in the presence of proper nutritional intake, is often one of the first (or only) signs of treatment failure.

Pediatric dosing of second-line anti tuberculosis drugs

When a liquid formulation is available, it should be used for patients less than 15 kg.

Most second-line TB drugs do not have paediatric liquid or tablet formulations, so it may be necessary to split the pills in order to approximate the correct dose. To split tablets into 0.75, it is suggested to split the tablet in half and then split a half tablet in half. Discard the smaller quarter tablet and give the child a half tablet plus the remaining quarter tablet.

Doses of most anti-TB drugs have not been established for children below 5 kg, but often the potential benefit outweighs the risks. In such cases, the child should be dosed as close to the middle of the mg/kg range as possible.

Drug	Daily Dose(MG/KG)	Frequency	Max.daily dose
isoniazid	7-15mg/kg	Once daily	300mg
rifampicin	10-20mg/kg	Once daily	600mg
ethambutol	15-25mg/kg	Once daily	1200mg
pyrazinamide	30-40mg/kg	Once daily	2000mg
Streptomycin	20–40mg/kg	Once daily	1000mg
Kanamycin	15–30 mg/kg	Once daily	1000mg
Amikacin	15–30 mg/kg	Once daily	1000mg
Capreomycin	15–30 mg/kg	Once daily	1000mg
Levofloxacin	15-20mg/kg<5years	twice daily	750 mg
	10-15mg/kg>5 years	Once daily	
Moxifloxacin	7.5–10mg/kg	Once daily	400 mg
Ethionamide	15-20mg/kg	Twice daily	1000mg
Prothionamide	15–20mg/kg	Twice daily	1000m g
Cycloserine	10–20mg/kg	Once or twice daily	1 g
PAS	200-300mg/kg for <30kg	Twice daily	12 g

Renal insufficiency

Great care should be taken in the administration of second-line drugs in patients with renal insufficiency, and the dose and/or the interval between dosing should be adjusted

Adjustment of ATT in Renal insufficiency

DRUG	CHANGE IN FREQUENCY?	RECOMMENDED FOR PATIENTS WITH CREATININE CLEARANCE <30ml/min OR ON HEMODIALYSIS
INH	No change	300mg daily
RIFAMPICIN	No change	600mg daily
PZA	YES	25-35 mg/kg per dose three times per week
ETHAMBUTOL	YES	15-25mg/kg per dose three times per week
GATIFLOXACIN	YES	400mg three times a week
LEVOFLOXACIN	YES	750-1000mg per dose three times per week
MOXIFLOXACIN	No change	400mg daily
CYCLOSERINE	YES	250 mg once daily or 500 mg/dose three times a week
PROTHIONAMIDE	No change	250-500mg per dose daily
ETHIONAMIDE	No change	250-500mg per dose daily
PAS	No change	4 g/dose. twice daily
STREPTOMYCIN	YES	12-15mg/kg per dose, two or three times per week
CAPREOMYCIN	YES	12-15mg/kg per dose, two or three times per week
KANAMYCIN	YES	12-15mg/kg per dose, two or three times per week
AMIKACIN	YES	12-15mg/kg per dose, two or three times per week

Liver disorders

Among the second-line drugs, ethionamide, prothionamide and PAS can be hepatotoxic, although less so than any of the first-line drugs.

Patients with a history of liver disease can receive the usual drug-resistant TB chemotherapy regimens provided there is no clinical evidence of chronic liver disease, hepatitis virus carriage, past history of acute hepatitis or excessive alcohol consumption.

In general, patients with chronic liver disease should not receive pyrazinamide. All other drugs can be used, but close monitoring of liver enzymes is advised.
In cases when it is necessary to treat drug resistant TB during acute hepatitis, the combination of four non hepatotoxic drugs is the safest option

Seizure disorder

If the seizures are not under control, initiation or adjustment of anti seizure medication will be needed before the start of drug resistant TB therapy.
Cycloserine should be avoided in patients with active seizure disorders that are not well controlled with medication. However, in cases where Cs is a crucial component of the treatment regimen, it can be given and the anti seizure medication adjusted as needed to control the seizure disorder.

Seizures that present for the first time during ATT are likely to be the result of an adverse effect of one of the anti tuberculosis drugs

Psychiatric disorders

Any psychiatric illness identified at the start of or during treatment should be fully addressed.
There is a high baseline incidence of depression and anxiety in patients with MDR-TB, often connected with the chronicity and socioeconomic stress factors related to the disease.

The use of cycloserine is not absolutely contraindicated for the psychiatric patient. Adverse effects from cycloserine may be more prevalent in the psychiatric patient, but the benefits of using this drug may outweigh the potentially higher risk of adverse effects.

Close monitoring is recommended if cycloserine is used in patients with psychiatric disorders.

Substance dependence

Patients with substance dependence disorders should be offered treatment for their addiction. Complete abstinence from alcohol or other substances should be strongly encouraged, although active consumption is not a contraindication for anti tuberculosis treatment.

HIV Infection

The recommended treatment of TB, whether drug-susceptible or-resistant, is the same for HIV-infected and non-HIV-infected patients, except for the use of thioacetazone, which should not be used in HIV-infected patients.

However the adverse events of drugs are more common in HIV patients. Deaths during treatment caused by TB itself or by other HIV related diseases are more frequent in HIV-infected patients, particularly in the advanced stages of immunodeficiency.

The use of ART in HIV-infected patients with TB improves survival and slows progression to AIDS. However, initiation of ART in HIV-infected patients with drug-susceptible or drug-resistant TB is often associated with adverse events that may lead to the interruption of both TB and/or HIV therapy.

Chapter 9

MONITORING PATIENTS ON TREATMENT

Monitoring evaluation	**Recommended frequency**
Evaluation by clinician	- Daily during the first 4 weeks of initial hospitalization followed by monthly consultations
Weight	- At baseline - every 2 weeks for first 3 months - Monthly from 4th month onwards
CXR	- At baseline and then every 6 months - if there is worsening of clinical condition - when surgical intervention considered
Sputum smears and cultures	- Sputum smears and cultures monthly from 4th month till sputum conversion - monthly smears and cultures every other month in the continuation phase
DST	- At baseline - When patient Remain Culture positive or revert after 4th month
S Creatinine	- At baseline - monthly while on injectable drug
S Potassium	- Monthly while on injectable agent - Every 1-3 weeks in HIV infected, diabetes
TSH	- Every 3 monthly if patient on ethionamide/prothianamide/PAS - Monthly monitoring for clinical signs/symptoms of hypothyroidsm
LFT	- Every 1-3 months - In HIV infected , monitor monthly - For patients with viral hepatitis, monitor 1 to 2 weeks for the first month then every 1 to 4 weeks

Chapter 10

MANAGEMENT OF PATIENTS WITH MDR-TB TREATMENT FAILURE

10.1 Assessment of patients at risk for failure

- Patients who do not show signs of improvement after four months of treatment

In all patients who show clinical, radiographical or bacteriological evidence of progressive active disease, or reappearance of disease after month 4 of treatment the following steps are recommended
:

• Review the treatment card for adherence.

•The treatment regimen should be reviewed in relation to medical history, contacts and all DST reports. If the regimen is deemed inadequate, a new regimen should be designed.

• The bacteriological data should be reviewed.

One single positive culture in the presence of an otherwise good clinical response can be caused by a laboratory contaminant or error, hence subsequent cultures that are negative may help prove that the apparently positive result did not reflect treatment failure and similarly positive smears with negative cultures may be caused by the presence of dead bacilli and therefore may not indicate treatment failure.

Repeated culture and smear negative results in a patient with clinical and radiographical deterioration may indicate that the patient has a disease other than MDR-TB.

• Confirm that the patient has taken all the prescribed medicines.

• A non-confrontational interview of the DOT worker should be carried out to rule out the possible manipulation of the DOT worker by the patient and if manipulation is suspected, the DOT worker should be switched to another patient, and the patient with suspected treatment failure should be assigned to a new DOT worker.

• Other illnesses that may decrease absorption of medicines (e.g. chronic diarrhoea) or may result in immune suppression (e.g. HIV infection) should be excluded.

• If surgical resection is feasible, it should be considered.

Signs indicating treatment failure include:

- Persistent positive smears or cultures past month 8–10 of treatment;
- Progressive extensive and bilateral lung disease on chest X-ray with no option for surgery
- High grade resistance with no option to add two additional agents
- Over all deteriorating clinical condition that usually includes weight loss and respiratory insufficiency.

10.2 Suspending therapy:

There are two important considerations in suspending therapy:

1. The patient's quality of life: the drugs used in MDR-TB treatment have significant adverse effects, and continuing them while the treatment is failing may cause additional suffering.

2. The public health concern: continuing a treatment that is failing can amplify resistance in the patient's strain, resulting in resistance to all known anti tuberculosis drugs; the "super-resistant" strain may cause subsequent infection of others.

The approach to suspending therapy should start with discussions among the DOTS PLUS Committee, and once the committee decides that treatment should be suspended, a clear plan should be prepared for approaching the patient and the family.

Supportive care for patients in whom all the possibilities of MDRTB treatment have failed

End of life supportive measures

- Pain control and symptom relief
- Relief of respiratory insufficiency
- Nutritional support
- Continuation of ancillary medicines as needed
- Hospitalization should be offered to families who want to keep the patient at hospital if possible
- Preventive measures including oral care, prevention of bedsores and prevention of muscle contractures are indicated in all patients
- Infection control measures should be continued

10.3 Follow-up after successful completion of MDR-TB treatment

After the patient has been cured of drug resistant TB, they have to be followed up as they may have sequelae from the disease that needs regular follow-up for care plus all cured patients are at risk for relapse of TB.

Patient should be evaluated at three, six and 12 months after treatment completion and should be advised to return to the clinic if there is cough of more than two weeks, or persistent fever and weight loss or for any medical concerns.

Sputum culture should be performed at six and 12 months after treatment completion to evaluate for possible recurrence or whenever relapse is suspected.

