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CLINICAL PRACTICE GUIDELINES

MANAGEMENT OF DRUG RESISTANT TUBERCULOSIS (1st EDITION)

Ministry of Health Malaysia

Academy of Medicine of Malaysia

Bahagian Kawalan Penyakit
Kementerian Kesihatan Malaysia

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STATEMENT OF INTENT

These clinical practice guidelines (CPG) are meant to be guides for clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not necessarily guarantee the best outcome in every case. Every healthcare provider use his/her own clinical judgment of unique patient based on the clinical picture presented by the patient and the management options available locally.

UPDATE

These guidelines were issued in 2016 and will be reviewed in 2020 or sooner if new evidence becomes available. When it is due for updating, the Chairman of the CPG or National Advisor of the related specialty will be informed about it. A discussion will be done on the need for a revision including the scope of the revised CPG. A multidisciplinary team will be formed and the latest systematic review methodology used by MaHTAS will be employed.

Every care is taken to ensure that this publication is correct in every detail at the time of publication. However, in the event of errors or omissions, corrections will be published in the web version of this document, which is the definitive version at all times. This version can be found on the websites mentioned above.

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GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for this Clinical Practice Guidelines (CPG) were from the Ministry of Health (MOH) and Ministry of Education. There was active involvement of a multidisciplinary Review Committee (RC) during the process of the CPG development.

A total of 14 clinical questions of the CPG were developed under different sections. Members of the DG were assigned individual questions within these sections (refer to Appendix 1 for Clinical Questions). The CPG was adapted from World Health Organization (WHO) Guidelines only as it is mostly well-accepted guidelines, namely:

Guidelines for the programmatic management of drug-resistant tuberculosis, emergency update 2008
Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update
Definitions and reporting framework for tuberculosis, - 2013 revision
Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis (2014)
WHO treatment guidelines for drug-resistant tuberculosis- 2016 update

The adaptation process followed the Manual on Adaptation of Evidence Based Clinical Practice Guidelines of the Ministry of Health, Malaysia (which was adapted from ADAPTE Resource Toolkit for Guideline Adaptation). Assessment of the WHO Guidelines showed that the quality [using Appraisal of Guidelines for Research and Evaluation (AGREE) II tool], currency, content, consistency and applicability of the documents justified them to be adapted for local use.

The CPG DG had decided that no literature search was required in the adaptation process because the evidence use is sufficient enough for management of DR-TB cases in the country. All statements and recommendations were modified and formulated (when necessary) with local practices taken into consideration. They were agreed upon by both the DG and RC.

On completion, the draft CPG was sent for review by WHO (author of the CPGs that being adapted) and external reviewers. It was also posted on the MOH Malaysia official website for feedback from any interested parties. The draft was finally presented to the Technical Advisory Committee for CPG, and the HTA and CPG Council MOH Malaysia for final review and approval.

OBJECTIVES

To provide evidence-based recommendations on the effectiveness and safe management of patients with drug-resistant tuberculosis

CLINICAL QUESTIONS

Refer to Appendix 1

TARGET POPULATION

All patients with drug-resistant tuberculosis

TARGET GROUP/USER

This document is intended to guide healthcare professionals and relevant stakeholders in the management of drug-resistant tuberculosis including:

- Doctors
- Pharmacists
- Allied health professionals
- Trainees and medical students
- Patients and their advocates

HEALTHCARE SETTINGS

Primary and secondary/tertiary healthcare

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1. INTRODUCTION

In the mid of the twentieth century, tuberculosis (TB) was thought to have been beaten. However, this disease is now back with a vengeance and drug resistant forms are increasing to almost an epidemic proportion in certain parts of the world. The burden of multidrug-resistant tuberculosis (MDR-TB) is increasing both globally and locally. WHO estimated about 480,000 people develop MDR-TB worldwide in 2013[1]. The number of people diagnosed with MDR-TB tripled between 2009 and 2013, and reached 136,000 worldwide. In Malaysia, there were 101 cases of MDR-TB reported in 2015 (refer to Fig. 1)[2]. The globalisation of the recent century has made the spread of diseases more rapid with massive migrations.

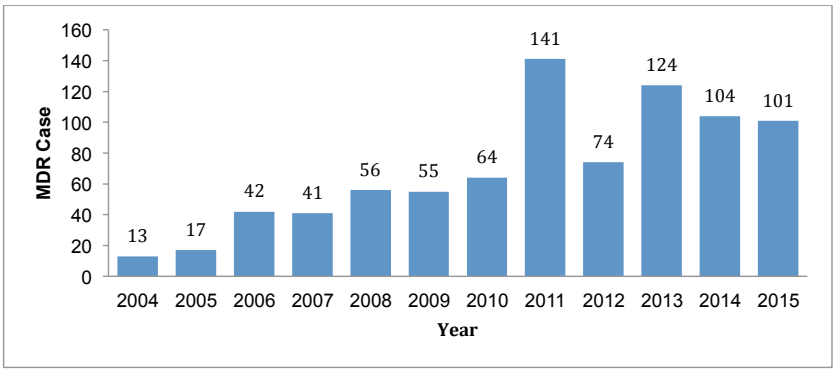


Fig. 1: Cases of MDR-TB, Malaysia (2004-2015)

Though MDR-TB has multifactorial causes, the main reason for the emergence of this scourge is improper treatment. This may be caused by non-compliance, poor treatment regimes, poor quality of drugs or concomitant medical diseases. Besides the toll on the health of individuals suffering from MDR-TB, the cost is also devastating economically. Estimated direct cost of the drug to treat one MDR-TB patient is RM 15,000.00 compared to RM250.00 for treatment of one drug susceptible TB patient. Currently, it is not just MDR-TB but extensively drug-resistant TB (XDR-TB) has emerged to further complicate the management of drug-resistant TB.

We are currently in urgent need to have guidelines locally to help guide and standardise management of DR-TB which include diagnosis, treatment, prevention and surveillance among healthcare providers in Malaysia. It was decided to adapt the World Health Organization (WHO) guidelines on the Programmatic Management of DR-TB which involves documents published in 2008, 2011, 2013, 2014 and the latest 2016 update in the development of the guidelines. The 2016 update introduces the concept of shorter MDR-TB treatment regime between 9-12 months for newly diagnosed patients. Besides improving compliance, it would also significantly reduce the cost of treating MDR-TB (refer appendix 2). These guidelines, the first in the country for the management of DR-TB, definitely are helpful to the healthcare providers in managing the medical condition more effectively and successfully.

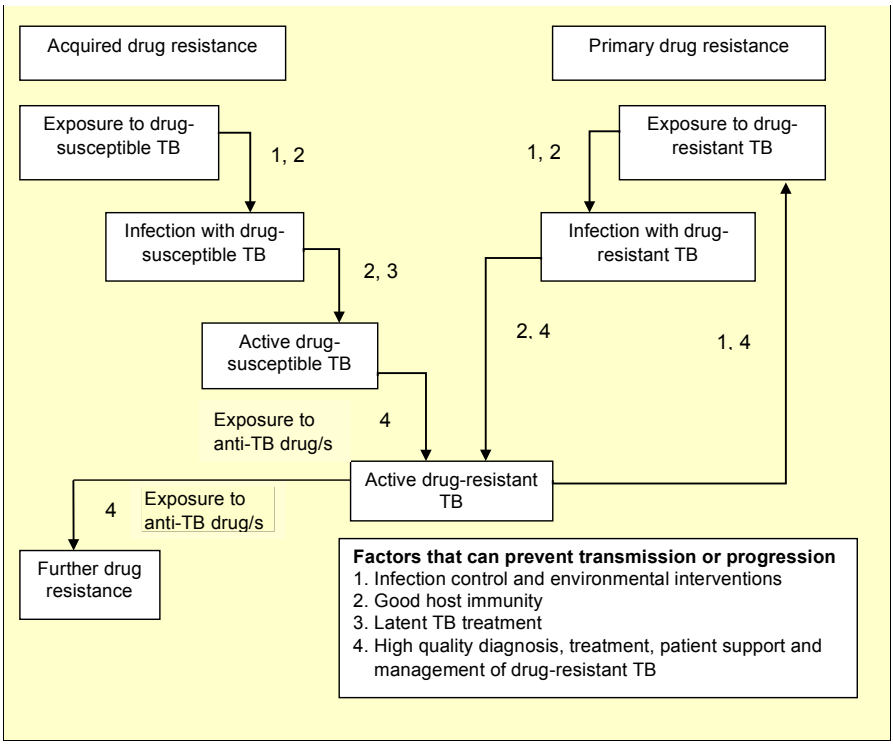
2. PREVENTION OF DRUG-RESISTANT TB

The best way to treat MDR-TB is to prevent it from happening in the first place. Doctors need to be familiar with causes of DR-TB and the two different pathways leading to formation of DR-TB, only then we can come up with interventions to interrupt this causation.

2.1 Causes of drug-resistant TB

2.1.1 Two pathways leading to drug-resistant TB

Drug-resistant TB has two developmental pathways that are interconnected with multiple factors (refer to Fig. 2).



Note: Pathways to development of drug-resistant TB. Arrows represent progression along the two pathways. Numbers represent factors that can contribute to the prevention of progression.

Fig. 2: Two pathways leading to drug-resistant TB

a. Acquired Drug Resistance

This pathway can be caused by inadequacies from all three components, the healthcare providers giving inappropriate treatment, inadequate or poor quality of drugs and the commonest cause, inadequate drug intake by patients (refer to Table 1).

Table 1: Factors contributing to poor TB treatment outcomes

Healthcare providers: inappropriate treatment	Drugs: inadequate supply/quality	Patients: inadequate drug intake or treatment response
• Inappropriate guidelines • Non-compliance with guidelines • Absence of guidelines • Poor training • Financial disincentives • Poor patient education • No monitoring of treatment • Poor management of adverse drug reactions • Poor treatment support • Poorly organised or funded TB control programmes	• Poor quality medicines • Unavailability of certain medicines (stock-outs or delivery disruptions) • Poor storage conditions • Wrong dose or combination • Poor regulation of medicines	• Lack of information • Lack of means to adhere to treatment (transportation, food, etc.) • Adverse effects • Social barriers • Human Immunodeficiency virus (HIV) • Diabetes mellitus • Undernutrition • Malabsorption • Substance abuse/dependency • Psychiatric condition

b. Primary drug resistance.

This pathway of resistance is caused by a person being directly infected with a drug-resistant TB strain.

2.2 Interventions to prevent drug-resistant TB

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

Five principal ways to prevent drug-resistant TB:

i. Early detection and high quality treatment of drug-susceptible TB
ii. Early detection and high quality treatment of drug-resistant TB
iii. Effective implementation of infection control measures.
iv. Strengthening and regulation of health systems.
v. Addressing underlying risk factors and social determinants.

3. FRAMEWORK FOR EFFECTIVE CONTROL OF DR-TB

The Tuberculosis Control Programme consists of five essential components of a framework that embodied the whole management aspect of TB. It is tailored according to local situation and integrated into Direct Observe Treatment Short-course (DOTS) based National Tuberculosis Programme (NTP).

3.1 DOTS framework as applied to the management of DR-TB

The DOTS strategy is applicable to the whole TB control including DR-TB, as the principles are the same.

3.1.1 Sustained political commitment

Political commitment is important in fostering national and international partnerships which should be linked to long-term strategic action plans prepared by NTPs. Long term investment and leadership run parallel in order to ensure an appropriate integration of DR-TB management into NTP. Appropriate integration refers to:

- securing adequate infrastructure,
- development and retention of human resources,
- interagency cooperation,
- enactment of necessary legislation,
- TB control policies enabling implementation of the programme
- facilitation of the procurement of quality-assured second-line drugs and equipment for diagnostic purposes

Effective TB control strategy and implementation can only takes place with a clear and sustained political commitment.

3.1.2 Rational case-finding strategy; accentuating on the importance of timely diagnosis through quality-assured culture, molecular testings and Drug Susceptibility Test (DST)

TB control largely depends on timely and correct diagnosis. Quality assurance and proficiency testing with a recognised reference laboratory such as one of the WHO-recognized National Reference Laboratory must be in place. Ideally, one culture/ DST centre is in place for every five million populations (1: 5,000,000). Unreliable laboratory results due to non-viable cultures, contamination, clerical or administrative error will give impact to NTP.

Recommendation 1

- All tuberculosis patients should have universal access to diagnostic test specifically Culture and Drug Susceptibility Test.

3.1.3 Case management (case holding) by appropriate treatment strategies with second-line drugs

An excellent DR-TB treatment centre delivers an optimal treatment regimen, in a patient-centered approach concept which includes DOT and monitoring of drug adverse reactions. To have this in place requires dedicated and committed expertise to consider several factors:

- Implementation of an appropriate substantial infection control
- A well-defined drug resistance surveillance (DRS) data
- Proper patient's documentation including TB drug history
- Structured procurement of second-line drug and flow of drug monitoring to end user
- Availability of DST to first- and selected second-line drugs
- Reliable options for delivering DOT consistently
- Addressing patients co-infected with HIV and diabetes

Standardized regimen for specific group of patients should be decided by DR-TB experts. MDR-TB patients may be given options between hospitalization and ambulatory treatment. However, health personnel need to look into several factors best suiting the severity of the disease, social aspect of the patients needs and preferred options of care. Ambulatory would be best if there is existing social support network available to facilitate adherence at the same time trained personnel to supervise DOT and identify adverse drug reactions.