Transfer of patients

When a patient is transferred to another centre then it is the responsibility of the DOT provider to contact the TB in charge/the DOT provider at the referred centre and also to ensure that a copy of the treatment card is sent along with the patient

10.4 Follow up of non adherent patient

The DOT provider will be responsible for follow up MDRTB patients within one day of missing the dose by contacting the patient and the family to find out why the patient has not appeared for DOT, and ensure that treatment is resumed promptly and effectively.

The situation should be addressed in a sympathetic, friendly, and non-judgmental manner. The DOT provider should listen and identify the reasons for why the patient missed a dose and should work with the patient and family to ensure treatment continuation and try to resolve the specific reason identified,

.

TB treatment should be provided on a voluntary basis and when a patient refuses treatment, this is usually due to insufficient counselling or lack of treatment support. Every effort possible should be made to make the patient adhere to treatment

The DOT provider should also inform the program Manager at the NTP as well as the consultant at the RMC regarding the patient

It is necessary that every dose of treatment is given under DOT and supervision is needed at all levels. A good supervisor will motivate the patient and also the DOT provider, since the treatment for MDR is a prolonged one adequate motivation ensures treatment compliance

10.5 Involuntary isolation as a last resort

In extremely rare cases, where all efforts to engage a patient to adhere to treatment have failed, the rights of other members of the community might justify the isolation of the contagious patient involuntarily.

Involuntary isolation should always be used as a very last resort, and only when all other measures fail to make the patient adhere to treatment has failed and It is essential that the decision and implementation complies with applicable ethical and human rights principles.

Furthermore, isolation should be least restrictive and intrusive with adequate infection control and reasonable social support measures in place.

Chapter 11

MONITORING & MANAGEMENT OF ADVERSE EFFECTS DURING TREATMENT

Monitoring for early detection of adverse reactions

Close monitoring of patients is necessary to ensure that the adverse effects of second line anti-TB drugs are recognized early by the DOT provider.
If the patient makes any complaint he/she should be asked in detail and the necessary action taken.

The DOT provider should be able to recognize adverse reactions like nausea, vomiting, diarrhoea, skin rash, ototoxicity, peripheral neuropathy, psychiatric symptoms and jaundice.2-5 Training should also be provided on the management of minor reactions and when the patients should be referred to the medical officer.

In addition to clinical monitoring, certain laboratory investigations may be required to detect certain occult adverse effects.

Common adverse reactions to the drugs used

Abdominal pain	Arthralgia	Seizures
Nausea/vomiting	Dizziness/vertigo	Hypothyroidsm
Diarrhoea	Peripheral neuopathy	Psychosis
Gastritis	Allergic reaction	Suicidal ideation
Electrolyte disturbance	Rash	visual disturbance
Hepatitis	Hearing disturbance	QT polongation
Nephrotoxicity	Tinnitus	Headache
Sleep disturbance	Anorexia	Depession

Management of adverse effects

Second-line drugs have many more adverse effects than the first-line anti-tuberculosis drugs.
Proper management of adverse effects begins with patient education. Before starting treatment, the patient should be instructed in detail about the potential adverse effects that could be produced by the prescribed drug regimen, and if and when to notify a health care provider.

Prompt evaluation, diagnosis and treatment of adverse effects are extremely important, even if the adverse effect is not particularly dangerous.
If the adverse effect is mild and not dangerous, continuing the treatment regimen, with the help of ancillary drugs if needed, is often the best option.
In patients with highly resistant TB, a satisfactory replacement drug may not be available, so that suspending a drug will make the treatment regimen less potent.

Some adverse effects may disappear or diminish with time, and patients may be able to continue receiving the drug if sufficiently motivated. The adverse effects of a number of second-line drugs are highly dose dependent. Management often requires the use of ancillary medications to eliminate or lessen the adverse effects.

COMMON ADVERSE EFFECTS, SUSPECTED AGENTS AND MANAGEMENT STRATEGIES

ADVERSE EFFECT	**SUSPECTED AGENT**	**MANAGEMENT**
Rash, allergic reaction and anaphylaxis	Any dug	1. For serious allergic reactions, stop all therapy till resolution 2. Eliminate other potential causes of allergic skin reactions 3. For minor reactions, continue drugs .and give a course antihistamines, Hydrocortisone cream for localized rash, or if other measures are not helpful Prednisone 10 to 20 mg per day for several weeks can be tried use of moisturizing lotion to alleviate dry skin 4. Once rash resolves, reintroduce drugs, one at a time with the one most likely to cause the reaction last. 5. Consider not reintroducing even as a challenge any drug that is highly likely to be the cause. 6. Suspend permanently any drug identified to be the cause of a serious reaction.
Seizure	**Cs, H, FQ**	1. Suspend suspected agent till seizure resolution 2. Initiate anti convulsant therapy 3. Increase pyridoxine to maximum daily dose(200mg) 4. Reintroduce suspended agent at a lower dose if essential to the regimen 5. Check electrolytes 6 When seizures have resolved, restart medications one at a time 7 Cs should not be restarted unless it is absolutely essential to the regimen and if reinitiated, start a dose one weight band lower.
Peripheral neuropathy	**Cs, H, Lzd** ,S, Km, Am,Cm ,Eto/Pto, FQ	1. Increase pyridoxine to maximum daily dose(200mg) 2. Change injectable to capreomycin if susceptible 3. Lower dose of cycloserine without compromising regimen 4. Initiate therapy with tricyclic antidepressants. NSAIDS may help alleviate symptoms 5. Cabamazepine 100-400mg can be tried 6. Gabapentin can be used at a maximum dose of 3600mg/day in 3-4 divided doses 7. Discontinue suspected agent if regimen is not compromised

Hearing loss and vestibular dysfunction	**S, Km, Am, Cm** Cs, FQs,H,Eto,Lzd	1 Change injectable to Cm if susceptible 2 If early symptoms change the injectable to twice/thrice per week 3 If symptoms worsen, with above adjustment, discontinue injectable agent
Electrolyte disturbances	**Cm ,Km ,Am ,S**	1. Check potassium. 2. If potassium is low, also check for magnesium and calcium 3. Replace electrolytes as needed.
Psychotic symptoms	**Cs, H**,FQ s	1. Stop suspected agent (1-4 weeks) while psychotic effects are being controlled 2. Initiate anti psychotic therapy if moderate to severe symptoms 3. Increase pyridoxine to maximum daily dose 4. Lower dose of suspected agent if regimen not compromised 5. Discontinue suspected agent if regimen is not compromised
Suicidal ideation	**Cs, H, Eto/Pto**	1. Hospitalize the patient and put under 24-hour surveillance. 2. Discontinue cycloserine. 3. Request psychiatric consultation. 4. Initiate antidepressant therapy. 5. Lower the dose of Eto/Pto to 500 mg daily until the patient is stable
hypothyroidsm	**PAS,Eto/Pto**	1. Initiate thyroxine therapy
Nausea and vomiting	**PAS, Eto/Pto, Bdq,** H, E, Z, Amx/Clv ,Cf,Z	1-Assess for dehydration, electrolyte disturbance and hepatitis 2-Initiate rehydration if indicated and correct electrolyte disturbances if any 3- Adjust medications and conditions without lowering the overall dose: –Give Eto/Pto at night –Give Eto or PAS twice or thrice daily –Give a light snack before the medications -Give PAS two hours after other anti-TB drugs. 4-Initiate anti emetic therapy –Metoclopramide 10 mg, 30 minutes before ATT –Ondansetron 8 mg, ½ hour before ATT & again eight hours after. 5-Decrease dose of the suspected drug by one weight class if this can be done without compromising the regimen It is rarely necessary to suspend the drug completely.
Gastritis and abdominal pain	**PAS,Eto/Pto,Cfz** FQs, H,E,Z	1 Evaluate for serious adverse effects, (pancreatitis, lactic acidosis and hepatitis.) 2. If symptoms are consistent with gastritis initiate therapy with H2-blockers or proton-pump inhibitors Avoid the use of antacids as they decrease absorption of FQs. 3. For severe abdominal pain stop suspected agent(s) for short periods of time (one to seven days). 4. Lower the dose of the suspected agent, if this can be done without compromising the regimen. 5. Discontinue the suspected agent if this can be done without compromising the regimen. 6. If antiacids must be used dosing of antiacids should be 2 hours before or 3 hours after ATT

Hepatitis	**Z,H,R.Eto/Pto**, PAS	1 If enzymes are more than 5 times the upper limit of normal, stop all hepatotoxic drugs and continue with at least three non hepatotoxic medications (eg:,the injectable agent, fQs and Cs). 2 If hepatitis worsens or does not resolve with the 3 drug regimen, then stop all drugs. 3 Eliminate other potential causes of hepatitis (viral hepatitis and alcohol induced being common causes) 4. Consider suspending the most likely agent permanently. 5. Reintroduce remaining drugs, one at a time with the least hepatotoxic agents first, while monitoring LFT every three days 6 If the most likely agent is not essential consider not reintroducing it
Renal toxicity	**S,Km,Am,Cm**	1.Discontinue suspected agent 2.Consider using capreomycin 3. Consider other contributing aetiologies (NSAIDs, diabetes, other medications,dehydration, congestive heart failure, urinary obstruction 4. Consider dosing 3 times a week if drug essential to regimen (monitoring creatinine) 5.Adjust all ATT according to creatinine clearance
arthralgias	**Z, Bdq,** FQ	1 Initiate NSAIDS 2 Lower dose of suspected agent if this can be done without compromising the regimen 3 Discontinue suspected agent if this can be done without compromising the regimen
Tendonitis and tendon rupture	**FQs**	1. If significant inflammation of tendons or tendon sheaths occur: Consider stopping FQ Give NSAIDs Rest the joint. 2. If treatment failure is likely without the FQ Reduce dose if possible Ensure joint is strictly rested Inform patient of the possible risk of tendon rupture and discuss the risks and benefits of ongoing use of the FQ

Chapter 12

MANAGEMENT OF CONTACTS OF MDRTB PATIENTS

"Close contacts" of MDRTB: people living in the same household as the index patient, or spending many hours a day together with the patient in the same indoor space.