3.1.4 Uninterrupted supply of quality-assured anti-TB drugs

In management of MDR/XDR-TB, treatment regimens are frequently changed due to drug adverse reaction, delayed DST result with poor response to treatment. This creates more complexity in second-line drugs management on top of its existing short shelf-life, limited global production and its high price. In order to ensure uninterrupted supply of second-line drug, the process of procurement must begin at least 6 months or more prior to anticipated need and it must be estimated accordingly to avoid wastage. It is important to ensure quality assured drug is used, recognized by WHO or that meet WHO GMP standards.

3.1.5 Standardised recording and reporting system

A complete recording system need to be specifically structured under the DR-TB control program. This is because it differs by categories and in cooperate a wide array of laboratory results consisting of culture and DST for first-line and second-line drugs. Its case monitoring is lengthy; with treatment delivery and response that can reach 24 months. Its cohort analysis includes interim indicators and the treatment outcome is only reached after two years or more. The registry and recording must follow the latest case definition by the WHO entitled Definitions and Reporting Framework for tuberculosis – 2013 revision with National adaptation is required. A good, specific recording; design for MDR/XDR-TB is essential for evaluating program performance and treatment effectiveness.

3.2 A plan for tailored integration of management of DR-TB into national programme

It is challenging to implement an integrated DR-TB management into the NTP. The integration needs full commitment from top down and bottom up in order to secure a sound, apprehensible and holistic approach covering advocacy, detection, treatment and patient's welfare. It should never be underestimated. It is undeniably that the process of integration is complex however there are many ways to ensure its implementation. It can be facilitated including through public private mix (PPM) approaches.

Assessment is an essential component of the integration process whereby it will facilitate the design and implementation plan to meet the gaps identified, in terms of both infrastructure and functioning of the health-care system. Quality-assured laboratories for diagnosis and monitoring of treatment response, delivery of DOT and use of quality-assured second-line drug should be met under all conditions to ensure proper case management and prevent the emergence of resistance to second-line drugs.

The following (refer to Table 2) is list of variables for a thorough assessment needed for integration of DR-TB management into NTP;

Table 2: List of variables for a thorough assessment needed for integration of drug-resistant TB management into NTP

- Magnitude and distribution of DR-TB
- Magnitude of HIV
- Prevailing patterns of drug resistance
- Options for DR-TB case-finding
- Existing infrastructure of the health-care system
- Available laboratory capacity
- Resources available for DOT over a prolonged period
- Infection control policy in place and adequate funding available for control measures
- Quality standards of the laboratory network
- Availability of human resources
- Training needs
- Existing legal framework for management of second-line drugs
- Needs for external technical assistance

4. DEFINITIONS OF CASE REGISTRATION AND TREATMENT OUTCOMES

Case definitions, patient registration categories and treatment outcome definitions are important in management of patients infected with drug-resistant TB strains who require second-line anti-TB medication.

4.1 Definitions of drug-resistance cases

Different patterns of drug resistance carry different implications for treatment and management. For the purposes of monitoring, drug-resistant cases are classified in categories based on DST in clinical isolates confirmed to be *M. Tuberculosis* (note, the categories are NOT mutually exclusive):

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

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

- **Confirmed RR-TB or MDR-TB.**
- **Presumptive RR-TB or MDR-TB.** Patients may be registered and started on second-line anti-TB treatment on the basis of significant risk for drug resistance and before laboratory confirmation of resistance, 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 Patient registration categories

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

- **New**. A patient who has received no or less than one month of anti-TB treatment. 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
- **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.
- **After failure of treatment with second-line drugs.** A previously treated DR-TB patient who has received full MDRTB treatment regimen.
- **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.

4.3 Treatment outcomes

Definitions of treatment outcomes for drug-resistant patients are shown in the following table 3.

Table 3: Treatment outcome definition

Cured	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase[a]
Treatment completed	Treatment completed as recommended by the national policy 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[a]
Treatment failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: • Lack of conversion[b] by the end of the intensive phase[a]; or • Bacteriological reversion[b] in the continuation phase after conversion[b] to negative; or • Evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs; or • Adverse drug reactions.
Died	A patient who dies for any reason during the course of treatment.
Lost to follow-up	A patient whose treatment was interrupted for two consecutive months or more.
Not 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.

[a] For Treatment failed, lack of conversion by the end of the intensive phase implies that the patient does not convert within the maximum duration of the intensive phase applied by the programme. If no maximum duration is defined, an 8-month cut-off is proposed. For regimens without a clear distinction between intensive and continuation phases, a cut-off eight months after the start of treatment is suggested to determine when the criteria for Cured, Treatment completed and Treatment failed start to apply.

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

Conversion (to negative): culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.

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

5. CASE FINDING STRATEGIES

The choice of approaches for case finding and enrolment in drug-resistant TB control programmes strive to identify patients and initiate adequate treatment for drug resistant cases in a timely manner. This prevents the patients from spreading the disease and acquiring further resistance and progressing to permanent lung damage. Case finding for drug-resistant TB refers to the process of:

- identifying individuals who may have drug-resistant TB;
- evaluating them appropriately;
- diagnosing drug-resistant TB;
- recording and reporting any drug-resistant TB diagnosed according to standardized criteria

5.1 Risk factors for DR-TB

Risk factors for DR-TB are shown in Table 4.

Table 4: Risk factor for DR-TB

Risk factors for DR-TB	Risk group
Failure of retreatment regimens with first line anti-TB drugs (SHREZ), (previously known as chronic TB cases)	Patients who are still sputum smear-positive at the end of a retreatment regimen have perhaps the highest MDR-TB rates in any group, often approaching 90%.
Failure of new TB regimens (HREZ)	Patients who, while on treatment, are sputum smear-positive at month five or later during the course of treatment. Not all patients in whom a regimen fails have drug-resistant TB, and the percentage may depend on a number of factors, including whether rifampicin was used in the continuation phase and whether directly observed therapy was used throughout treatment.
Exposure to a known drug resistant TB case	Most studies have shown that close contacts of MDR-TB patients have very high rates of MDR-TB.
Failure of anti-TB treatment in the private sector	Anti-TB regimens from the private sector can vary greatly. A detailed history of drugs used is essential. If both isoniazid and rifampicin were used, the chances of MDR-TB may be high. Sometimes second-line anti-TB drugs may have been used, and this is important information for designing the retreatment regimen.

Patients who remain sputum smear-positive at the end of two months of a first-line anti-TB drug regimen	Many programmes may choose to perform culture and DST on patients who remain sputum smear-positive at month two. This group of patients are at risk for DR-TB.
Relapse and return after loss to follow-up, without recent treatment failure	Evidence suggests that most relapse cases and those that return after loss to follow-up (without recent treatment failure) do not have drug-resistant TB. However, certain patient histories may point more strongly to possible drug-resistant TB; for example, erratic drug use or early relapses.
Exposure in institutions that have drug-resistant TB outbreaks or a high drug-resistant TB prevalence	Patients who frequent homeless shelters, prisoners and health-care workers in clinics, laboratories and hospitals can have high rates of drug-resistant TB
Residence in areas with high drug-resistant TB prevalence	Drug-resistant TB rates in many areas of the world can be high enough to justify routine DST in all new cases.
History of using anti-TB drugs of poor or unknown quality	The percentage of drug-resistant TB caused by use of poor quality drugs is unknown but considered significant. All drugs should comply with acceptable international quality assurance standards.
Comorbid conditions associated with malabsorption or rapid-transit diarrhoea	Malabsorption may result in selective low serum drug levels and may occur in either HIV-negative or HIV-positive patients.
HIV	An association between HIV and MDR-TB has been recorded in some parts of the world, and numerous drug-resistant TB outbreaks have been documented in HIV positive patients. It is strongly recommended that all individuals with HIV-associated TB have DST to rule out drug-resistant TB and to avoid high rates of mortality due to unrecognized drug-resistant TB in these patients.

S=streptomycin; H=isoniazid; R=rifampicin; E=ethambutol; Z=pyrazinamide.

5.2 Diagnosing XDR-TB

The two strongest risk factors for XDR-TB are:

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

All patients diagnosed with MDR-TB should preferably be tested for XDR-TB.

5.3 DR-TB case finding in paediatric patients

The best strategy for detection of drug-resistant TB, and the WHO recommended strategy, is to use rapid DST. The WHO 2011 update of Guidelines for the programmatic management of drug-resistant tuberculosis, specifically states: Rapid DST of isoniazid and rifampicin or of rifampicin alone is recommended over conventional testing at the time of diagnosis of TB, subject to available resources. However, this is based on very low quality evidence.

Paediatric cases require adjustments in diagnostic criteria. Most young children will not be able to produce adequate sputum specimens upon request. Sputum induction with nebulised hypertonic saline may facilitate collection of tracheobronchial secretions, especially in children who have a dry cough or no cough. Gastric lavage on an empty stomach is the other option for collecting specimens for Xpert MTB/RIF and culture and DST.

6. LABORATORY ASPECTS

Definitive diagnosis of drug-resistant TB (DR-TB) requires that *Mycobacterium tuberculosis* (MTB) bacteria to be detected and determined its resistance to anti-TB drugs. This chapter describes standards for laboratory services needed to diagnose and treat drug-resistant TB in the context of existing laboratory capacity.

Laboratory detection of DR-TB consist of;
- identification of the isolate as belonging to the MTB complex.
- drug susceptibility testing (DST)
- WHO-endorsed molecular test to detect TB DNA and mutations associated with resistance

6.1 Essential laboratory services and infrastructure

Culture isolation method is essential for monitoring DR-TB patients' response to therapy. Minimum requirement in DR-TB programme also includes the capacity to reliably identify *M. tuberculosis* and detect resistance to rifampicin and isoniazid.

The roles of laboratory in DR-TB are;
- diagnostic and clinical services
- surveillance of drug resistance patterns; for providing information on the degree and trends in drug resistance, for developing appropriate treatment modalities, and for evaluating the impact of control program interventions.

Quality Management System (QMS) is necessary for the laboratory to be implemented to ensure that all aspects of laboratory diagnostic services are performed properly and allow for the detection of any laboratory errors. QMS is necessary to ensure accurate detection of drug resistance and also to avoid false diagnoses. In addition, documented first-line DST proficiency, preferably by the reference laboratory, is strongly recommended for drug-resistant TB control programmes.

Quality Management System should include;
- standard operating procedures (SOPs)
- internal quality control
- external quality assessment

Establishing and maintaining laboratory networks is challenging, difficult and costly. Adequate human and financial resource allocation is therefore crucial to ensure the availability of qualified and trained laboratory staff and for the functioning of the laboratory infrastructure with appropriate level of biosafety, well-maintained equipment and sufficient consumables.

6.2 Organisation of the TB laboratory network

TB laboratory networks have a pyramidal structure with peripheral laboratories (health clinics/ smear microscopy centre) accessible to all presumptive/known TB patients, intermediate laboratories (culture centres/ID and DST centres) and a single/central laboratory (National TB Reference Laboratory). Different levels of biosafety precautions are needed depending on the type of test being performed and the risk of generation of infectious aerosol, with the most

hazardous procedure are involving the manipulation of positive cultures for identification and performing DST. Supranational laboratory is recognised to strengthen and support the national reference laboratory. To strengthen and support the national reference laboratory, Queensland Mycobacterium Reference Laboratory has been recognised as the SRL for Malaysia.

6.3 Specimen collection and transport of infectious substances

Good quality specimens especially sputum are essential for proper TB laboratory diagnosis. Therefore, specific measures must be taken to minimise exposure during sputum collection as coughing produces potentially infectious aerosols.

Patient must also be given effective instructions from a trained staff on collecting samples. Adequate material such as using wide-mouthed containers that are sterile, clear and leak-proof (with screw caps) and procedures must also be available. The specimen containers should be promptly transported to the laboratory using appropriate packaging for safe transport of infectious materials.

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

Recommendation 2

- Specimens should be collected in open air, well-ventilated areas, where infectious droplets are rapidly diluted and ultra violet rays can inactivate tuberculosis bacilli to reduce risk of transmission.
- Specimens should be submitted to the laboratory and processed for culture within 24 hours from collection. Delayed specimens should be kept refrigerated at 4°C and transported to the laboratory in cold chain.
- Specimen containers should be transported to the laboratory using appropriate packaging for safe transport of infectious materials.

6.4 Mycobacteriology laboratory services for drug-resistant TB programmes

6.4.1 Microscopy

Smear microscopy is the front-line tool for TB (but not for DR-TB) diagnosis. The main purposes of microscopy for drug-resistant TB are:

- to assess initial bacterial load, specimen triage to different diagnostic algorithms,
- monitor response to therapy,
- in the TB culture centres: to confirm the presence of AFB rather than contaminants in the culture media, before proceeding to rapid identification tests.

Light emitting diode (LED) fluorescence microscopy is recommended to increase the test sensitivity and to reduce the turnaround time required allowing the screening of a larger number of slides at the peripheral level

6.4.2 Xpert MTB/RIF

Xpert MTB/RIF assay, is a cartridge-based fully automated molecular diagnostic assay that can identify MTB complex DNA and the mutations associated with rifampicin resistance directly from sputum specimens, in less than two hours. The Xpert MTB/RIF assay has similar sensitivity, specificity and accuracy as culture on solid media and has been recommended by WHO as the initial diagnostic test among people at risk of MDR-TB. Therefore, Xpert MTB/RIF should be implemented to increase and expand access to accurate TB diagnosis (5). Figure 3 shows using the Xpert MTB/RIF assay as the initial diagnostic test for TB followed by culture and DST. Indication of using Xpert MTB/RIF as initial diagnostic test is listed in Appendix 3.

Recommendation 3

- Xpert MTB/RIF should be used in addition to conventional microscopy, culture and DST as the initial diagnostic test in adults and children suspected of having MDR-TB or HIV-associated TB. It may be used as a follow-on test to microscopy in adults and children clinically suspicious of TB where MDR-TB and HIV is of lesser concern, especially in further testing of smear-negative specimens where resources are available.

Xpert MTB/RIF assay cannot be used as a replacement for smear and culture isolation for monitoring the response of DR-TB patients to therapy

6.4.3 Line probe assay

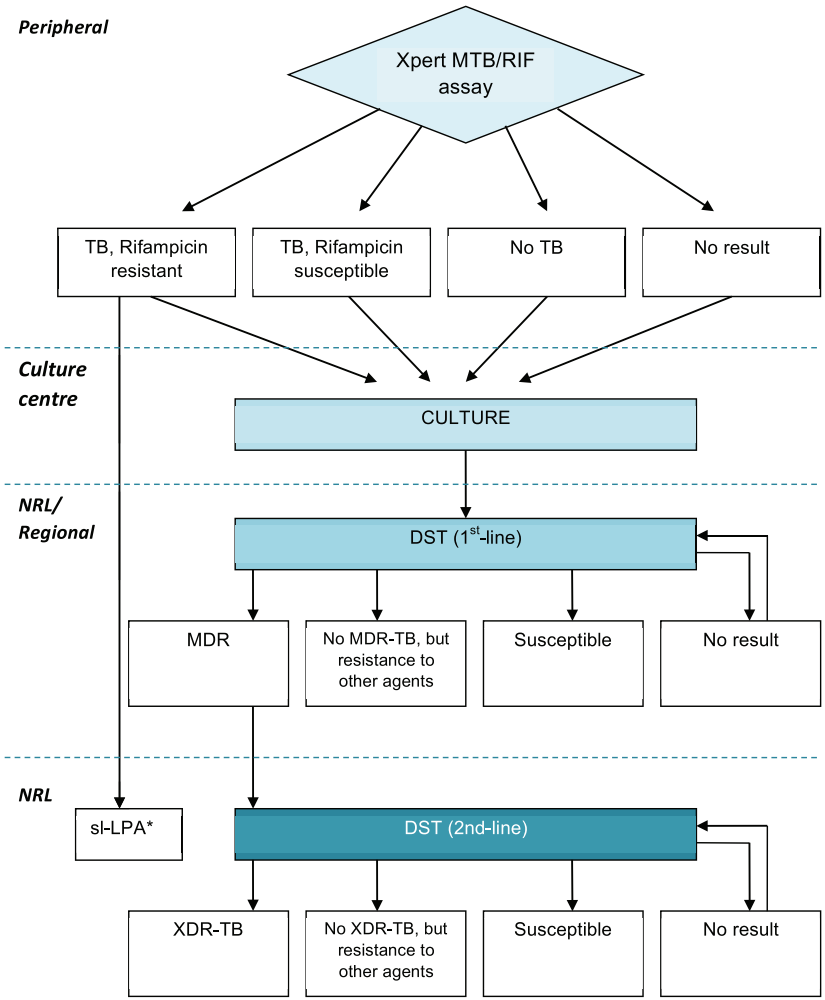
Line probe assay (LPA) allows rapid detection of resistance to rifampicin (alone or in combination with isoniazid). LPAs are suitable for use at the central or national reference laboratory level, with potential for decentralization to regional level if the appropriate infrastructure can be ensured.

For patients with confirmed rifampicin-resistant TB or MDR-TB, SL-LPA may be used as the initial test to detect resistance to fluoroquinolones and second-line injectable drugs. This recommendation applies to the use of SL-LPA for testing sputum specimens (direct testing) and cultured isolates of M. tuberculosis complex (indirect testing) from both pulmonary and extrapulmonary sites.

6.4.4 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 (appropriate digestion and decontamination, as well as good quality culture media and incubation conditions) are critical to optimize the yield of culture. Laboratory errors, may lead to false-negative or false-positive results. Therefore, laboratory findings should always be correlated with the patient's clinical condition and any diagnostic test should be repeated if necessary.

The recovery of tubercle bacilli is higher and the time to detection is shorter with liquid culture compared to solid culture methods. However, as it is more sensitive, it has higher contamination rates than solid media.



** if patient was previously exposed to floroquinolone*

Fig 3: Using the Xpert MTB/RIF assay as an initial diagnostic test for TB followed by culture and DST

6.4.5 Identification of MTB

All mycobacterial isolates from solid or liquid cultures must be identified to allow differentiation of the M. tuberculosis complex from NTM prior to DST. Several ways can be used such as phenotypic tests, immunochromatographic assay (ICA) or genotypic assay. At a minimum, laboratories supporting DR-TB control programmes should be able to conduct identification tests for M. tuberculosis complex that follow international guidelines.

6.4.6 Drug susceptibility testing (DST)

DST plays an important role in most strategies to identify and treat patients with, or at high risk of DR-TB.

- **Phenotypic DST (Conventional DST)**

Phenotypic DST involves culturing of M. tuberculosis bacteria in the presence of anti-TB drugs to detect inhibition of growth. It allows the detection of drug resistance regardless of the mechanism or molecular basis and can be performed as direct or indirect tests on solid media or in liquid media. The most commonly used methods for solid media are the proportion, absolute concentration, and resistance ratio methods; and for liquid culture systems is the proportion method.

For second-line DST, broth or liquid methods and the proportion method on solid medium give similar results[5]. The absolute concentration and resistance ratio methods for second-line DST have not been validated, and neither have any of the non-commercial methods. The current status of DST methods, consensus on reliability and reproducibility, and critical concentrations for different methods for second-line DST is given in Table 5.

Table 5: DST methods and critical concentrations for first-line and second-line DST

Drug group[a]	Drug	DST method available	DST critical concentrations (µg/ml)			
			Löwenstein Jensen[b]	Middle brook 7H10[b]	Middle brook 7H11[b]	MGIT 960
First-line oral anti-TB agents	Isoniazid	Solid, liquid	0.2	0.2	0.2	0.1
	Rifampicin[c]	Solid, liquid	40.0	1.0	1.0	1.0
	Ethambutol[d]	Solid, liquid	2.0	5.0	7.5	5.0
	Pyrazinamide	Liquid	-	-	-	100.0
Fluoroquinolones	Ofloxacin[f]	Solid, liquid	4.0	2.	2.0	2.0
	Levofloxacin	Solid, liquid	-	1.0	-	1.5
	Moxifloxacin[g]	Solid, liquid	-	0.5/2.0	-	0.5/2.0
	Gatifloxacin[h]	Solid	-	0 1.0	-	-

Second-line injectable agents	Streptomycin[e]	Solid, liquid	4.0	2.0	2.0	1.0
	Kanamycin	Solid, liquid	30.0	5.0	6.0	2.5
	Amikacin	Solid, liquid	30.0	4.0	-	1.0
	Capreomycin	Solid, liquid	40.0	4.0	-	2.5
Other core second-line agents[i]	Ethionamide	Solid, liquid	40.0	5.0	10.0	5.0
	Prothionamide	Solid, liquid	40.0	-	-	2.5
	Cycloserine	Solid	30.0	-	-	-
	Linezolid	Liquid	-	-	-	1.0
	Clofazimine	None	-	-	-	-
Add-on agents (not part of the core MDR-TB regimen)	High dose isoniazid	Liquid	-	-	-	-
	Amoxicillin/ clavulanate	None	-	-	-	-
	Para-aminosalicylic acid	Solid, liquid	1.0	2.0	8.0	4.0

[a] WHO Guidelines for the programmatic management of drug-resistant TB.
[b] Indirect proportion method recommended. Other solid media methods (resistance ratio) have not been adequately validated for second-line drugs. Concentrations for the absolute concentration method were not evaluated.
[c] Rifampicin borderline resistance more frequently missed by mycobacteria growth indicator tube (MGIT). Prevalence and geographical distribution of borderline resistance not clear, and final Löwenstein-Jensen (LJ) interpretations should be made after 6 weeks
[d] Ethambutol 5µg/ml in mgIT is not equivalent to other methods. Ethambutol testing in 7H11 not equivalent to 7H10. There is insufficient evidence to recommend a change in concentration for any method
[e] Streptomycin has a bimodal distribution of MIC values. There is insufficient evidence to recommend a change.
[f] Ofloxacin concentration in LJ media increased to 4.0ug/ml. There is insufficient data to extrapolate change in 7H10 or 7H11 methods.
[g] Moxifloxacin. Two concentrations are proposed. In programmes using both ofloxacin/levofloxacin and moxifloxacin, possible testing is for moxifloxacin only at both concentrations OR test ofloxacin/levofloxacin and moxifloxacin at higher concentration. In programmes using ofloxacin/levofloxacin only test only these drugs. In programmes using only moxifloxacin, test at higher concentration of moxifloxacin only.
[h] Use of gatifloxacin should always be appropriately monitored (see Chapter 11).
[i] Routine DST is not recommended. Linezolid suitable for testing in MGIT only.

- **Genotypic DST**

Molecular LPA and the Xpert MTB/RIF are currently the only two molecular technologies endorsed by WHO for the genotypic detection of rifampicin resistance.

For patients with confirmed rifampicin-resistant TB or MDR-TB, SL-LPA may be used as the initial test, instead of phenotypic culture-based DST, to detect resistance to injectable drugs and floroquinolone if resources are available. Direct testing for smear positive sputum specimen (1+ and above) and indirect testing of MTB culture for those with low bacteria load

The advantages of rapid rifampicin testing include prompt screening of patients at risk of MDR-TB, earlier identification of patients on inappropriate first-line regimens, and allows for early interruption of MDR-TB transmission.

However, the use of molecular tests for rapid detection of MDR-TB still does not eliminate the need for conventional culture and DST capability. The recommended algorithm for interpretation of Genotypic DST results is depicted in figure 4.

- **Limitations of DST**

Limitations of DST are;

i. **first-line DST**
   - most reliable for rifampicin and isoniazid.
   - less reliable and reproducible for streptomycin, ethambutol and pyrazinamide (pyrazinamide testing can only be performed on liquid media after appropriate pH adjustment).

ii. **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; in addition, data correlating DST results to the clinical outcome are still insufficient.

6.5 Rational use of DST in DR-TB programmes

Maintaining proficiency in DST requires good laboratory technique and infrastructure, as well as an adequate workload (numbers of specimens) to be tested. In many settings, this implies centralization of laboratory services for DST.

WHO policy guidance on DST 2014 (5) is as follows:

- Laboratory capacity to reliably detect rifampicin resistance and/or MDR-TB through molecular tests and/or quality-assured DST of isoniazid and rifampicin resistance is a minimum requirement for drug-resistant-TB programmes.
- Formal links with one of the laboratories of the SRL network is needed to ensure appropriate infrastructure for the procedures being performed and proper diagnostic algorithms and quality assurance mechanisms in place.
- Strategies for laboratory services in support of drug-resistant TB programmes should follow a systems approach (refer to figure 5) and take into account the DST limitations outlined

above. DST should be focused on those drugs for which reliable and reproducible methods are available.

- DST methods for the second-line injectable drugs (amikacin, kanamycin, capreomycin) and fluoroquinolones are accurate and reproducible. However, routine DST for second-line drugs should not be performed unless the required laboratory quality and biosafety standards are met, infrastructure and capacity have been established, rigorous quality assurance is in place, and sustainable high proficiency has been demonstrated for isoniazid and rifampicin testing. In order to retain proficiency and expertise, it is recommended that second-line DST only be performed if at least 200 specimens are tested per year. As the National TB Reference Laboratory, only National Public Health Laboratory can perform the test.
- At present, routine DST for other core second-line agents and add-on agents (not part of the core MDR-TB regimen) is not recommended as accuracy and reproducibility of laboratory testing cannot be guaranteed.
- Strains should be tested for resistance to the fluoroquinolone(s) used in a programme's treatment strategy. Cross-resistance is not complete between older- and newer-generation fluoroquinolones.