Treatment of latent MDRTB with second line anti-TB drugs is not recommended

The need for contact tracing is to find and treat contacts that have active TB that would help in decreasing transmission of multidrug-resistant strains. The experience with treatment of latent MDRTB in close contacts is limited, and therefore routine treatment of latent MDR-TB with second-line anti TB drugs is not recommended at this time.

The clinician should inquire at all opportunities to about the health of the MDR-TB patient's family contacts such as at every clinical evaluation for the development of any TB symptoms. The DOT provider should also educate the patient and family and explain the importance of notifying quickly regarding contacts that develop symptoms of active disease

Close contacts of MDR-TB patients with TB symptoms should undergo diagnostic workup including

- Clinical evaluation at RMC at IGMH by physician/ pulmonologist
- chest radiograph
- sputum investigations, ideally a rapid diagnostic method
- HIV testing (if anyone in the household is known to be HIVpositive)
- In children in addition a tuberculin skin testing with purified protein derivative

In contacts suspected of having extra pulmonary TB, bacteriological confirmation is often difficult. Sputum culture should always be done, since patients with extra pulmonary TB often have subtle pulmonary involvement. DST should be done for all contacts with a suspicion of extra pulmonary TB.

If the initial investigation is not suggestive of active TB, the contact should continue to be monitored closely by the clinical team.

Contacts with bacteriologically confirmed TB, but without confirmation of MDRTB: As confirmation of drug resistance by culture based methods will take months. Hence these patients will be empirically treated with the same regimen as the index patient while DST is pending.
If the DST eventually shows that the contact was infected outside the home by a susceptible strain, the contact can be switched to a regimen of first line drugs

Contacts with extra pulmonary TB: Samples of pleural, peritoneal tissue and cerebrospinal fluid for TB culture are often culture negative, and there is no need to wait for bacteriological confirmation in these cases. Xpert MTB/RIF can be done on a number of body fluids and tissues. Close contacts with evidence of extra pulmonary TB should be started on empiric treatment with the same regimen as the index patient

Contacts with culture negative TB: While it is important to make an effort to confirm the diagnosis of MDRTB in close contacts, it is often counterproductive especially in children, who are often unable to produce good sputum samples. Once a child contact of MDRTB meets the criteria for diagnosis with active TB, he/she should be started empirically on treatment with the same regimen as the index patient

Chapter 13

INFECTION CONTROL

Transmission of TB is a recognized risk in health care facilities and communities, especially with inadequate TB infection control measures. Infection control measures and practices should be promoted in the household and congregate settings as well.

Health care facility:

- Staff protection should be assured only by masks with a high-efficiency air intake filter, and fitting tightly around the face so that no air can come in from besides the mask.
- Hospital infection control Policies and procedures should be in place
- Health workers who have contact with DR-TB patients should know their HIV status. If they do not, they should be encouraged to be tested for HIV
- Anyone who coughs should be educated on cough etiquette and respiratory hygiene, and should be provided with surgical masks
- Transmission of MDR-TB is a recognized risk for laboratory workers. Instructions on safe handling of specimens are to be strictly followed.

Household:

- Ensuring adequate ventilation/open windows

- Anyone who coughs should be educated on cough etiquette and respiratory hygiene, and should follow such practices at all times.

- Smear positive TB patients should spend as much time as possible outdoors and sleep alone (if possible) in a separate, adequately ventilated room; and if possible spend as little time as possible in congregate settings or in public transport

- Patients should also wear personal masks to minimize dispersal of bacilli when they talk, cough, yawn or sneeze. These can be simple surgical masks; they will retain the droplets expelled by the patient effectively.

- Family members living with HIV should not provide care for patients with culture positive MDR-TB. If there is no alternative, HIV positive family members should wear N95 respirator or equivalent.

- Children below five years of age should spend as little time as possible in the same living spaces as culture positive MDR-TB patients. Such children should be followed up regularly for early detection of TB disease

- Ensuring that household members are screened for TB and DR-TB every six months.

- Culture positive XDR-TB patients should be in respiratory isolation at all times, especially when treatment options have been exhausted, and any person in contact with such a patient should wear a N95 respirator or equivalent.

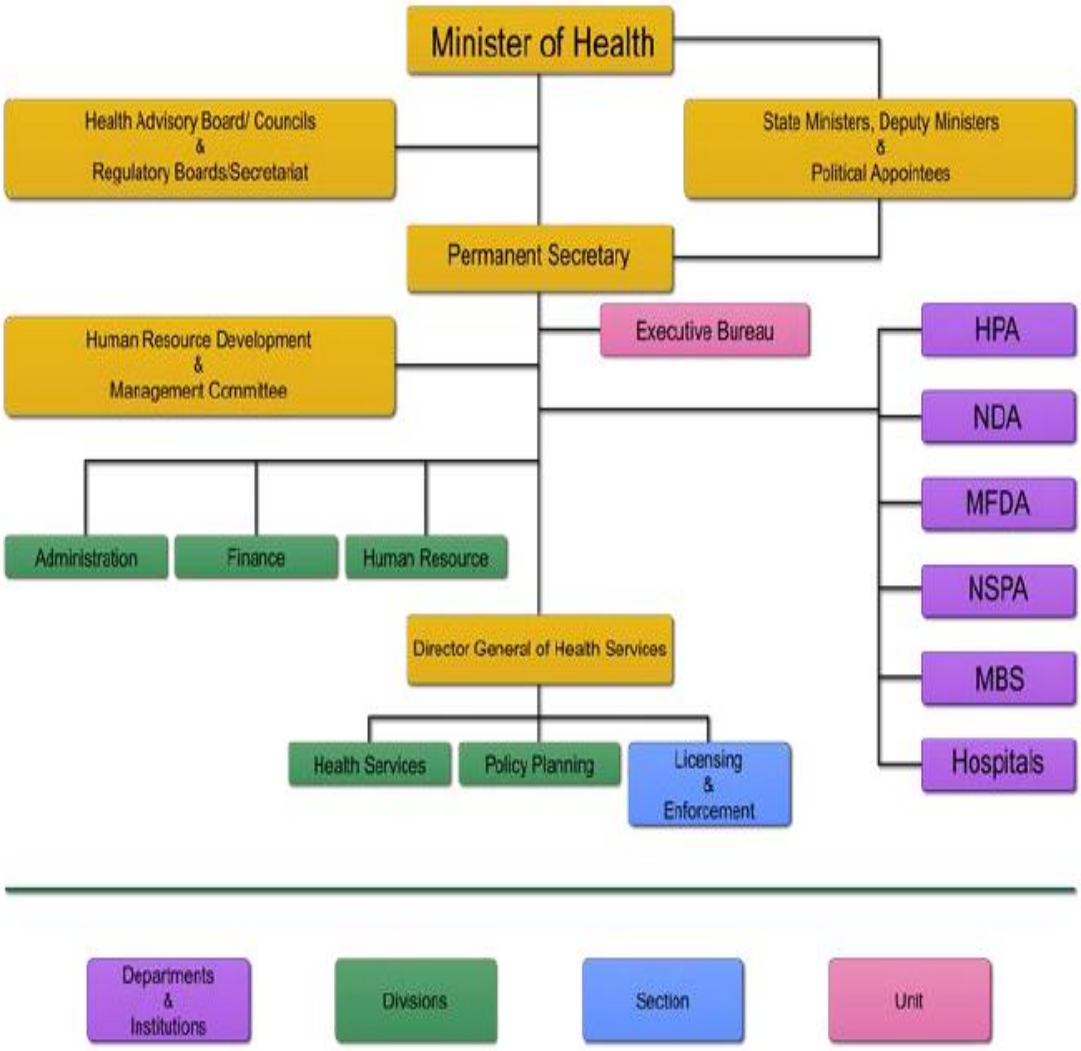
Home Visits:

- Health care provider should wearing an N95 respirator
- Keeping home visits and whenever possible, conduct these outside or in a well ventilated room with as much distance as possible from the patient
- Educating the patient on cough hygiene and avoiding close contact
- Providing the patient with a surgical mask

Patient Transport

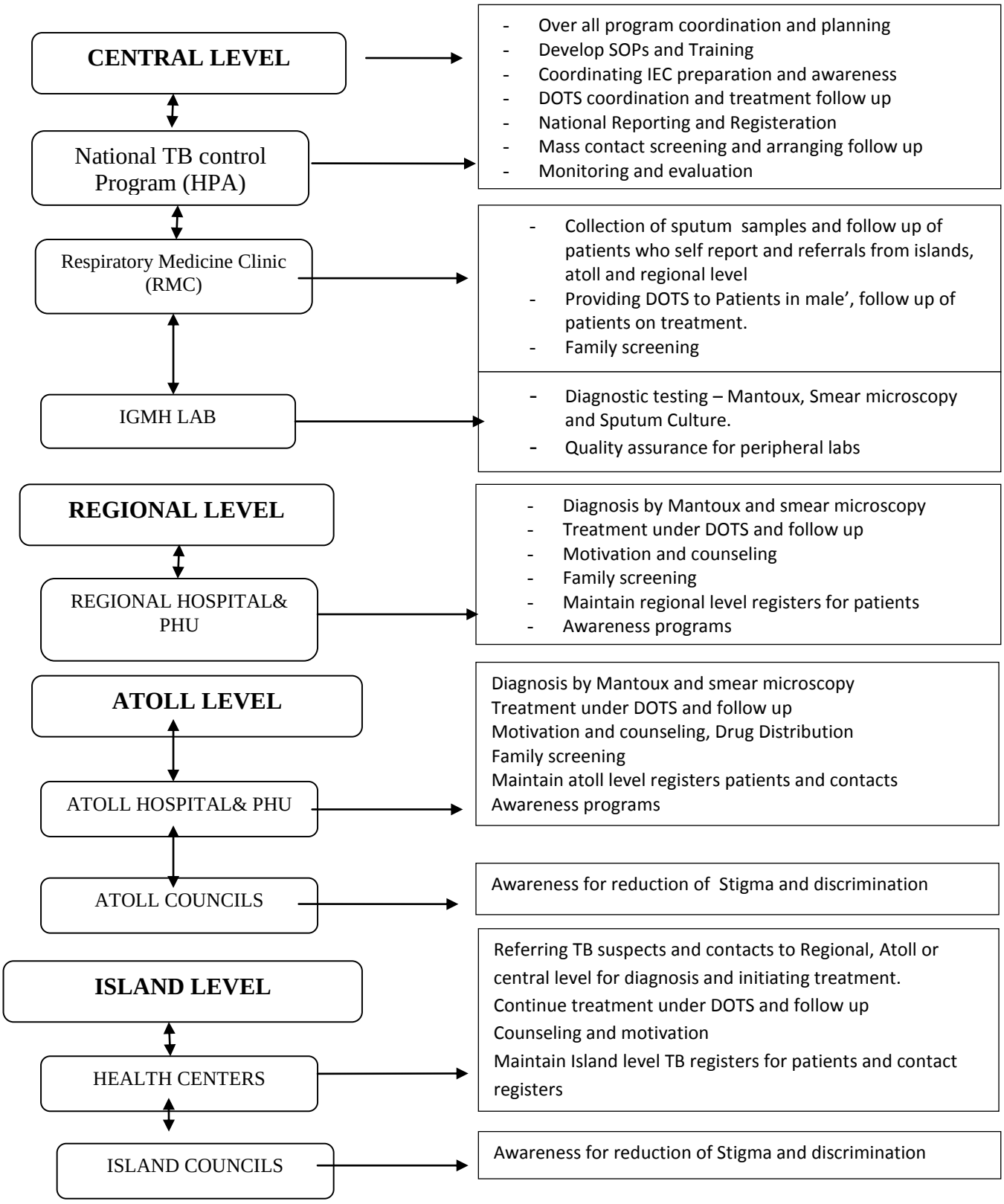
- Use compartmentalised vehicles separating the airspace of the driver from that of the passengers
- Open windows
- Provide surgical mask for patient
- Provide N95 masks for medical staff and driver
- Educate patient

Annexe1
Organizational chart of Ministry of Health



Annexe 2

Organizational Chart of Health service delivery for TB control



Annexe3

Baseline data at MDRTB treatment initiation

DOMAIN	DATA ELEMENT	REMARKS
Location	Geographic area	Island, city in which the patient is started on treatment
	Facility name	
Identification and demographic	Patient ID number	
	Patient name	
	Date of birth	If full date un known ,then year of birth or age
	Origin	Country of birth/citizenship
	Civil status	Married, single, widow/er, divorced
	Employment	Employed, retired, student, unemployed
	Imprisonment	If yes, to identify if current/previous and duration of imprisonment
Baseline clinical assessment	date of registration	
	Date of diagnosis	when the patient was first diagnosed with the current episode of RR-/MDR-TB; usually based on clinical manifestations, or radiology plus bacteriology and DST
	Site of disease	Pulmonary, extra pulmonary (exact site)
	Previous TB	Yes, no, unknown If Yes, date of diagnosis , number of treatments, drug regimen, duration and DST pattern
	Previous TB treatment outcome	If previously treated the outcome of the latest episode (cured, completed, failed, lost to follow up, unknown
	Other medical history	at least HIV/AIDS, diabetes, malnutrition, renal & hepatic insufficiency, cirrhosis, arrhythmias, COPD, convulsions, psychiatric conditions, drug & alcohol use, smoking
	History of allergy or ADRs	Indicate the medicine and classify the type of reaction
	Currently pregnant	Yes, no, uncertain (LMP may be recorded)
	Breastfeeding infant	Yes, no
	Contacts	Line list, for each close contact at home and elsewhere, the: relationship, age, history of TB and TB treatment, current clinical manifestations of TB and results for any testing done
	Patient symptoms	Fever, weight loss, cough, haemoptysis, dyspnoea, others (specify)
	Patient height	
	Patient weight	
	Abnormalities noted at examination	
	Functional status	Not ambulatory; ambulatory; able to work

.

Baseline bacteriology & drug susceptibility testing (DST	Date sample collected	
	Date result issued	
	Microscopy	
	Culture	
	DST	
	Xpert MTB/RIF test Use	
Results of other baseline investigations	Date sample collected	
	HIV test	Positive, negative, indeterminate
	Glucose	
	Electrolytes	Levels of potassium, magnesium, calcium
	Renal function	Urea, creatinine, creatinine clearance
	Liver function	ALT (SGPT), AST (SGOT), bilirubin, albumin
	Blood indices	Haemoglobin, haematocrit, leukocytes, platelets
	Electrocardiogram	
	Chest radiography	Cavitary; extent of parenchymal disease; uni- or bilateral (useful in grading extent and severity of disease)
	Other	Specify (e.g., thyroid stimulating hormone
Treatment Given	Date treatment start	
	Date treatment stop	
	Anti-TB medicine	For each medicine give: name, dosage, frequency, route
	Other medicines and traditional medicines	For each medicine given in the past 30 days name, indication, dosage, frequency, route, and if it is currently being used

Annexe 4
DOTS Providers Procedures

Patients presenting to the health facility

1. **TB patients on treatment for DOTS and follow up (including referred patients from the central level or any other health facility)**
2. **TB suspects referred to the health facility**
3. **Close Contacts of TB patients for counseling and screening**

1. TB patients on treatment for DOTS/ follow up (Including Referred patients from central and any other health facility)

a. DOTS should be started ONLY after consulting with doctor in charge.
b. All patients on treatment should receive DOTS.
c. Counseling shall be provided by the DOT provider to the patients
d. Once the patient presents to the health facility, the DOTS provider should check the patient card, give the medicine and tick mark the card that the dose has been given.
e. The DOTS provider should inquire during the visit for any medication side effects and if noted should be seen by the doctor
f. Patient weight should be monitored each month and documented on the treatment card by the DOT provider
g. The DOTS provider should report to the doctor, the persistence or reappearance of symptoms of TB (including weight loss) or if there are treatment interruptions
h. The DOTS provider should ensure that the patient reports to the clinic for sputum smears at end of intensive phase (sputum should be collected after giving the last dose of intensive phase), end of 5th month and end of treatment. DOTS Provider must call and trace the patients if they fail to report on the specified days.
i. Sputum smear and culture results should be documented on the TB Treatment Card by the DOTS provider.

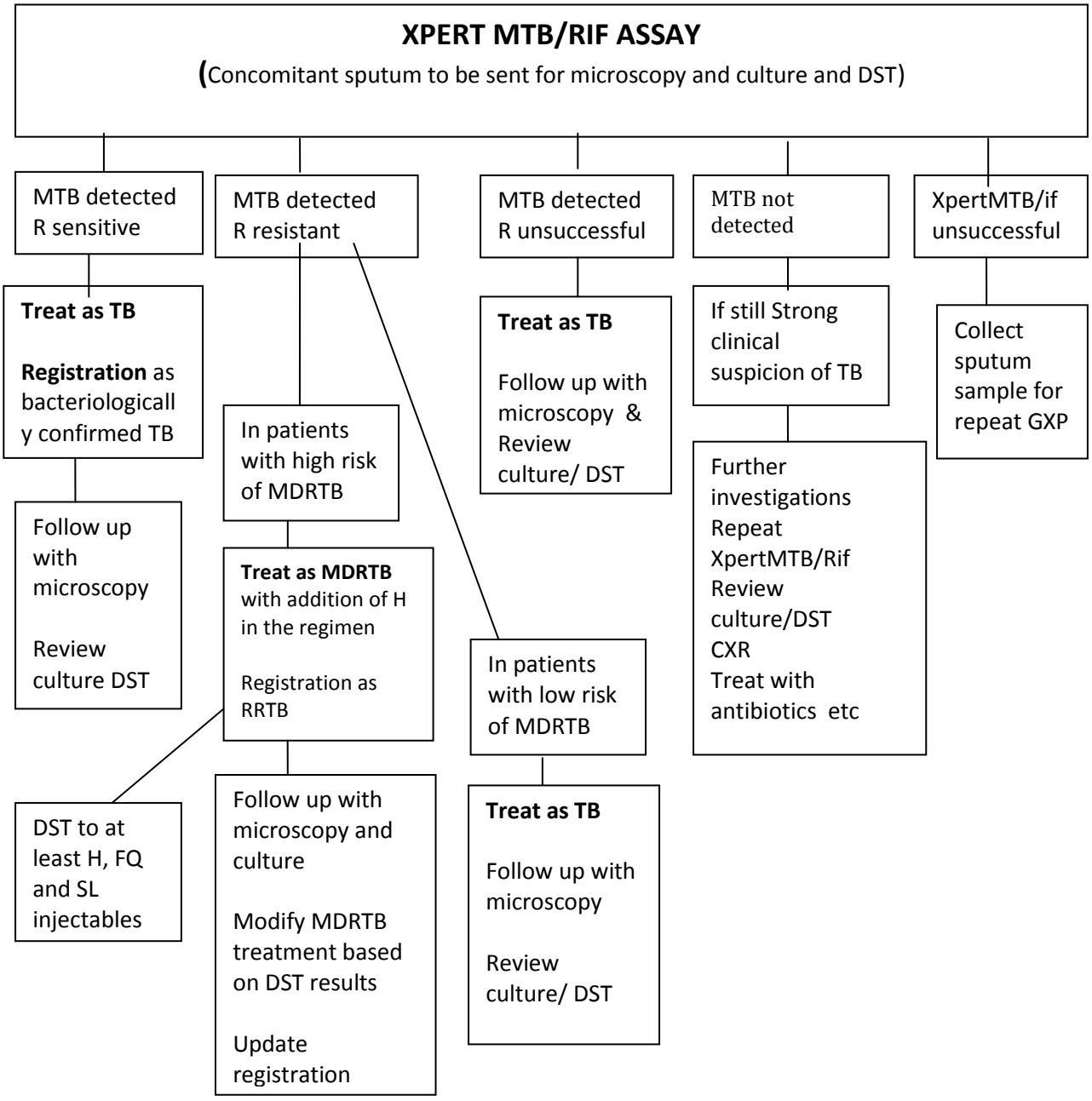
2. TB suspects

a. Once the patient presents at the clinic, the DOT provider provider should check if mantoux, sputum smears and chest X-ray has been done and if not done, send sputum smears and guide the patient to get a CXR done
b. The DOT provider should Schedule an appointment for the doctor's consultation day as soon as all investigations are completed
c. Treatment should be started ONLY after consultation with the physician / MO in charge
d. Any new patient getting registered should be notified to the national program by the DOT provider