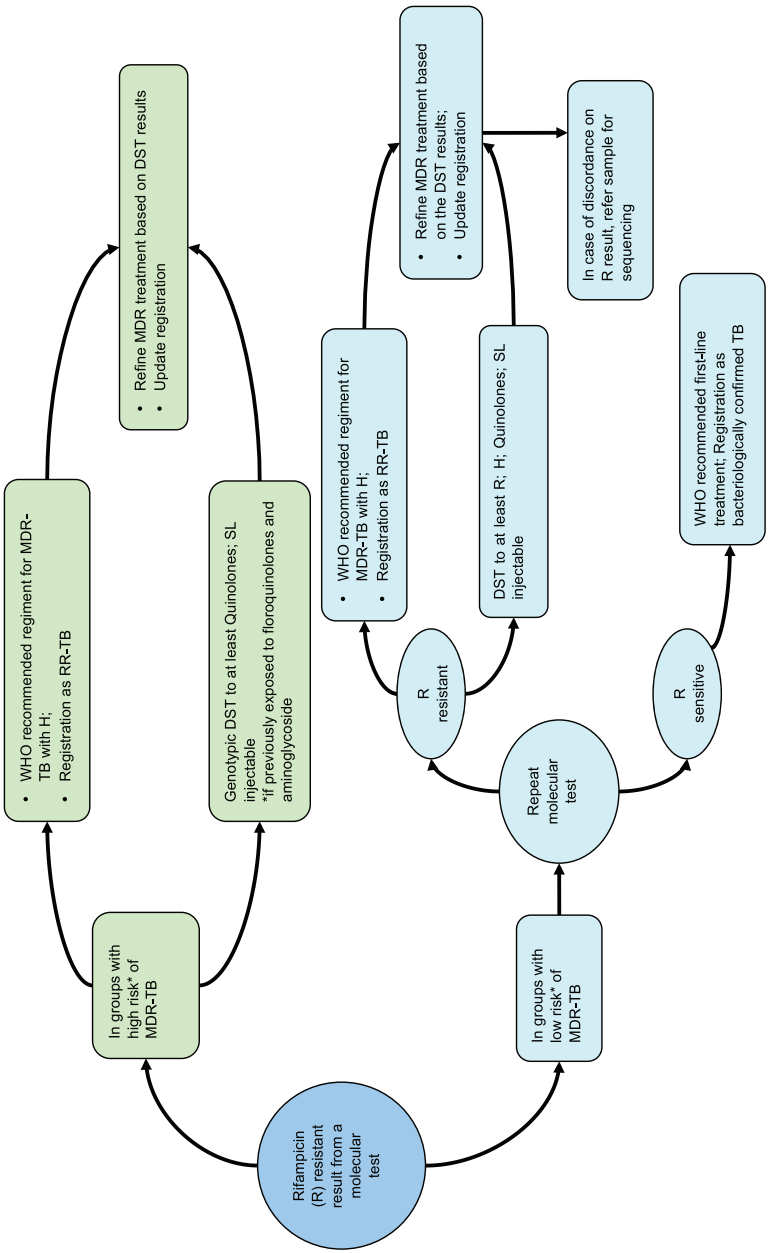
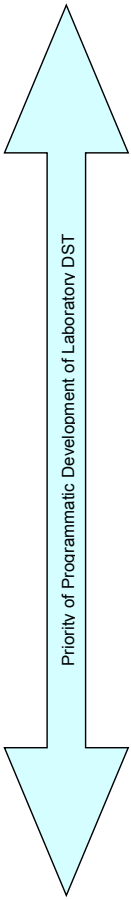


Fig. 4: Algorithm for interpretation of Genotypic DST results



	HIGH PRIORITY
Implement DST to H and R **Implement wide access to Xpert MTB/RIF as the initial diagnostic test in individuals suspected of MDR-TB (adults and children)**	High proficiency in DST to H and R should be a priority for the correct identification of patients to be placed on second-line anti-TB drug regimens. Conventional DST to H and R can be done at a central laboratory while fast detection by Xpert TB/RIF should be widely available, as programmatically relevant.
Expand phenotypic DST to other drugs. ii. **Second-line injectable agents; amikacin, kanamycin, capreomycin** iii. **Fluoroquinolones**	In settings where XDR is a concern, DST to second-line injectable agents and fluoroquinolones will be needed to rapidly allow the identification of XDR-TB patients. Given the variability in cross-resistance reported for the aminoglycosides and polypeptides, it is recommended that testing for kanamycin, amikacin and capreomycin is done. Selection of the most appropriate fluoroquinolone (among the new generation molecules) for DST is based on treatment strategy (because cross-resistance is not complete between older and newer generations of flouroquinolones, it cannot be assumed that resistance to one confers resistance to one confers resistance to all fluroquinolones
	LOW PRIORITY
Expand phenotypic DST to other core second-line agents[i] and add-on agents (not part of the core MDR-TB regimen)	Other core second-line agents DST is not recommended for routine testing for individual patient care. When performed in proficient laboratories, it may provide surveillance data information for empiric MDR regiment design. DST for other core second-line agents and add-on agents (not part of the core MDR-TB regimen) is not yet standardized.

Fig. 5: Systematic approach to implementation of DST under routine programme

6.6 Testing and reporting: turnaround time

To ensure rapid diagnosis of M. tuberculosis and DR-TB, laboratories should define standard turnaround times, which should be strictly followed. A summary of TB diagnostic methods and DST methods and turnaround times are provided in Table 6.

Table 6: Summary of TB diagnostic and DST methods (non WHO endorsed tests are not included) and turnaround time

Diagnostic Platform	Test Name	Turnaround Time	Description and Comments
Smear Microscopy	Conventional light microscopy – Ziehl	2- 24 hours	Less sensitive than fluorescent/LED microscopy
	Conventional fluorescence microscopy		Requires a quartz-halogen or high-pressure mercury vapour lamp. Sensitivity is improved over light microscopy; observation time is reduced. Expensive
	LED fluorescence microscopy		LED microscopes improve sensitivity by 10% over conventional light microscopy. Observation time is similar to conventional fluorescence microscopy. LED conversion kits for light microscopes are available
Solid culture	Lowenstein-Jensen Ogawa	3 weeks (smear positive) 4 – 8 weeks (smear negative)	Egg-based medium, inexpensive
Automated liquid culture		8 -10 days (smear positive) 2 – 6 weeks (smear negative)	Liquid culture systems. Fully automated systems that use either fluorimetric or colourimetric detection
Molecular testing	Line Probe assay (LPA)	1-2 days or 7 days if batching of test (direct on smear positive respiratory specimen only),	2 molecular LPAs have been developed to detect MTBc resistant: i. MDR-TB LPA ii. SL-LPA
	Xpert MTB/RIF	2 -24hours	A fully automated test working in a dedicated platform performing detection of MTB and R resistance, using real time PCR. Results are available in 2 hours.

7. TREATMENT STRATEGIES FOR MDR-TB AND XDR-TB

It is critical for a country to know the prevalence of drug resistance in new patients and retreatment cases. As for Malaysia, estimated RR/MDR-TB cases among notified TB pulmonary cases in Malaysia for new cases was 1.5% and previously treated cases was 3.1% for year 2015. Therefore, access to quality assured DST is valuable and important. Mechanism for collection of the data and statistic, notification, registration and updating the patient monitoring and response in the TB information system is very important.

Drug resistance surveillance(DRS) data can also be used as a tool to monitor the frequency of usage of each second-line anti-TB as some second-line anti-TB drugs may have been used more frequently than the others. Some will likely be effective in drug-resistant TB treatment regimens, while others may have been used extensively, and therefore, have a high probability of ineffectiveness in a large proportion of drug-resistant TB patients.

7.1 Definitions of terms used to describe treatment strategies

The following are definitions of terms often used to describe treatment strategies (refer to table 7);

Table 7: Definition of treatment strategies

Treatment Strategies	Definition
Standardized treatment	DRS data from representative patient populations are used to base regimen design in the absence of individual DST. All patients in a defined group or category receive the same regimen. Suspected MDR-TB should be confirmed by DST whenever possible.
Individualized treatment	Each regimen is designed based on the patient's past history of TB treatment and individual DST results.

7.2 Classes of anti-TB drugs

WHO has reclassified the second-line anti-TB drugs based on the available evidence and the associated level of certainty. It considers the balance between anticipated desirable and undesirable effects and feasibility of implementation (refer Table 8).

Table 8: Medicines recommended for the treatment of rifampicin-resistant and MDR-TB (WHO 2016)

Group name	Name of the drugs	Abbreviation
A. Fluoroquinolones[1]	Levofloxacin Moxifloxacin Gatifloxacin	Lfx Mfx Gfx
B. Second-line injectable agents	Amikacin Capreomycin Kanamycin (Streptomycin)[2]	Am Cm Km (S)

C. Other core second-line agents[1]		Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine	Eto / Pto Cs / Trd Lzd Cfz
D. Add-on agents (not part of the core MDR-TB regimen)	D1	Pyrazinamide Ethambutol High-dose isoniazid	Z E Hh
	D2	Bedaquiline Delamanid	Bdq Dlm
	D3	p-aminosalicylic acid Imipenem-cilastatin[3] Meropenem[3] Amoxicillin-clavulanate[3] (Thioacetazone)[4]	PAS Ipm Mpm Amx-Clv (T)

[1] Medicines in Groups A and C are shown by decreasing order of usual preference for use (subject to other considerations; see text)
[2] Refer to the text for the conditions under which streptomycin may substitute other injectable agents. Resistance to streptomycin alone does not qualify for the definition of extensively drug-resistant TB (XDR-TB) (26)
[3] Carbapenems and clavulanate are meant to be used together; clavulanate is only available in formulations combined with amoxicillin
[4]HIV-status must be tested and confirmed to be negative before thioacetazone is started

Clarithromycin and other macrolides are no longer included among the medicines to be used for the treatment of MDR-TB. For weight based dosing anti-TB drugs refer to Appendix 4.

7.3 Standard code for TB treatment regimens

There is a standard code for writing TB treatment regimens. Each anti-TB drug has an abbreviation (refer to Table8).

A drug-resistant TB regimen consists of two phases:
a) First/intensive phase is the period in which the injectable agent is used
b) Second/maintenance phase is after the injectable agent has been stopped.

How to write the regime:

- The two phases are generally separated by a backslash (/).
- The number before each phase stands for phase duration in months, and this number is the minimum amount of time that the stage should last.
- The number in subscript (e.g. 3) after a letter is the number of drug doses per week. If there is no number in subscript, treatment is daily (injectables are generally given for 5–6 days per week).
- The drugs in the higher groups are written first followed by others in descending group order.

Eg: 8 Km-Lfx-Eto-Cs-Z / 12 Lfx-Eto-Cs-Z
8 Km_5-Lfx-Eto-Cs-Z / 12 Lfx-Eto-Cs-Z
4-6 Km_5-Mfx-Pto-Cfz-Z-Hhigh-dose -E / 5 Mfx-Cfz-Z-E.

7.4 Role of DST

DST for some first-line and most second-line anti-TB drugs does not detect with 100% certainty the sensitivity of a drug. DST for ethambutol, streptomycin, pyrazinamide, Group A, C and D drugs presents problems with accuracy and reproducibility in most settings. DST to pyrazinamide is not reliable and for this reason it is considered an acceptable practice to use pyrazinamide in a regimen even when a laboratory result demonstrates resistance. More studies need to be done to evaluate pyrazinamide DST in the future. Ethambutol is not routinely added to conventional MDR regimen, however, it can be used if the criteria of it being a likely effective drug are met.

The Xpert MTB/RIF assay can be used as initial diagnostic tool for MDR-TB if available. Malaysia advocate that Xpert MTB/RIF to be used for diagnosis of rifampicin resistance in adults and children:

a. *Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in adults suspected of having MDR-TB or HIV-associated TB (strong recommendation, high-quality evidence).*
b. *Xpert MTB/RIF should be used rather than conventional microscopy, culture and DST as the initial diagnostic test in children suspected of having MDR-TB or HIV-associated TB (strong recommendation, very low-quality evidence).*

7.5 Designing and administrating an MDR regimen

This section describes the methods for designing and administrating an MDR regimen. It applies to standardised and individualised regimens.

7.5.1 General principles

The following are the basic principles involved in the treatment of MDR-TB;

a. usage of “likely effective” drugs.
   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 on the patient’s strain indicates that it is susceptible to the drug
   - No known resistance to drugs with high cross-resistance
   - No known close contacts with resistance to the drug
   - Drug resistance surveys demonstrate that resistance is rare to the drug in patients with similar TB history.
   - In the treatment of patients with MDR-TB, ethionamide (or prothionamide) should be used provided no contraindication such as a severe adverse effects.
   - More than five drugs can be used depending on the effectiveness of the drugs for example in XDR-TB.

b. dosage and frequency of the drugs
   - The drug dosage is usually determined by age and weight.
   - All anti-TB drugs can be started at full dose. However, if tolerance is an issue, cycloserine, ethionamide and PAS dosing can be increased gradually over a two-week period.
   - Pyrazinamide, ethambutol and fluoroquinolones should be given once a day.
   - Ethionamide/prothionamide, cycloserine and PAS have traditionally been given in split doses during the day to reduce adverse effects.

- Injectable drugs can be given once daily, five to seven days a week. If adverse effects occur, injectable agent may be given three times a week, preferably only after culture conversion.
- Oral drugs are to be given seven days a week under DOT.
- Pyrazinamide can be used for the entire treatment since many drug-resistant TB patients have chronically inflammed lungs as Pyrazinamide is more effective in the acidic environment. In Rifampicin Resistant patients, high-dose isoniazid may be included in the MDR regimen until DST to isoniazid is available.

c. addressing the Adverse effect
   - To avoid the drugs that is known to have a strong contraindication of usage due to drug–drug interactions, overlying toxicities, co-morbidities, history of severe allergy or other adverse reactions and pregnancy.
   - Any adverse effects of drugs that occurs should be managed immediately and adequately to relief suffering, minimize the risk of treatment interruptions, and prevent morbidity and mortality due to serious adverse effects.

d. TB-HIV co-morbidity
   Antiretroviral therapy (ART) is recommended for all patients with HIV and drug-resistant TB, irrespective of CD4 cell-count, as early as possible following initiation of the anti-TB treatment.

7.5.2 Suggestion for conventional DR-TB regimen

Table 9 shows suggestion for conventional DR-TB regimen.