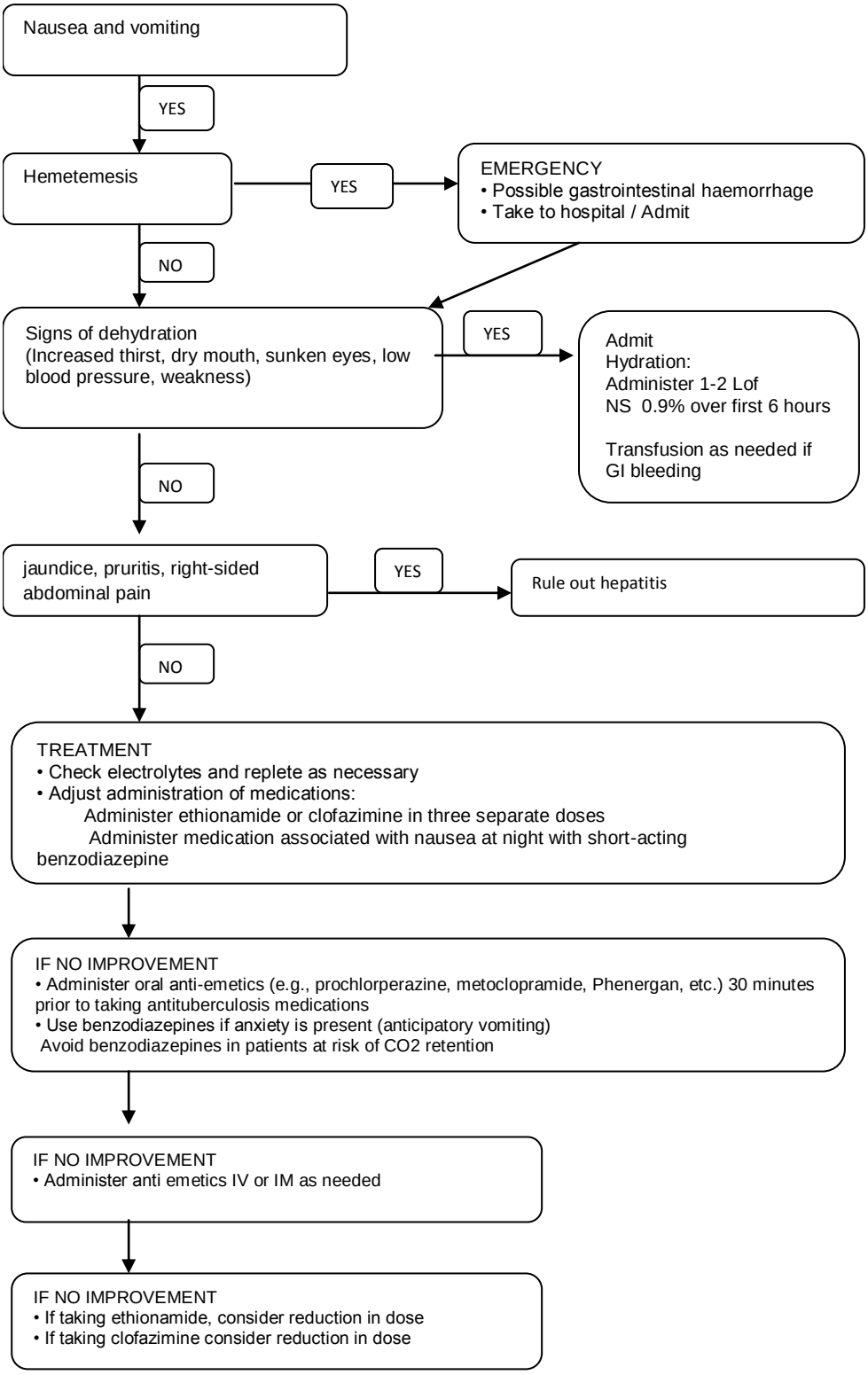
3. Close Contacts of TB patients for counseling and screening

a. All pulmonary TB patients, especially those who are sputum positive should be counseled to get their close contacts to the clinic for screening
b. A contact list should be made for each sputum positive patient.
c. For all contacts with Mantoux test positive, the DOTS provider should send sputum smears and get a Chest X-ray done, then Schedule an appointment for the doctor's consultation. If the sputum is positive, same-day appointment must be made with the available physician or MO in-charge.
d. For contacts with Mantoux test negative, the DOTS provider should reassure them before sending home, and make arrangements for follow-up if required.
e. Note outcomes and plan in TB contact register.

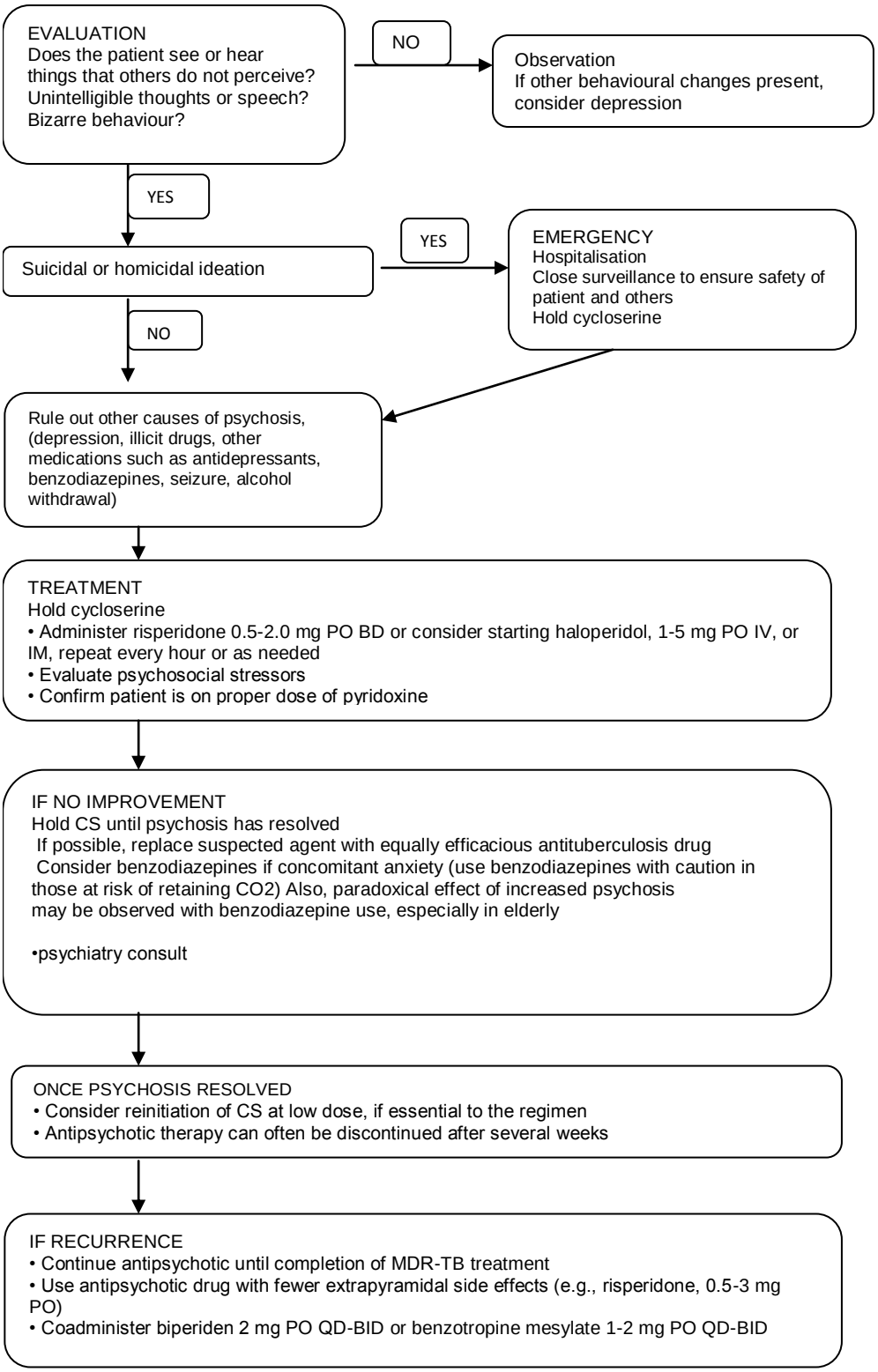
Annexe 5. Algorithm using XpertMTB/Rif for diagnosis of TB and Rifampicin resistance