Table 9: Suggestion for conventional DR-TB regimen

	Drug Group	Name of Drugs	Remark
Step 1	Choose one from Group A	Levofloxacin Moxifloxacin Gatifloxacin	Use a later generation fluoroquinolone. If levofloxacin (or ofloxacin) resistance is documented, use moxifloxacin. Avoid moxifloxacin if possible when using bedaquiline
Step 2	Choose one from Group B	Kanamycin Amikacin Capreomycin	Choose a drug based on DST and treatment history. Streptomycin can be used as the injectable agent of the core MDR-TB regimen, if none of the three other agents can be used and if the strain can be reliably shown not to be resistant.
Step 3	Choose at least two from Group C	Ethionamide/prothionamide Cycloserine/terizidone Linezolid Clofazamine	Add two or more Group C drugs until there are at least four second-line anti-TB drugs likely to be effective. Ethionamide/prothionamide is considered the most effective

				Group C drug. Consider treatment history, side-effect profile, and cost. DST is not considered reliable for the drugs in this group.
Step 4	Add Group D1 drugs to strengthened the regimen	Pyrazinamide Ethambutol High-dose Isoniazid		Pyrazinamide is routinely added in most regimens; ethambutol can be added if the criteria for an effective drug are met. If isoniazid is unknown or pending it can be added to the regimen until DST results become available,
Step 5	If the minimum of effective TB medicines cannot be composed as above, an agent from group D2 and other agents from D3 may be added to bring the total to five.	D2 D3	Bedaquiline Delamanid *p-aminosalicylic acid* Imipenem-cilastatin[1] Meropenem[1] Amoxicillin-clavulanate[1] (Thioacetazone)	Consider adding Group D2 and D3 drugs if four second-line anti-TB drugs are not likely to be effective from Groups A-C. If drugs are needed from this group, it is recommended to add two or more. DST is not standardized for the drugs in this group.

[1]Carbapenems and clavulanate are meant to be used together; clavulanate is only available in formulations combined with amoxicillin

Conventional Treatment

In patients with rifampicin-resistant or multidrug-resistant TB, a regimen with at least five effective TB medicines during the intensive phase is recommended, including pyrazinamide and four core second-line TB medicines - one chosen from group A, one from group B, and at least two from group C (conditional recommendation, very low certainty in the evidence). If the minimum of effective TB medicines cannot be composed as above, an agent from group D2 and other agents from D3 may be added to bring the total to five.

In patients with rifampicin-resistant or multidrug-resistant TB, it is recommended that the regimen be further strengthened with high-dose isoniazid and/or ethambutol

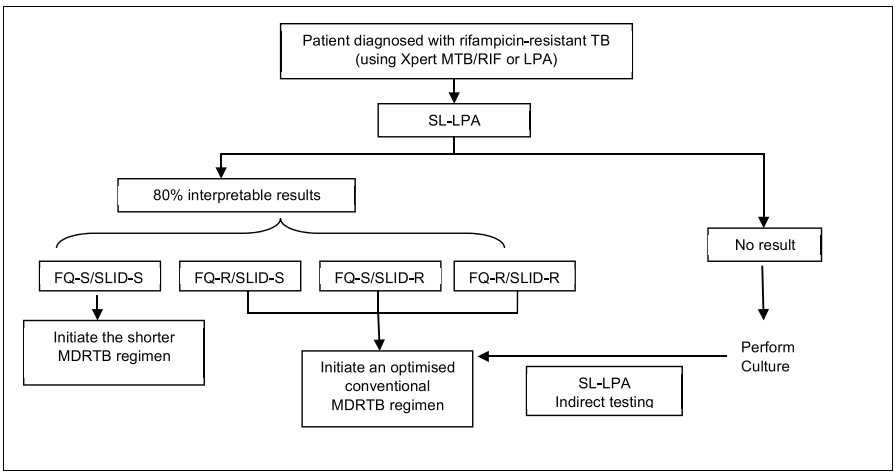
However, WHO suggested for a new shorter MDRTB regimen:

Standardized shorter MDR-TB regimen with seven drugs and treatment duration of 9 months. The Shorter MDRTB regimen may be extended to 6 months of intensive phase, in case of lack of sputum conversion, with total duration of treatment of 12 months.

It is indicated in MDR-TB or rifampicin-resistant-TB, regardless of patient age or HIV status, who has not been previously treated with second-line drugs and in whom resistance to fluoroquinolone and second-line injectable agents has been excluded or is considered highly unlikely.

Exclusion criteria: 2nd line drug resistance, extrapulmonary disease and pregnancy and patient that has previously received 2nd line drugs in the past.

Figure 6 shows proposed testing algorithm for the second-line probe assay (SL-LPA)



FQ: Fluoroquinolone SLID: Second-line injectables drug S: sensitive R: resistant

Fig 6: Testing algorithm for the second-line line probe assay (SL-LPA)

Shorter MDR-TB treatment regimens (for weight dosing refer appendix 4)
The suggestion was an intensive phase of 4 months (extended to 6 months in case of lack of sputum smear conversion) including the following drugs:

- High dose Moxifloxacin or Gatifloxacin
- Aminoglycoside
- Ethionamide
- Clofazimine
- High-dose isoniazid
- Pyrazinamide
- Ethambutol

This was followed by a maintenance phase of 5 months with the following medicines:

- High dose Moxifloxacin or Gatifloxacin
- Clofazimine
- Ethambutol
- Pyrazinamide.

Monitoring for effectiveness, harms and relapse will be needed. Patient-centred care and social support will be essential to enable patient adherence. Programmatic use is feasible in most settings.

Patients on Shorter MDRTB regimen are advice to convert to conventional TB treatment when:

- Lack of response to treatment (e.g. no sputum smear conversion by 6 months or deterioration of clinical condition despite treatment);
- Patient is treated for more than one month, interrupts treatment and returns after an interval >2 months (i.e. fulfils another exclusion criterion);
- Emergence of another exclusion criterion (e.g. EP-TB disease, pregnancy, intolerance to a medicine in the regimen) etc.

Recommendation 4

- In patients with rifampicin-resistant or multidrug-resistant TB, a regimen with at least five effective TB medicines during the intensive phase is recommended, including pyrazinamide and four core second-line TB medicines - one chosen from group A, one from group B, and at least two from group C. If the minimum of effective TB medicines cannot be composed as above, an agent from group D2 and other agents from D3 may be added to bring the total to five.
- In patients with rifampicin-resistant or multidrug-resistant TB, it is recommended that the regimen be further strengthened with high-dose isoniazid and/or ethambutol.
- In patients with rifampicin-resistant or multidrug-resistant TB who have not been previously treated with second-line drugs and in whom resistance to fluoroquinolones and second-line injectable agents has been excluded or is considered highly unlikely, a shorter MDR-TB regimen of 9months may be used instead of a conventional regimen

7.6 Duration of second-line anti-TB regimens

The intensive phase is defined as the time MDR-TB patient is on injectable anti-TB drugs.

Recommendation 5

- In the conventional treatment of patients with MDR-TB, an INTENSIVE PHASE of eight months is suggested for most patients, and the duration may be modified according to the patient's response to therapy.
- In the treatment of patients newly diagnosed with MDR-TB, TOTAL TREATMENT duration of 20 months is suggested for most patients, and the duration may be modified according to the patient's response to therapy.
- Shorter MDR-TB regimen duration is 9-12months.

7.7 Extrapulmonary and central nervous system drug-resistant TB

The same strategy and duration to pulmonary drug resistant tuberculosis are applied to extrapulmonary drug resistant tuberculosis. However, in central nervous system involvement, the regimen should include drugs with adequate penetration into the cerebrospinal fluid (refer Table 10).

Table 10: Drug penetration through blood brain barrier

Penetration to CSF	Medications
Good	Isoniazid Pyrazinamide Prothionamide Ethionamide Cycloserine. Imipenem* Meropenem
Good penetration only in the presence of meningeal inflammation	Kanamycin Amikacin Streptomycin
Poor or no Penetration	PAS Ethambutol
Variable cerebrospinal fluid penetration	Levofloxacin Moxifloxacin
Better penetration of based on animal studies	Moxifloxacin
No Data available	Clofazimine Clarithromycin

*High rate of seizure reported in children with meningitis treated with imipenem

Ethionamide (or prothionamide), cycloserine (or terizidone) and linezolid have good CNS penetration. CSF penetration is good but variable for levofloxacin and moxifloxacin. Pyrazinamide has good CNS penetration, although caution should be exercised as a large percentage of MDR-TB strains may be resistant. Isoniazid penetrates the CNS very well, with higher doses reaching adequate MICs in the cerebrospinal fluid. Due to its good CNS penetration, high-dose isoniazid is recommended to be used as part of the treatment regimen unless high-level resistance is known to exist.

No recommendation is possible at this stage to use the shorter regimen in patients with extrapulmonary MDR-TB in view of the findings from studies of shorter MDR-TB regimen were limited to patients with pulmonary disease.

7.8 Surgery in treatment of DR-TB

Surgery in DR-TB is an adjunct to the medical treatment. Resection is done to those patients with disease localized to a lobe or lung. Large case series analysis has proven resection surgery to be effective and safe under appropriate surgical conditions. It is considered an adjunct to chemotherapy and appears to be beneficial for patients when skilled thoracic surgeons and excellent postoperative care are available.

General indications for resection surgery include

- Patients that remain smear-positive, with resistance to a large number of drugs
- Localized pulmonary disease

Contraindications for resection surgery are:

- Very sick patients with co-morbidities
- Older patients
- Those with extensive disease

Recommendation preoperative investigations:

- Computerized tomography
- Pulmonary function testing
- Quantitative lung perfusion/ventilation

Timing for surgery is important in such that the patient has the best possible chance of cure with the least morbidity. It can be done earlier in the course of disease usually after at least 2 months of medical therapy. This is to decrease the bacterial infection in the surrounding tissue. Nevertheless, even with successful resection, the intensive phase and total treatment duration should be guided by the recommendations in Sections 7.8.

Environmental control in specialized surgical facilities should include stringent infection control measures, given that infectious substance and aerosols are generated in large quantities during surgery, mechanical ventilation and post-operative pulmonary hygiene manoeuvres.

Recommendation 6

- In patients with rifampicin-resistant or multidrug-resistant TB, elective partial lung resection (lobectomy or wedge resection) may be used alongside a recommended MDR-TB regimen (conditional recommendation, very low certainty in the evidence).

7.9 Corticosteroids as adjuvant therapy in drug-resistant TB treatment

The role of adjuvant therapies has not been well established except in specific indications. It should be given in tapering dose over several weeks.

Corticosteroids can be beneficial in conditions like severe central nervous system or pericardial involvement.

7.10 Nutritional support

Nutritional support is one of the important factors in the management of DR-TB as TB itself causes malnutrition and DR-TB exacerbates by poor nutritional status. Furthermore, the second-line anti-TB can also cause GI disturbance and decrease the appetite making adequate nutrition a challenge. Therefore, nutritional assessment counselling should be integrated in the multidisciplinary team throughout the duration of illness. Peripheral neuropathy is a known neurological side effect of some of second-line anti-TB drugs.

Vitamin B6 (pyridoxine) should be given to all MDR-TB patients receiving cycloserine or terizidone, and a high dosage of isoniazid or linezolid to prevent neurological side effects

7.11 Treatment strategies of XDR-TB

There is very limited data on XDR-TB management. However, there are recent studies and meta-analysis suggested:

Success in XDR-TB patients was highest if at least six drugs were used in the intensive phase and four in the continuation phase.

The use of later-generation fluoroquinolone significantly improved treatment outcomes in patients with XDR-TB, even though DST demonstrated resistance to a representative fluoroquinolone.

Treatment management for patients with documented or almost certain XDR-TB are as below (refer Table 11);

Table 11: Treatment management for patients with documented or almost certain XDR-TB

Step 1	Use a higher-generation fluoroquinolone Group A such as moxifloxacin or gatifloxacin.
Step 2	Use an injectable agent Group B to which the strain is susceptible and consider an extended duration of use (12 months or possibly the whole treatment). If resistant to all injectable agents it is recommended to use one the patient has never used before or consider designing the regimen without an injectable agent.
Step 3	Use all Group C agents that have not been used extensively in a previous regimen or any that are likely to be effective
Step 4	Use pyrazinamide and any other Group D1 agent that may be effective.
Step 5	Use Group D2 and D3 agents that have not been used extensively in a previous regimen or any that are likely to be effective

Generally, XDR-TB patients generally receive at least 24 months of therapy in most. The duration maybe modified according to patient's response to treatment

8. MONO-RESISTANT AND POLY- RESISTANT STRAINS

Mono- and poly-resistant TB strains are picked up during case-finding for MDR-TB. DST should be done in all patients before treatment using a rapid test that detects resistance to isoniazid and rifampicin.

It is important to address this situation as treating patients who have mono- or poly-resistant strains using the standardised first-line anti-TB drug regimens has been shown to increase the risk of treatment failure and further acquired resistance. This may eventually lead to MDR-TB if it is not properly managed.

8.1 Treatment of patients with mono- and poly-resistant strains

Table 12 shows the various regimens for mono- and poly-resistant strains. There is a lack of randomized clinical trials to determine the best treatment for these strains. The regimens have been based on observational cohort studies and the recommendations of expert panels, taking into account the evolving DST globally. The regimes have been suggested with the underlying assumption that the pattern of drug resistance has not changed between the initial sputum collections and initiating the re-design of the anti-TB drug regimen.

In patients with rifampicin-resistant TB, a regimen with at least five effective TB medicines during the intensive phase is recommended, including pyrazinamide and four core second-line TB medicines - one chosen from group A, one from group B, and at least two from group C (conditional recommendation, very low certainty in the evidence). If the minimum of effective TB medicines cannot be composed as above, an agent from group D2 and other agents from D3 may be added to bring the total to five (refer to Table 8, Chapter 7). It is recommended that the regimen be further strengthened with high-dose isoniazid and/or ethambutol (conditional recommendation, very low certainty in the evidence).

Table 12: Suggested regimens for mono- and poly-drug resistance (when further acquired resistance is not a factor and laboratory results are highly reliable)

Pattern of drug resistance	Suggested regimen	Minimum duration of treatment (Months)	Comments[a]
H (± S)	R, Z and E (+/-FQ)	6–9	Consider using Xpert MTB/RIF at month 0, 2, and 3 and if rifampicin resistance is found, switch to full MDR-TB treatment. Some experts add a FQ to the regimen.
H and E (± S)	R, Z and fluoro quinolones	9–12	Consider using Xpert MTB/RIF at month 0, 2, and 3 and if rifampicin resistance is found switch to full MDR-TB treatment and check DST to first- and second-line anti-TB drugs. Some experts recommend using a second-line injectable agent for the first three months

H, E, Z, (± S)	R, FQ, plus ethionamide, plus a second-line injectable agent for the first 2 to3 months (+/- Z)	18	A longer course (6 months) of the second-line injectable may strengthen the regimen for patients with extensive disease. Z should be added if resistance is uncertain. Consider using Xpert MTB/RIF at month 0, 2 and 3 and if rifampicin resistance is found switch to full MDR-TB treatment and check DST to second-line anti-TB drugs. If culture positive after month 2, repeat DST to first- and second-line anti-TB drugs.
R mono- or poly-drug resistance	Full MDR-TB regimen plus H	Refer to Chapter 7 for MDR-TB regimen, treatment and monitoring.	

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

9. TREATMENT OF DRUG-RESISTANT TB IN SPECIAL CONDITIONS AND SITUATIONS

Management of DR-TB in certain groups of patient such as pregnancy, renal failure, liver disease and etc. may require different approach and modification due to the risks of treatment complications. The benefit and risk of treatment to the patients should be considered before it is initiated and frequent monitoring may be necessary.

9.1 Pregnancy

DR-TB is seen frequently in young people as well as women of childbearing age. Toxicity of the drugs used in DR-TB treatment during pregnancy creates anxiety not only for patients but also for clinicians.

DR-TB and its treatment during pregnancy pose great risk to the mother and fetus however pregnancy is not a contraindication for treatment of active drug-resistant TB. A decision to start treatment especially in the first trimester or to postpone should be agreed upon by the patient and the doctor.

Recommendation 7

- All female patients of child bearing age who are diagnosed DR-TB should be tested for pregnancy.
- Pregnant patients should be started on treatment as soon as the diagnosis is made. However, treatment may be delayed until the second trimester if the patient is stable with minimum disease.
- The treatment regimen should contain three or four second-line anti-TB drugs which are likely to be effective plus pyrazinamide and reinforced with an injectable agent and other drugs as needed immediately postpartum.
- Fluoroquinolones, cycloserine, paraaminosalicylic acid (PAS) and amoxicillin/clavulanate) should be considered as the drug of choice when selecting drugs for MDR-TB treatment.
- Injectable agents should be avoided. However, capreomycin may be considered in life threatening situation due to MDR/XDR TB.
- Capreomycin thrice weekly from the start may be considered to decrease drug exposure to the foetus if an injectable agent need to be given.
- Injectable agent may be given for three to six months postpartum even in the middle of treatment but it is not necessary if the patient remain well and past eight months period for injectable agent.
- Ethionamide should be avoided due to risk of nausea and vomiting associated with pregnancy, and potential teratogenic effects.
- Termination of pregnancy should be considered if the mother's life is compromised.[4]
- Treatment should be given for duration the same as for standard MDR-TB treatment.

9.2 Breastfeeding

Transmission of DR-TB during breast feeding may occur from the mother to the baby especially in smear positive cases. Small concentration of all second-line drugs is found in breast milk, however any effect to breast fed infant has not been established.

Recommendation 8

- Breastfeeding woman who has active drug-resistant TB should receive a full course of anti-TB treatment.
- The infant formula is preferred to reduce transmission and avoid side effects of drugs in smear positive mother;
    i. the care of infant should be left to family members until smear become negative
    ii. the mother should wear surgical mask whenever the mother and infant are together and they should be in well-ventilated areas or outdoors until sputum negative.

9.3 Contraception

There are potential drug-drug interactions between anti-TB and contraceptive pills which may reduce drug's efficacy or increase toxicity.

There is no contraindication to the use of oral contraceptives with non-rifamycin containing regimens for MDR-TB, however some patient may develop nausea and vomiting which may affect absorption and reduce efficacy of oral contraceptive drugs. Rifampicin used for patients with mono- and poly-resistant TB but who are susceptible to rifampicin interacts with the contraceptive drugs resulting in decreased efficacy of protection against pregnancy

Recommendation 9

- All sexually active women receiving therapy for drug-resistant TB must use effective contraception.
- Patients who vomits after taking anti-TB drugs should be advised to take their contraceptive at different time, use barrier methods or contraceptive implants.

A woman on oral contraception while receiving rifampicin treatment may choose between two options:

- use an oral contraceptive pill containing a higher dose of estrogen (50ug) or
- use another form of contraception

Condoms are a reasonable solution for patients who do not want to take additional pills and/or when protection against sexually transmitted diseases is also needed.
Medroxyprogesterone intramuscular injections and other methods of contraception can also be considered (refer to medical eligibility criteria for contraception WHO 2004 document).

9.4 Renal insufficiency

Renal insufficiency can be due to longstanding TB infection, previous use of aminoglycoside and other causes. In administration of second-line drugs in patients with renal insufficiency, the dose and/or the interval between dosing should be adjusted accordingly (refer table 13) and renal function monitoring should be done closely.

Table 13: Adjustment of anti-TB drugs in renal insufficiency

Drug	Recommended dose and frequency for patients with creatinine clearance <30 ml/min or for patients receiving haemodialysis (unless indicated dose after dialysis)
Isoniazid	No adjustment necessary
Rifampicin	No adjustment necessary
Pyrazinamide	25–35 mg/kg per dose three times per week (not daily)
Ethambutol	15–25 mg/kg per dose three times per week (not daily)
Rifabutin	Normal dose can be used, if possible monitor drug concentrations to avoid toxicity
Rifapentine	No adjustment necessary
Streptomycin	12–15 mg/kg per dose two or three times per week (not daily)b
Capreomycin	12–15 mg/kg per dose two or three times per week (not daily)b
Kanamycin	12–15 mg/kg per dose two or three times per week (not daily)b
Amikacin	12–15 mg/kg per dose two or three times per week (not daily)b
Ofloxacin	600–800 mg per dose three times per week (not daily)
Levofloxacin	750–1000 mg per dose three times per week (not daily)
Moxifloxacin	No adjustment necessary
Gatifloxacin	400 mg three times a week
Cycloserine	250 mg once daily, or 500 mg/dose three times per weekc
Terizidone	Recommendations not available
Prothionamide	No adjustment necessary
Ethionamide	No adjustment necessary
Para-aminosalicylic acide	4 g/dose, twice daily maximum dosed
Bedaquiline	No dosage adjustment is required in patients with mild to moderate renal impairment (dosing not established in severe renal impairment, use with caution).
Linezolid	No adjustment necessary
Clofazimine	No adjustment necessary
Amoxicillin/clavulanate	For creatinine clearance 10–30 ml/min dose 1000 mg as amoxicillin component twice daily; for creatinine clearance <10 ml/min dose 1000 mg as amoxicillin component once daily
Imipenem/cilastin	For creatinine clearance 20–40 ml/min dose 500 mg every 8 hours; for creatinine clearance <20 ml/min dose 500 mg every

9.5 Liver disorders

All first-line drugs such as isoniazid, rifampicin and pyrazinamide are associated with hepatotoxicity. Rifampicin is least likely to cause hepatocellular damage, although it is associated with cholestatic jaundice. Pyrazinamide is the most hepatotoxic of the three first-line drugs. Among the second-line drugs, ethionamide, prothionamide and PAS can also be hepatotoxic, although less so than any of the first-line drugs. Fluoroquinolones can rarely cause hepatitis.

Patients with history of liver disease can receive the usual anti-TB drug regimens provided there is no clinical evidence of severe chronic liver disease, hepatitis virus carriage and recent history of acute hepatitis or excessive alcohol consumption.

Hepatotoxic reactions to anti-TB drugs may be more common in DR- TB patients and should be anticipated.

Recommendation 10
- Patients with chronic liver diseases should not receive pyrazinamide but all other drugs can be used with close monitoring of liver enzymes.

In acute hepatitis, it is possible to defer anti-TB treatment until it has been resolved but in other cases when it is necessary to treat drug-resistant TB during acute hepatitis, the combination of four non hepatotoxic drugs is the safest option.
Viral hepatitis should be treated if medically indicated and treatment can occur during drug-resistant TB treatment.

9.6 Seizure disorders

The initial step in evaluating patients with current or previous seizure disorder is to assess whether the seizure is under control and whether the patient is taking antiepileptic drugs. Initiation or adjustment of antiepileptic drugs is needed if the seizure is not under control as well as correcting underlying conditions or causes of seizures.

Cycloserine should be avoided if possible in patients with active seizure disorders that are not well controlled

Recommendation 11
- The risks and benefits of using cycloserine should be discussed with the patient and the decision on whether to use cycloserine should be made together with the patient.
- High dose isoniazid should be avoided in patients with active seizure disorders because it carries higher risk of seizure.
- Pyridoxine (vitamin B6) can be used prophylactically in patients with seizure disorders to protect against the neurological adverse effects of isoniazid or cycloserine.

Prophylactic dose of pyridoxine for at-risk patients on isoniazid is 10 to 25 mg/day and for patients on cycloserine is 25 mg of pyridoxine for every 250 mg of cycloserine daily.

Isoniazid and rifampicin use in mono and poly-resistant cases may interfere and interact with many of the antiepileptic medications.

9.7 Psychiatric disorders

Treatment of MDR TB patients with pre-existing psychiatric illness often complicated. Incidence of depression and anxiety in patients with drug-resistant TB is high and often due to chronicity and socioeconomic stress factors related to the disease.

Recommendation 12
- Careful evaluation of any psychiatric illness should be done before initiation of DR-TB treatment.
- Psychiatric patients should be evaluated by a health care worker with psychiatric training before the start of treatment for drug-resistant TB.

Treatment with psychiatric medication, individual counselling and/or group therapy may be necessary.

Cycloserine can be used in patients with psychiatric disorders because its benefits may outweigh the risk, however close monitoring of psychiatric symptom is recommended. All health care workers treating drug-resistant TB should work closely with a mental health specialist and easy access to emergency and other psychiatric treatment should be made available easily.

9.8 DR-TB in children

Children with DR-TB generally acquire the disease transmitted from adult with drug-resistant TB. Young children living with DR-TB patients, have high risk of being infected and developing active DR-TB. The clinical presentation of drug-resistant TB in children is similar to drug-sensitive TB disease.

Criteria for suspecting DR-TB in children include:
- Close contact with a person with confirmed or suspected DR-TB.
- History of previously treated TB present with recurrence of the disease.
- Failure to respond to first line TB treatment despite good adherence.

The diagnostic workup of DR-TB in a child should include the following:
- clinical evaluation by a paediatrician (including history and physical examination)
- a chest radiograph and other diagnostic tests (as indicated)
- tuberculin skin testing
- sputum / gastric lavage investigations: smear microscopy, culture and rapid DST (Xpert MTB/RIF assay)
- HIV testing

In cases of extrapulmonary TB, fine needle aspiration or biopsy should be considered. Specimens obtained must be sent for diagnostic TB testings, also microbiological culture and histopathological examination to rule out other infective or non-infective diseases.

Recommendation 13
- Children with DR-TB should be referred to paediatrician with experience in TB management.

Information on paediatric DR-TB and reported experience on the use of second-line drugs (injectable anti-TB) for extended periods in children is very limited. Thus far, the second-line anti-TB drugs were reported to be well tolerated in children who have received the therapy. However, in children with mild forms of disease, second-line anti-TB drugs may be avoided. If the use of the drugs is inevitable the risks and benefits of each drug should be discussed with family members at the outset of therapy.

DST should be used to guide therapy when available and treatment may be guided by the anti-TB history and DST results of the adult contact. Refer to figure 7.