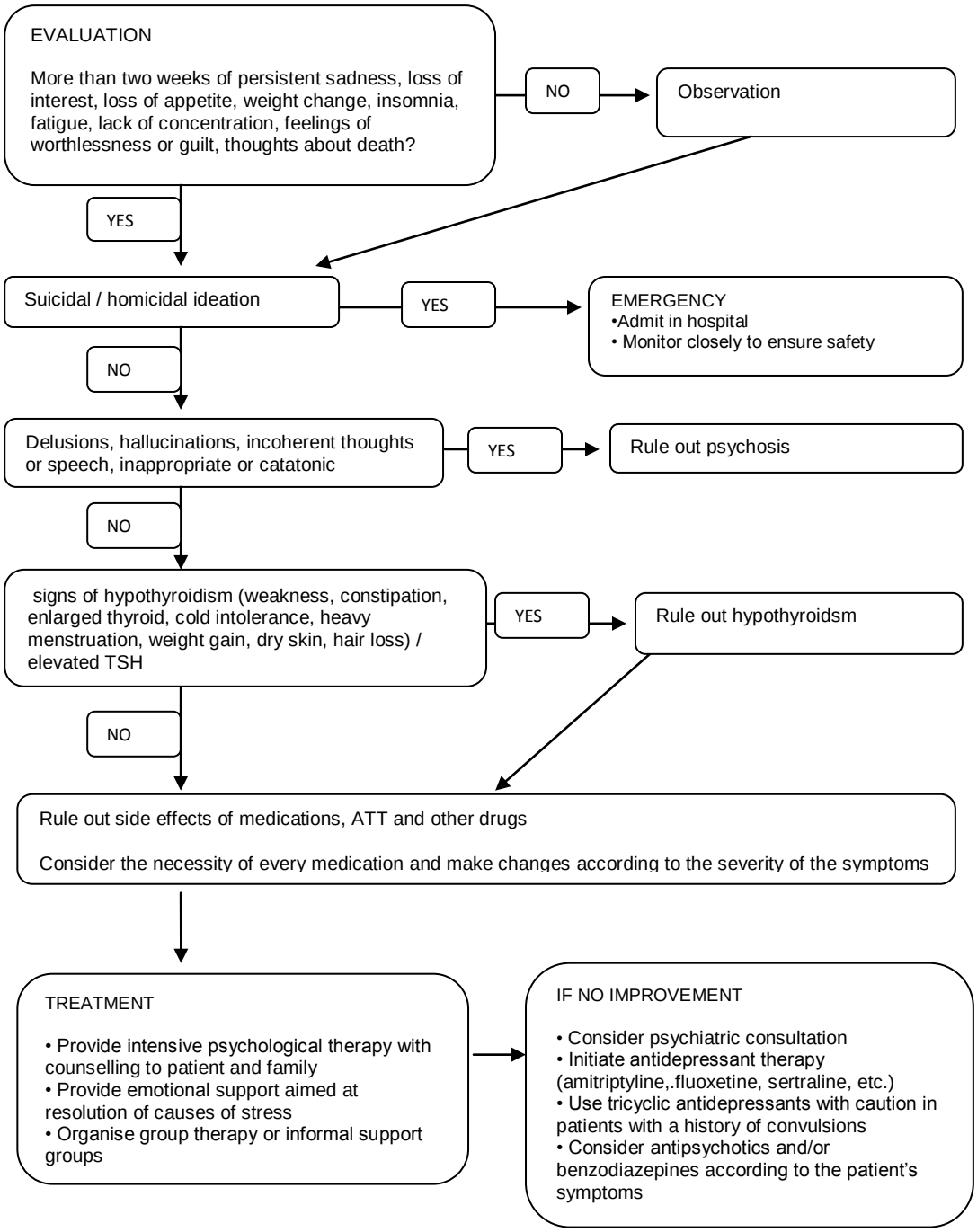
Annexe6. Algorithm for management of nausea and vomiting



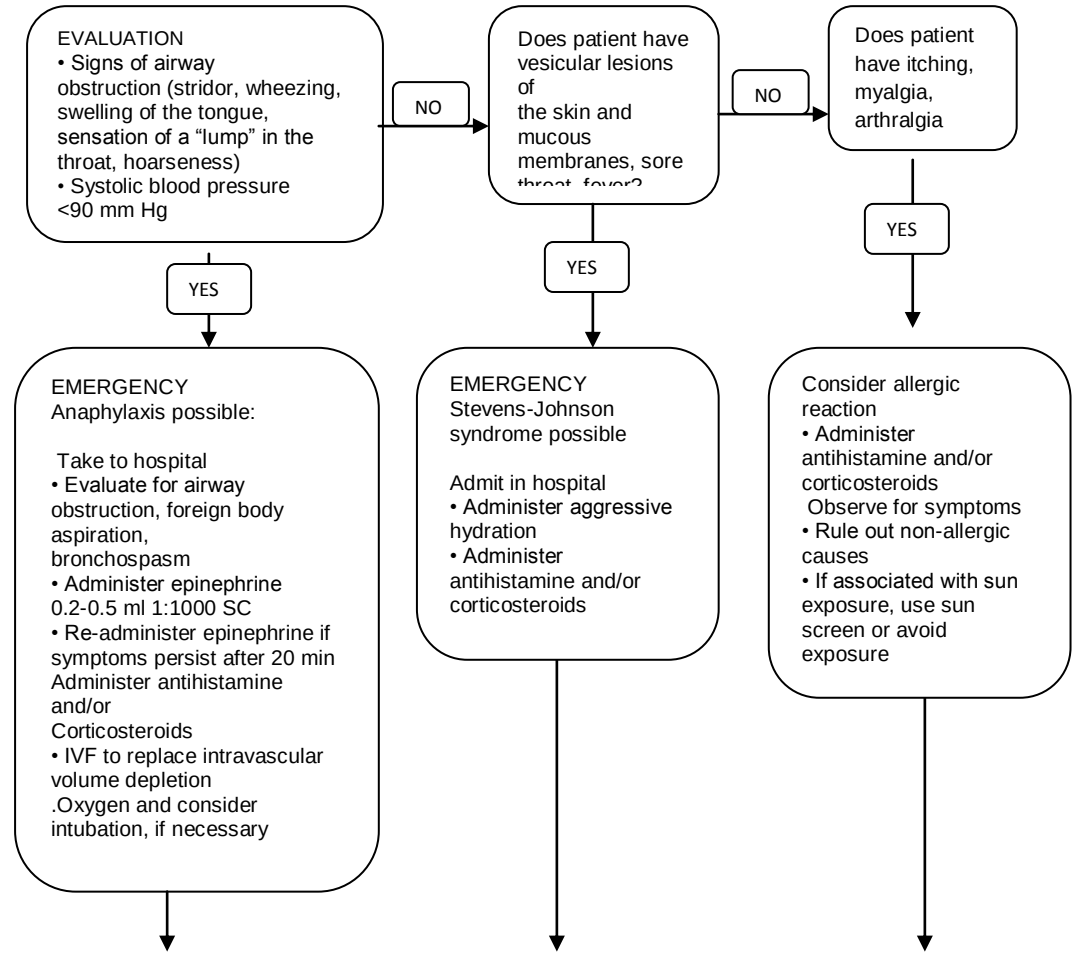
Annexxe7. Management algorithm for psychosis



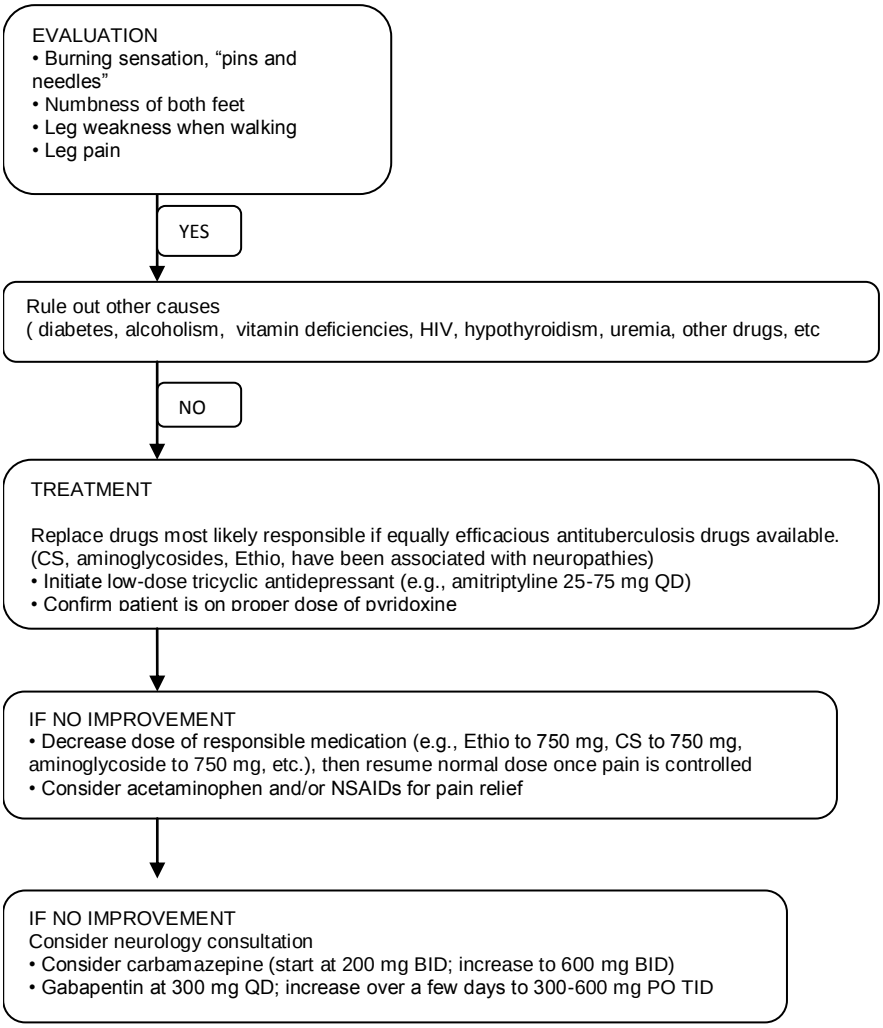
Annexe8. Management algorithm for depression



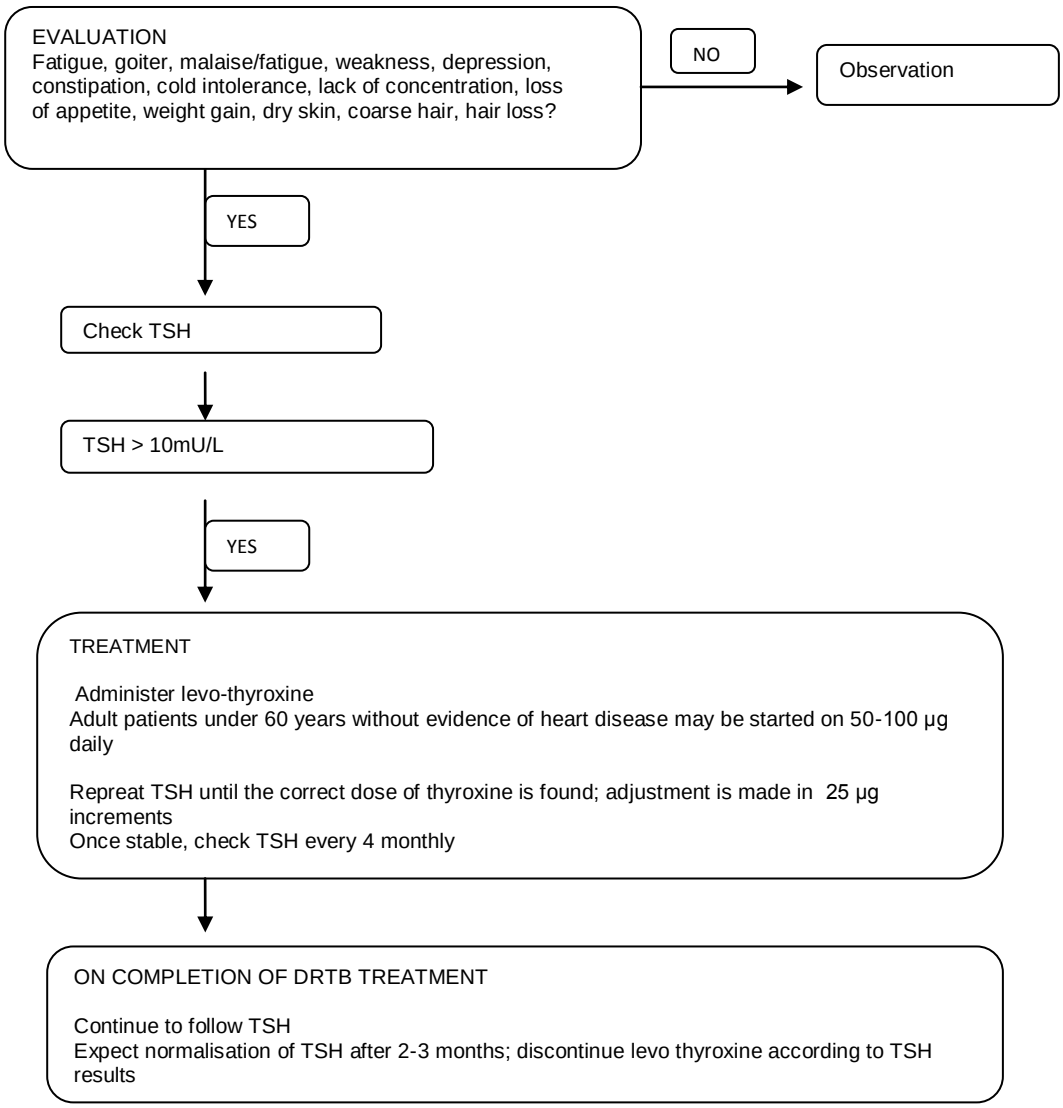
Annexe9. Management algorithm for anaphylaxis and allergic reactions



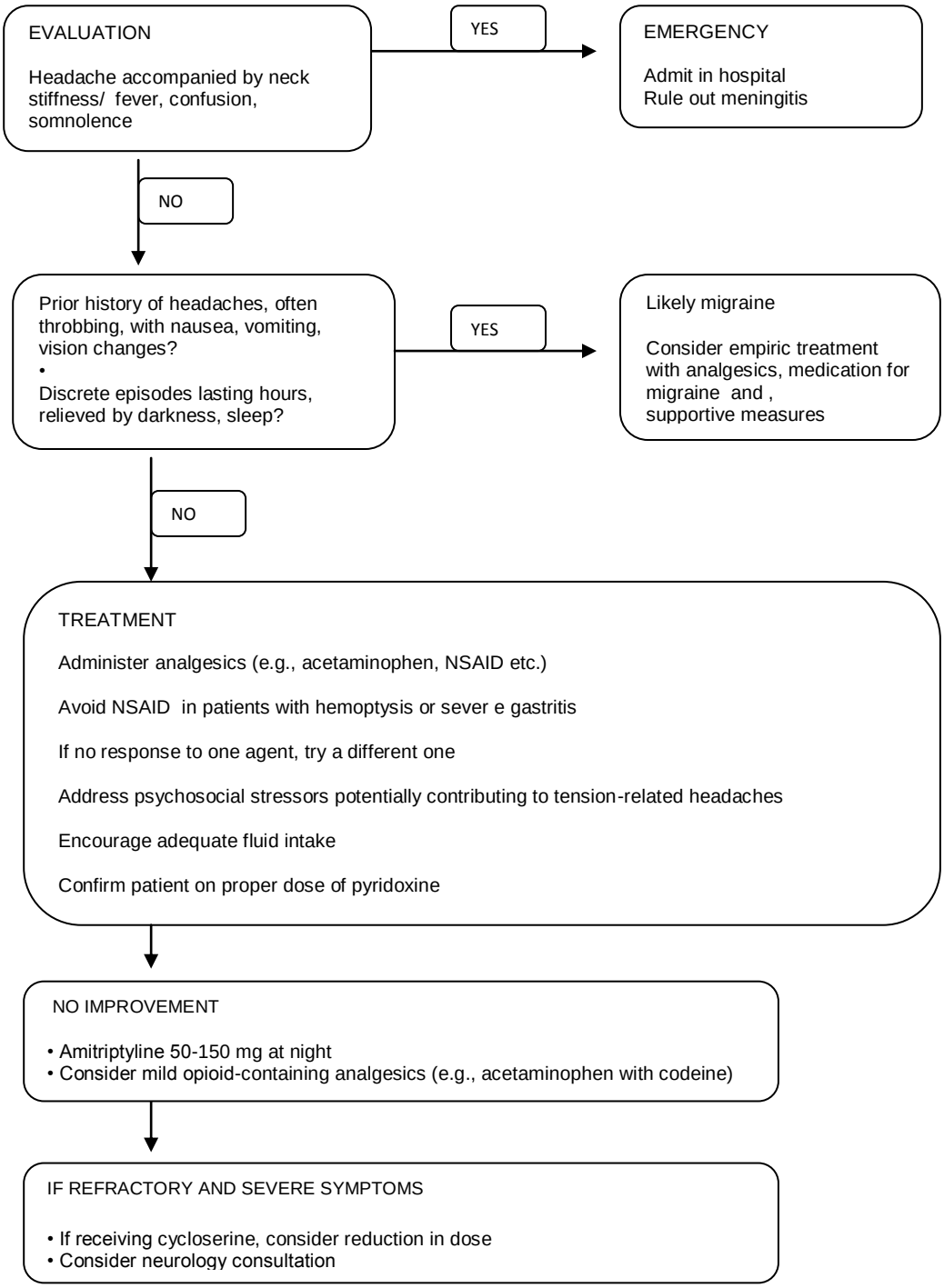
Annexe10. Management algorithm for peripheral neuropathy



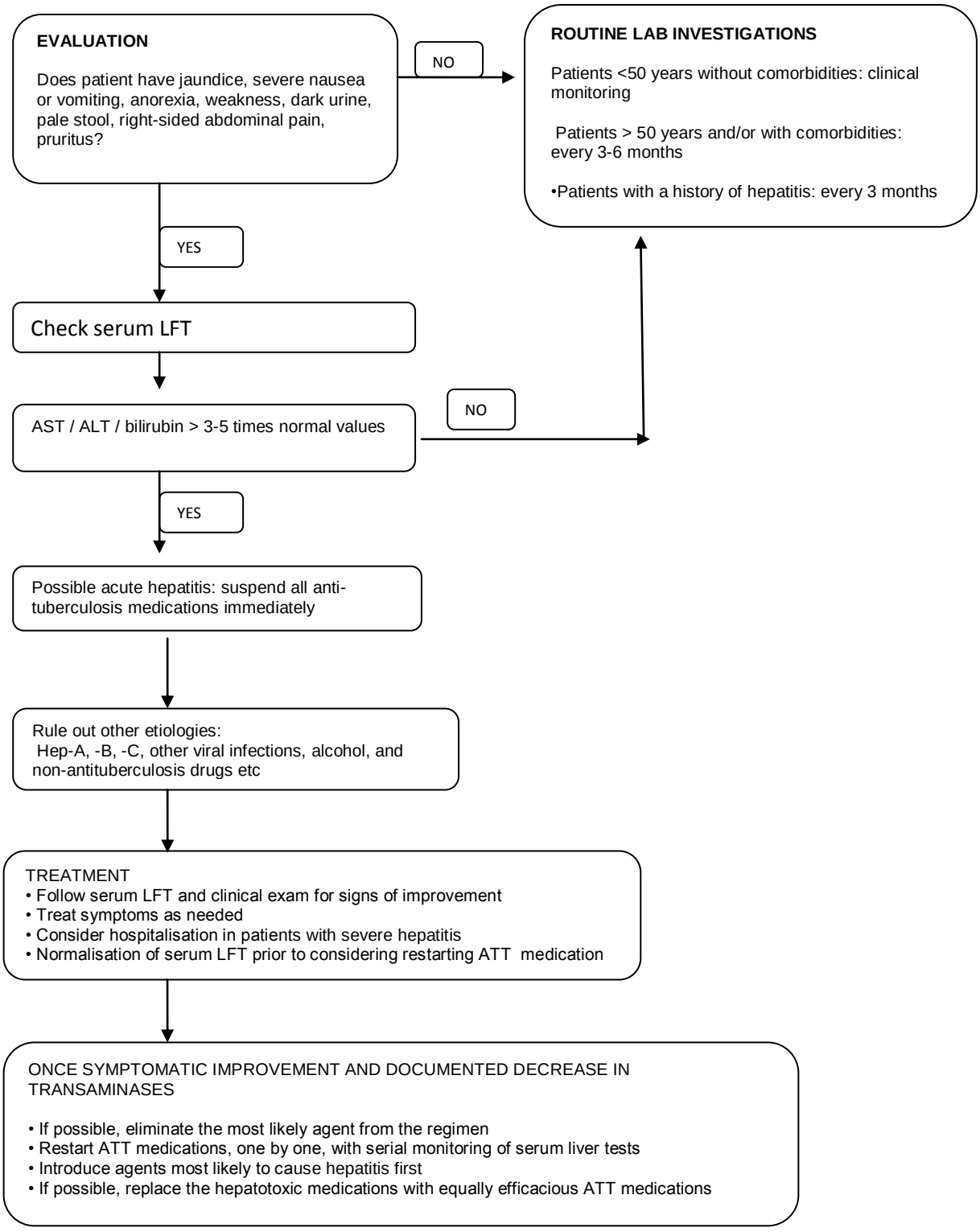
Annexe11. Management algorithm for hypothyroidism