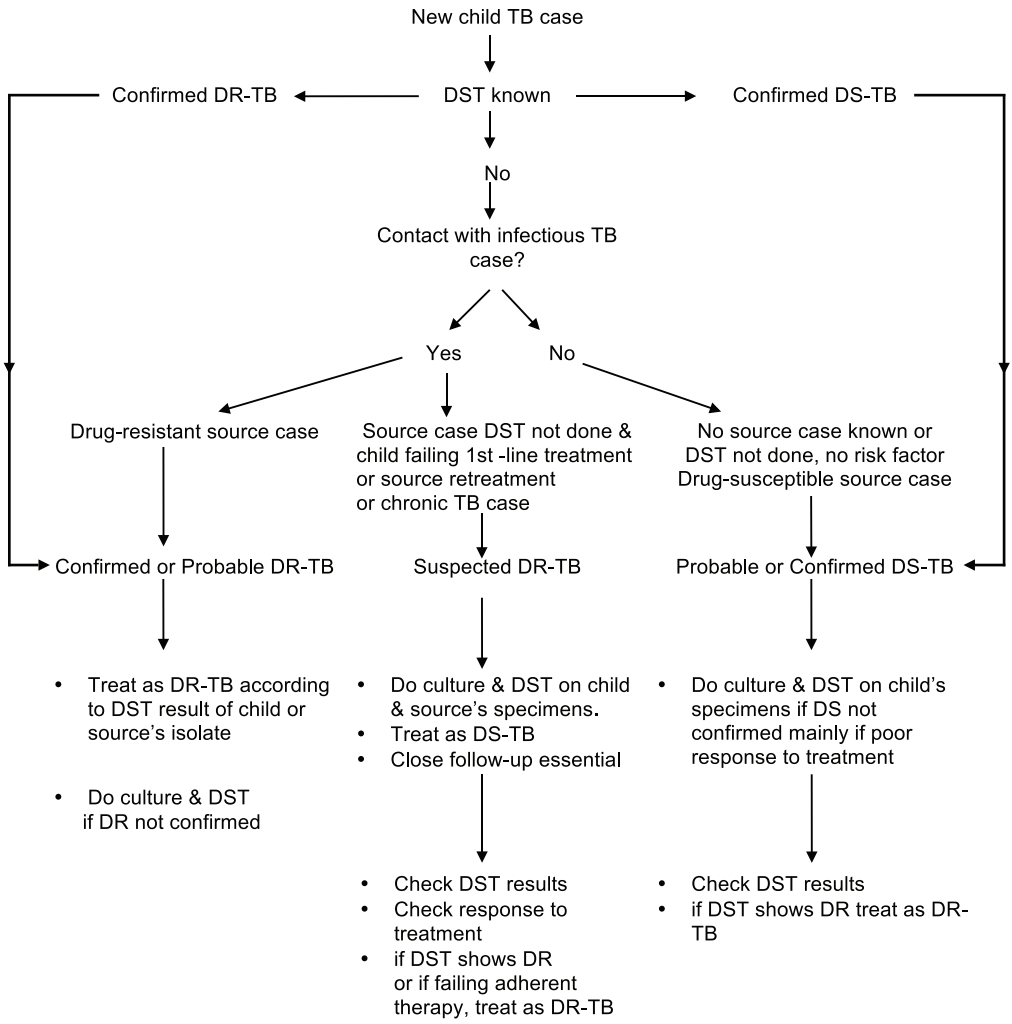


Fig 7: Diagnostic algorithm for the diagnosis of DR-TB in children

9.9 Treatment of DR-TB in children

Recommendation 14		
Resistance	**Treatment**	
	Intensive	**Maintenance**
• Monoresistance Isoniazid For more extensive disease, consider adding fluoroquinolone and prolonging treatment to 9 months.	2 HRZE	4HRE
• Rifampicin- resistant • MDR-TB	Same regimen and duration as adult with some exceptions in the choice of drug group*	

Table 14 shows treatment of DR-TB in children. Dosing of anti-TB drugs in children is weight based, WHO recommended the higher end of the dosage range.

Table 14: Treatment of DR-TB in children

*Group B agents is recommended only in children with severe clinical manifestations and fluoroquinolones resistant**.** Group D2 agents (bedaquiline and delamanid) are not recommended in view of inadequate data of the usage in children so far.

Table 15: Recommended anti-TB drugs and fluoroquinolones dosages in children

Drug	**Dose (range) in mg/kg/day**	**Maximum daily dose**
Isoniazid (H)*	10 – 15 mg/kg	300 mg
Rifampicin (R)	10 – 20 mg/kg	600 mg
Pyrazinamide (Z)	30 – 40 mg/kg	2g
Ethambutol (E)	15 – 25 mg/kg	1g
Levofloxacin	7.5 – 10	750
Moxifloxacin	7.5 – 10	400

*For MDRTB, if isoniazid is prescribed higher dose of 15–20 mg/kg body weight/day is recommended and pyridoxine 5 - 10 mg daily need to be added.

Conventional Treatment for DR-TB in children
In children with rifampicin-resistant or multidrug-resistant TB, a regimen with at least five effective TB medicines during the intensive phase is recommended, including pyrazinamide and four core second-line TB medicines: one chosen from group A, at least two from group C and agents from group D1 or group D3 may be added to bring the total to five.

The following assessment of the child should be undertaken during each clinic visits:
- symptom assessment
- assessment of treatment adherence
- enquiry about any adverse events
- weight measurement
- dosages should be adjusted to account for any weight gain during follow-up visits.

10. DR-TB AND HIV INFECTION

HIV is a significant risk factor for all forms of TB, both drug-susceptible and drug-resistant. The presence of HIV coinfection makes the prevention, diagnosis and treatment of DR-TB more challenging, especially in MDR- and XDR-TB.

HIV infected patients are more likely to have smear-negative TB or extrapulmonary TB (including MDR-TB and XDR-TB).
DR-TB is associated with higher mortality rates in the HIV-infected patients

Early diagnosis of the DR-TB and HIV infection, prompt treatment with appropriate 2nd line anti-TB drugs, timely initiation of antiretroviral therapy, strong infection control measures and good social support are all crucial components in management of DR-TB in people living with HIV.

For patients with advanced HIV disease, mycobacterial culture of sputum and other fluids (e.g. blood, pleural fluid, ascitic fluid, cerebrospinal fluid and bone-marrow aspirates) and histopathology (e.g. lymph node biopsies) are helpful in diagnosis.

ART is recommended for all patients with HIV and DR TB requiring second-line anti-TB drugs, irrespective of CD4 cell-count, as early as possible (within the first 8 weeks) following initiation of anti-TB treatment

A common first line ART regime used in HIV infected patients with MDR-TB is AZT + 3TC + EFV. TDF is generally avoided due to the overlapping renal toxicity with the injectables, but AZT (anaemia) and d4T (peripheral neuropathy) have even more common side effects that may make them unsuitable for some MDR- and XDR-TB patients. If TDF is used, additional monitoring of renal function and electrolytes is indicated.

Immune reconstitute inflammatory syndrome (IRIS) is an augmented inflammatory response that occurs in patients commenced on HAART and anti-TB drugs.
IRIS generally presents within three months of the initiation of ART and is more common with a low CD4 cell count (<50 cells/mm3).
This syndrome can present as a paradoxical worsening of the patient's clinical status

The treatment of DR-TB in patients with HIV is very similar to that in patients without HIV, with the following exceptions: the need of ART and possibility of IRIS, the potential drug-drug interaction between ART and anti-TB drugs and more frequent adverse effects requiring more intense monitoring.

People living with HIV need to be given the same consideration for treatment with the shorter MDR-TB treatment regimen as people who are HIV seronegative.

The composition of the treatment regimen for MDR-TB does not differ for people living with HIV. However, thioacetazone should not be given to patients who are HIV positive; if it is being considered as part of a treatment regimen HIV infection needs to be reliably excluded in the patient.

Recommendation 15

- Provider-initiated HIV testing and counselling should be performed in all TB suspects
- Mycobacterial cultures should be sent. DST should be done at the start of anti-TB to avoid mortality due to unrecognized DR-TB in HIV-infected patients
- Xpert MTB/RIF should be used as the initial diagnostic test in HIV- associated TB (WHO 2014)
- The extent (or prevalence) of anti-TB drug resistance in HIV-infected patients should be determined
- Antiretroviral therapy should be initiated promptly in DR-TB/HIV patients, irrespective of CD4 cell-count, within the first 8 weeks of starting anti-TB drugs (WHO 2011, 2014)
- Co-trimoxazole preventive therapy (CPT) should be provided to all HIV- infected patients with active TB
- Additional nutritional and socioeconomic support may be implemented
- Effective infection control measures should be ensured
- Overlapping toxicities with ART and DR-TB therapy should be closely monitored

For drug- drug interaction summary and potential overlapping and additive toxicities of ART and anti-TB treatment refer to Appendix 5.

11. INITIATING TREATMENT AND MONITORING OF TREATMENT

Proper treatment initiation is crucial in ensuring the success of DR-TB treatment. It requires collaboration of medical doctors, patient,family members and public health personel. One should anticipate multiple medical and social issues in patient with DR-TB. Proper treatment initiation includes:

i. Medical evaluation.
ii. Counseling of patient.

11.1 Initial medical evaluation

Pretreatment assessment should be systematically conducted on all patients to identify those at risk of adverse effects and poor outcomes, and to establish a baseline information.
The required initial pretreatment clinical investigation includes a thorough medical history and physical examination. The conditions to be screened for at initial medical evaluation are presented in Table 16.

Table 16: Conditions to be screened for at initial medical evaluation

• HIV infection	• Acute or chronic liver disease	• Pregnancy
• Diabetes mellitus		• Breast feeding
• Hypertension	• Mental illness	• Seizures
• Renal insufficiency	• Drug or alcohol dependency	• Malnutrition
• Thyroid diseases		

All patients starting MDR-TB treatment should have the following examinations done:

i. Weight and height
ii. Chest radiograph
iii. Acid-fast smear, mycobacterial cultures and DST to both first- and second-line drugs
    - The initial evaluation may require a repeat or confirmation DST, or further DST for other anti-TB drugs.
    - For a patient to be considered bacteriologically positive, a culture, or molecular test or sputum smear must be positive at the start of DR-TB treatment.
    - The collection date of the sample should be less than 30 days before, or maximum seven days after the initiation of - DR-TB treatment. Specimens collected prior to start of treatment are preferred
iv. Full blood count, renal, electrolytes (potassium, magnesium and calcium) and liver function test, thyroid function test and HIV testing
v. Pregnancy test for women of childbearing age
    - Methods of preventing pregnancy during treatment for women of childbearing age should be discussed and agreed upon with the patient during the initial visit
vi. Audiometry
vii. Electrocardiogram
viii. Baseline psychosocial assessment by trained personnel in the skills of psychosocial management during MDR-TB treatment

11.2 Counseling of the patient for treatment and education

Preparing the patient for treatment involves educating the patient and family, including the understanding of disease, drugs used, length of treatment, possible side effects and support that will be available for the patient. It also includes information on how the patient can protect his/her family and household members from getting TB. Educating the patient should ultimately help the patient obtain better adherence.

Patient education takes place over several visits with different health care providers. There should be a well-formulated plan on how to educate both the patient and their family/care givers so that they have complete information.Table 17 provides a short checklist for the health care provider to help best prepare the patient for treatment.

Table 17: Clinician checklist to go over with the patient before treatment starts

- Discuss where treatment will start. If at a hospital, estimate the approximate length of stay. If at home ask about the home living situation and whether or not the patient feels home treatment will be possible.
- Inform the patient the about the length of treatment; that it will be for at least 20 months but may be longer.
- Educate the patient about the drugs and possible side effects: there are at least five anti-TB drugs, of which one is an injectable agent. Inform patients that they must report any side effects of the medications immediately.
- Educate the patient about monitoring requirements for smear, culture and laboratory tests.
- Make a follow-up plan for seeing the doctor and inform the patient if he/she has problems they should be seen sooner. Make sure they know how to make an appointment if they need to be seen before the next routine visit.
- Instruct patients what to do in case of an emergency (like severe shortness of breath).
- Educate patients how DR-TB can be transmitted and some basics about household infection control. The patient is most infectious during the first few days or weeks of treatment when he/she is still smear positive.
- Windows and doors should be left open in the home to increase ventilation.
- A smear positive patient should wear a surgical or cloth mask at all possible times.
- it is safer to visit with family and friends if the patient is outdoors in the open air.

11.3 Monitoring treatment response

Monitoring response to treatment is done through regular history taking, physical examination, chest radiograph and laboratory monitoring. The classic symptoms of TB – cough, sputum production, fever and weight loss – generally improve within the first few weeks. Persistence of these classical symptoms may suggest treatment failure, but at times can persist in patients with extensive lung damage despite culture conversion.

The chest radiograph may appear unchanged in the first few months of treatment or show only slight improvement, especially in patients with chronic pulmonary lesions. Chest radiographs should be taken at least every six months or when indicated:

- to document progress
- to use for comparison if the patient's clinical condition changes

Monthly monitoring of sputum smears and cultures throughout treatment enables the programme to timely identify conversion or failure to convert. The most important evidence of improvement is conversion of the sputum culture to negative. Sputum smear is still useful due to its shorter turnaround time. Delayed detection of failure can increase transmission and increase the probability of acquisition resistance to the patient's strain, making it harder to cure the patient after failure.

Recommendation 16

- The use of sputum smear microscopy and culture rather than sputum smear microscopy alone is recommended for the monitoring of patients with multidrug- resistant TB (MDR-TB) during treatment.

Culture conversion should not be taken as equivalent to cure. Monthly sputum smear and TB culture should continue to be performed during maintanence phase. This is because Initial culture conversion is not always maintained. Some patients can have culture reversion in a later date.

Molecular tests such as Xpert MTB/RIF and line probe assays should not be used to monitor response to treatment.

DST can be repeated for patients who remain smear and culture positive or who are suspects for treatment failure. In such cases, it is usually not necessary to repeat DST within less than two to three months of the previous DST.

A key component of monitoring the progress of treatment is patient-centred DOT. All treatment should be given under daily DOT and DOT providers should be trained on the symptoms of adverse effects and treatment failure.

Table 18 summarizes the activities for monitoring treatment response.

Table 18: Activities for monitoring treatment response

Monitoring evaluation	Recommended frequency
Evaluation by clinician	*During the intensive phase*: • Every day during the first week if hospitalized and at least every week if treated as an outpatient,until the treatment is well tolerated. • Once stable the patient is seen at least once a month. *During the maintanence phase*: • Monthly assessment unless there is a medical necessity to see the patient more often. • The DOT supporter sees the patient daily between consultations and signals any concerns to the clinician.
Treatment adherence and tolerance	Daily at every DOT encounter by the DOT provider.
Sputum smears and culture	Monthly thoughout the treatment period.

Weight	At baseline, then every two weeks for first three months and then monthly.
Height	At start of treatment for all (to be able to assess BMI throughout treatment); monthly for children (to assess growth).
DST	At baseline for first- and second-line anti-TB drugs. Repeat DST for patients who remain culture-positive or revert after month four.
Chest radiograph	At baseline, and then every six months unless otherwise indicated.