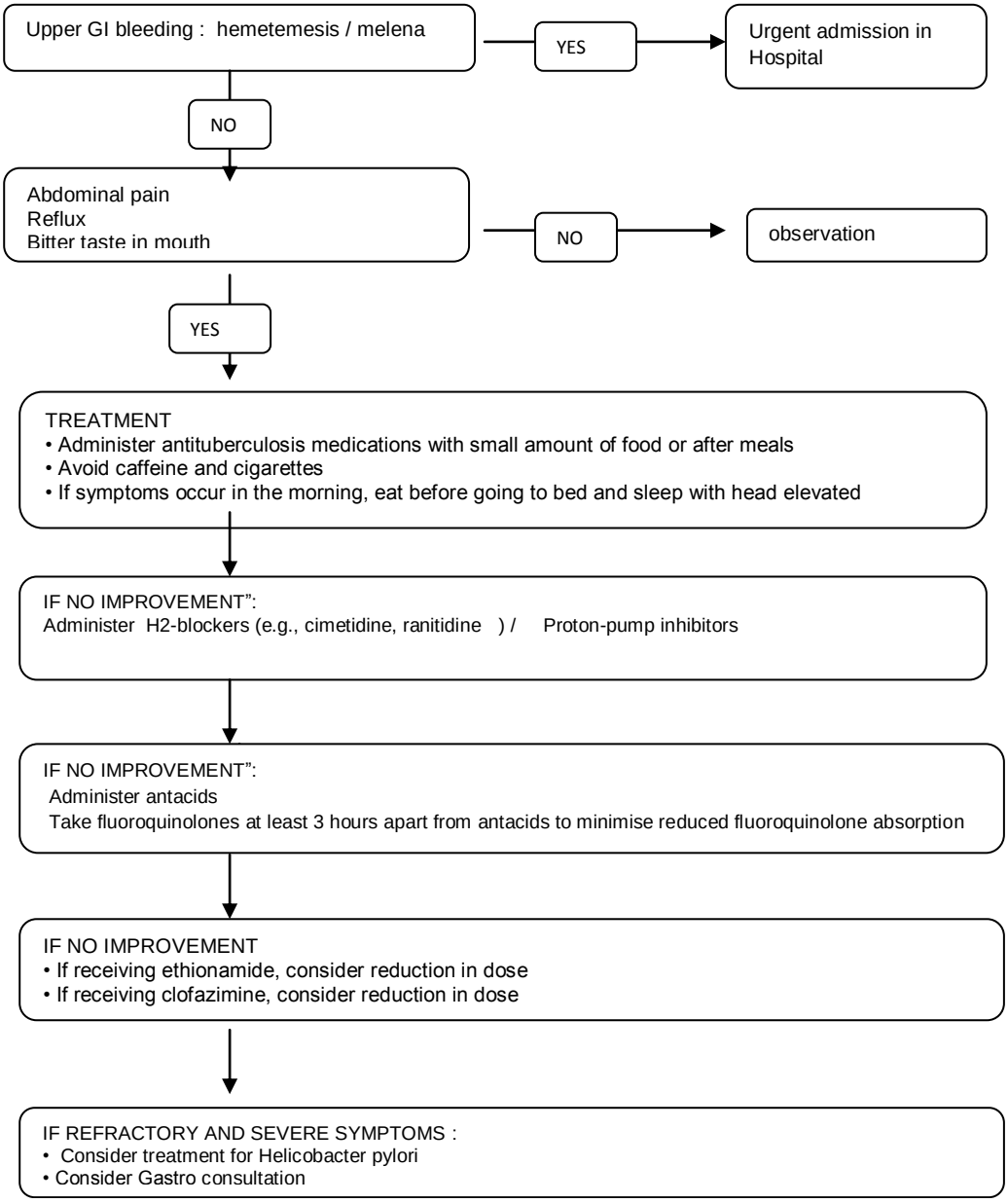
Annexe12. Management algorithm for headache



Annexe13. Management algorithm for hepatitis



Annexe14. Management algorithm for gastritis



Annexe 15

بسم الله الرحمن الرحيم

Health Protection Agency

Republic Of Maldives

Phone: 3014494 Fax: 3014484 email: ntp.maldives@gmail.com

TB MONTHLY REPORTING FORM

Name of the Facility:……

Reporting Period:……/……/…… to ……/……/……

TB BUFFER STOCK

DRUGS/COMMODITY	STOCK RECEIVED		DURING MONTH		BALANCE
	DATE RECEIVED	EXPIRY DATE	AMOUNT USED	EXPIRY DATE	
TB KITS					
MANTOUX					

TB PATIENTS CURRENTLY ONTREATMENT

TBPATIENT No	NAME	ADDRESS	ISLAND	TREATMENT STARTED	
				DATE	FACILITY

TB PATIENTS WHO DEFAULTED

TB PATIENT NO	NAME	ADDRESS AND ISLAND	DEFAULT DATE	REASON

Report prepared by: Designation:

Date: Signature:

INSTRUCTIONS

This entire form is to be completed by the Atoll hospital with relevent information collected from the islands in the Atoll·

- TB Buffer Stock is kept in every Atoll hospital for easy access to the drugs if any patient is been diagnosed within the Atolls·
- All TB patients currently on treatment in the Atoll (including island level) should be listed in this form·
- If Any deafults are recorded in any island of the Atoll, it should be mentioned in this form with the relevent reason for the deafult·

  (For monitoring purposes in this form,**treatment outcome="default" if a patient has not taken anti-TB drugs for 3 or more consecutive days after starting treatment, or has missed receiving treatment intermittently more than 3 times for a period of 2 weeks)**

  If a patient has defaulted as in the above definitions, every effort must be taken to trace the person and continue regular treatment· If patient cannot be traced within 1 week of the date of defaulting, **please report this patient to NTP immediately** by phone and fax or email without waiting to send as monthly report·

Anexxe16

Health Protection Agency
Republic Of Maldives
Phone: 3014494 Fax:3014484 email: ntp.maldives@gmail.com
TB Case Notification Form

This form is to be used to report newly infected TB case to Health Protection Agency

1. Name of the Facility

Name of Facility: _____ Date of Submission: _____/_____/_____
DD ***MM*** ***YYYY***

Email/Telephone Number: _____

2. Case Details

Case Classification: Suspect ☐ Probable ☐ Confirmed ☐

Full Name: _____ Permanent Address: _____
Current Address: _____ Contact No : _____
Sex: Male ☐ Female ☐ Age (Years): ____ Type of TB: Pulmona ☐ Extra Pulmonar ☐
Site : _____
Date of Consultation: _____
Occupation: _____

4. Classification of current diagnosis (Please tick)

New ☐ Relapse ☐ Re-treatment ☐ Failure ☐

5.Treatment Category

Cat I ☐ Cat II ☐ 2nd line Drugs

6. Details of Drugs (as prescribed)

7. Investigation Report

Sputum result

	Date	Result
1st Sample		
2nd Sample		
3rd Sample		

X-Ray result

Date	Findings (+/-)

Instructions

Reporter Details
Name: **Designation:** **Signature:**

- All the Health facilities should fill the first three parts of the form. This includes
  1. Name of the facility
  2. Case details
  3. Patient information
- If the case is a confirmed case the health facility should fill the entire form.
  Including the:
  4. Classification of current diagnosis
  5. Treatment Category
  6. Details of category drugs
     - Name of the drugs, dosage ,route and the duration of the treatment should be specified.
  7. Investigation Report
     - Sputum result should be written for all three samples with the date
     - If X-ray done specify the date and in the findings column write if positive(+) or Negative.
     - '***Positive***' means the X-ray has features that are compatible with pulmonary TB
     - '***Negative***' means that the X-ray has no features that are suggestive or compatible with pulmonary TB.

Annexxe 17
Sputum collection and reporting form

SPUTUM EXAMINATION RESULT FOR AFB

Name of requesting Health Centre:_____ Date: _____

Name of patient: _____ Age: _____ Sex: ☐M ☐ F

Permanent address: _____

_____

Type of TB: ☐ Pulmonary

☐ Extra-pulmonary Site: _____

Reason for examination ☐ Diagnosis

☐ Follow-up

For follow-up smears: Patient's register number _____

Laboratory Serial Number: _____

Visual appearance of sputum:	Mucopurulent	Blood-stained	Saliva
Specimen 1	☐	☐	☐
Specimen 2	☐	☐	☐
Specimen 3	☐	☐	☐

Microscopy Result (staining method: Ziehl-Neelsen)

Date	Specimen	Result*	Positive (grading)			
			3+	2+	1+	AFB#(1-9)
	A					
	B					
	C					

* Write "neg" (negative) or "pos" (positive)
# 1-9 AFB grading column: write the exact numbers per 100 hpf

Date: _____ Signature _____

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