Follow-up schedule for clinical and laboratory follow-up for uncomplicated MDR-TB patients is shown in Table 19.

More frequent screening may be advisable for certain types of patients as below:

i. Creatinine and potassium may be done more frequently in the elderly, DM, HIV coinfected, and those with pre-existing renal disease.

ii. Liver function tests may be done every 1-3 weeks in patients with active liver disease.

iii. TSH shoud be done every three months if receiving ethionamide/prothionamide and p-aminosalicylic acid (PAS), otherwise every six months if receiving ethionamide/ prothionamide or PAS, but not both together. Monthly monitoring for clinical signs/symptoms of hypothyroidism is also necessary.

iv. Regular HIV serology testing in high HIV prevalence settings.

v. Monitoring of adverse effects of other specific drugs should be carried out as required.

MDR-TB treatment chart can be used during follow up (refer appendix 6).

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

Review patient for history and physical examination. Checks sputum culture six monthly for two years after completion date to evaluate for possible recurrence.

Table 19: Follow-up schedule for uncomplicated MDR-TB patients

Month	Clinical Consultation	Weight	Smear	Culture	DST	Chest Radiograph	LFT	Cr, K	TSH	Audiometry	HIV Testing
0 (baseline)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
1	Every day in the first week then monthly once stable	✓	✓	✓			✓	✓		✓	Repeat if indicated
2		✓	✓	✓			✓	✓		✓	
3		✓	✓	✓			✓	✓	✓	✓	
4	Monthly	✓	✓	✓	If culture pos.		✓	✓		✓	
5		✓	✓	✓			✓	✓		✓	
6		✓	✓	✓	If culture pos.	✓	✓	✓	✓	✓	
7		✓	✓	✓			✓	✓		✓	
8		✓	✓	✓	If culture pos.		✓	✓		✓	
9		✓	✓	✓			✓	If on inj.		If on inj.	
10		✓	✓	✓	If culture pos.		✓	If on inj.		If on inj.	
11		✓	✓	✓			✓	If on inj.		If on inj.	
12		✓	✓	✓	If culture pos.	✓	✓	If on inj.	✓	If on inj.	
Until completion		Monthly	Monthly	Monthly	If culture pos.	Six monthly	Monthly		Six monthly		

Abbreviations: pos. = positive; inj = injectable drug; LFT = liver function testing (liver enzymes); Cr = creatinine; K = potassium.

12. MANAGEMENT OF ADVERSE EFFECTS

Up to 70% of patients developed some forms of adverse effects from the MDRTB treatment. Some patients may need treatment interrupted or modified due to adverse effect. Managing adverse reaction is vital to ensure success to treatment. Ignoring patient's compliant on adverse drug effect will only leads to non-compliant and failure of treatment.

12.1 Monitoring for adverse effects during treatment

Close monitoring of patients is necessary to ensure that the adverse effects of second-line anti-TB drugs are recognized quickly. All patients on second-line anti-TB drugs should be put under DOT. The major advantage of DOT is the ability to monitor adverse effect early, besides ensuring compliance.

All DOT providers should be trained to screen patients regularly for symptoms of common adverse effects. During each patient visit, a systematic method for screening of drugs adverse reaction should be done by DOT provider. Some common adverse drug events are listed in table 20.

Table 20: Common or relevant adverse effects of drug-resistant TB therapy

Nausea/vomiting	Abdominal pain	Visual disturbances
Diarrhoea	Anorexia	Seizures
Arthralgia	Gastritis	Hypothyroidism
Dizziness/vertigo	Peripheral neuropathy	Psychosis
Hearing disturbances	Depression	Suicidal ideation
Headache	Tinnitus	Hepatitis (hepatotoxicity)
Sleep disturbances	Allergic reaction	Renal failure (nephrotoxicity)
Electrolyte disturbances	Rash	QT prolongation

There are a number of relatively common toxicities that are complicated to monitor, and can be life threatening or very disabling to the patient; they necessitate extra attention in monitoring (refer to table 21).

Table 21: Common toxicities that is complicated to monitor and need extra attention in monitoring

Side effect	Comments
Nephrotoxicity	Cause by injectable agents (aminoglycosides and capreomycin) Risk factors: patient with low baseline Glomerular Filtration Rate (GFR), HIV, diabetes, concomitant administration of nephrotoxic agents and advanced age. Generally renal function should be done at least monthly. However, for those patients with higher risk, more frequent renal function should be done.
Electrolyte wasting	Late complication of injectable drugs, both aminoglycosides and capreomycin. Serum electrolyte should be monitor at least monthly.

Hypothyroidism	Cause by PAS and/or ethionamide/ prothionamide. Symptoms are subtle in the early stage. Patients should be routinely screened for hypothyroidism with a serum TSH at baseline and every three months for the first six months, then every six months thereafter
Ototoxicity	Due to injectable agents. Manifested by hearing loss, tinnitus and/or other vestibular symptoms, such as nystagmus, ataxia. Hearing loss begins at higher frequencies and progresses to low frequencies; speech freguency (lower frequency) is affected late. It is generally non-reversible. Audiometry for baseline and/or follow-up testing is required to pick up early hearing loss. It is recommended to do audiometry every month while on the injectable agent
Psychiatric disturbances	Psychosis and depression can result in thoughts of suicide and even suicide. Assessment of the patient's psychosocial condition should be performed monthly.

12.2 Management of adverse effects

Proper management of adverse effects begins with education of all stakeholders involved in treatment and care. Prompt evaluation, diagnosis and treatment of adverse effects are important, even if the adverse effect is not particularly dangerous. Patients may have significant fear and anxiety about an adverse effect if they do not understand why it is happening. These emotions can result in non-compliance to treatment.

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. The adverse effects of a number of second-line drugs are highly dose dependent. Reducing the dosage of the offending drug is another method of managing adverse effects but only in cases where the reduced dose is still expected to produce adequate serum levels and not compromise the regimen. Lowering the dose by more than one weight class should be avoided.

Temporarily suspending the offending drug can be tried initially to alleviate adverse effects. The offending drug can be re-introduced later if needed, in smaller dose initially and slowly titrate up to optimal dose to improve tolerability.

Suspending permanently the offending drug may be the last option in dealing with serious adverse effect. Usually required replacement with another effective agent. However, a satisfactory replacement may not be available, and this can resulting in lots of regimen efficacy, thus potentially treatment failure.

Some adverse effects may disappear or diminish with time, and patients may be able to continue receiving the drug if sufficiently motivated.

Pyridoxine (vitamin B6) should be given to all patients receiving cycloserine or terizidone to help prevent neurological adverse effects. The recommended dose is 50 mg for every 250 mg of cycloserine (or terizidone) prescribed. Appendix 7 summaries the common adverse effects, the likely responsible anti-TB drugs and the suggested management strategies for adverse effects.

13. TREATMENT DELIVERY AND COMMUNITY BASED DRUG-RESISTANT TB SUPPORT

Treatment adherence is one of the important factors to achieve successful DR-TB treatment. Although treatment has been provided at hospital and clinic settings, the delivery of such care and support at community-based setting or ambulatory care is now being emphasised. The multidisciplinary team involves community health workers (CHWs).
Adherence to therapy requires adequate support measures which include enablers and incentives:

- TB health education should include topic on adherence to therapy and continuously given throughout the course of treatment. The education can be provided by HCWs and the materials used are culturally-sensitive.
- DOT is a must in all DR-TB which can be provided by any trained and reliable supervisor in all settings. It should be patient and family friendly. Strict confidentiality should be maintained.
- Socioeconomic problems should be addressed to enable patients and families to adhere which include enablers and incentives
- Psychosocial and emotional support by multidisciplinary team should be offered to overcome stigma and adverse effects of long term treatment
- A workable system for monitoring and tracing for lost to follow up patient must be in place. The approach should be in a sympathetic and non-judgemental.

Patients with DR-TB are more likely to have history of non-adherence. Adherence is difficult because of prolonged treatment regimens, multiple drugs and adverse effects. The choice for treatment delivery setting should emphasise on steady drugs supply, free of charges and reliable network of educated providers.

13.1 Community based care

Community based care should be provided by the community or organizations where patient are given ambulatory treatment. CHWs need appropriate training, support, continuous supervision by health personnel, visit patient at home or workplace and ideally should not be a family member to prevent patient manipulation.

Recommendation 17

- ❖ State and District TB Organiser should use various strategies to improve treatment adherence such as
  - TB health education
  - DOT supervision
  - socioeconomic and emotional support
  - monitoring of adverse effects
- ❖ Ministry of Health and State Health Department should incorporate community-based care and support into their National/ State Strategic Plan for TB.

Community care supporter can be local health personnel, former or current patient, affected families, associations, cooperatives, grass root organisation, local NGOs, community volunteers and many more.

Function of Community Care Supporters

- Assist on treatment delivery, early detection and simple care for adverse reactions, prompt referral, and psychological support
- Ensure highly effective adherence through DOT by former patient or local community member.
- Assist contact tracing to improve new case detection and infection control.
- Promote health education on simple infection control practices at home
- Assist in recording and reporting of data within family and community assist in training using materials written in lay languages and peer educators.
- Involvement in giving support to reduce stigma. Identify socioeconomic and psychological needs and help to channel effective and timely support.

CHWs and community based support advocacy can facilitate patient access to hospital, during hospitalisation and when returning to ambulatory treatment. Ownership by the community supporters is more sustainable. Monitoring of CHWs should be done by health staff. A communications network should be clear and in place between community volunteers and health staff.

14. PALLIATIVE AND END-OF-LIFE CARE

Patients who their second-line anti-TB have been stopped because of treatment failure still need to be alleviated of their suffering and prevent further transmission.

14.1 Approach to suspending therapy

Medical therapy suspension is recommended when there are no more options of drugs to be prescribed and surgery is also not an option.
Three considerations that then need to be considered are:

- the patient's quality of life: Adverse effects from drugs of a failing regime may cause unnecessary suffering.
- the public health interest: Continuing a failing regime will create highly resistant strains that will infect others.
- the model of care available: The available resources to provide palliative care and infection control.

A multi-disciplinary team consisting of physicians, nurses, DOT providers, patients and their carers must come up with a plan that covers all the above.

14.2 Palliative and end-of-life care for patients in whom all the possibilities of treatment have failed

Palliative care delivery can be delivered either in a hospital, palliative care units and patient's home. The benefits for MDR-TB patients to receive palliative care are that it:

- provides relief from respiratory distress, pain and other symptoms;
- affirms life and regards dying as a normal process;
- intends neither to hasten nor to postpone death;
- integrates the psychological and spiritual aspects of patient care;
- offers a support system to help patients live as actively as possible until death;
- offers a support system to help the family cope during the patient's illness and in their own bereavement;
- uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated;
- enhances quality of life, and may also positively influence the course of illness; and
- is applicable early in the course of illness, in conjunction with second-line anti-TB medications, with the main therapy intended to prolong life through cure.

Supportive care measures are summarized in Table 22.

14.3 Infection control measures and domicile considerations for the end-of-life MDR-TB patient

Patients whom treatment has been stopped remain infectious. Environmental and Personal Protection measures must be in place. Particulate respirators (N95) masks must be used by care givers and health care providers.

Table 22: End of life supportive measures

- **Relief from dyspnoea.** Oxygen may be used to alleviate shortness of breath in some cases but there is no significant evidence to generalize its practice. Morphine provides significant relief from respiratory insufficiency and should be offered according to established clinical protocols available in the medical literature.
- **Relief from pain and other symptoms.** Paracetamol, or codeine with paracetamol, gives relief from moderate pain. If possible, stronger analgesics, including morphine, should be used when appropriate to keep the patient adequately comfortable. The WHO has developed analgesic guides, pain scales and a three step "ladder" for pain relief.
- **Infection control measures.** The patient who is taken off anti-TB treatment because of failure often remains infectious. Infection control measures should be continued with reinforcement of environmental and personal measures, including N-95 mask use for caregivers.
- **Nutritional support.** Small and frequent meals are often best for a person at the end of life. It should be accepted that the intake will reduce as the patient's condition deteriorates and during end-of-life care. Nausea and vomiting or any other conditions that interfere with nutritional support should be treated.
- **Regular medical visits.** When MDR-TB treatment stops, regular visits by health-care providers and the support team should be continued to address medical needs and ensure that infection control practices are being followed.
- **Continuation of ancillary medicines.** All necessary ancillary medications should be continued as needed. Codeine helps control cough, as well as pain. Other cough suppressants can be added. Bronchospasms can be controlled with a metre-dosed inhaler with a spacer or mask. Depression and anxiety, if present, should be addressed. Antiemetic's may still be needed and fever treated if the patient is uncomfortable.
- **Hospitalization, hospice care or nursing home care.** Having a patient die at home can be difficult for the family and the other way around. Home-based care should be offered to patients and families who want to keep the patient at home, whenever appropriate infection control practices can be followed. Institutionally based end of- life care should be available to those for whom home care is not feasible or desirable. Availability of respiratory isolation facilities is essential when a patient is transferred to institutionally based palliative care for medical reasons and the patient remains infectious.
- **Preventive measures.** Oral care, prevention of bedsores, bathing and prevention of muscle contractures are indicated in all patients. Regular scheduled movement of the bedridden patient is very important. Encourage patients to move their bodies in bed if able. Keeping beds dry and clean are also important.
- **Provide psychosocial support**. Psychological counselling to the patient and family caregivers is critical at this stage, especially to assist patients in the planning of decisions related with the end of life, and provide emotional support, especially in settings in which strong stigma is attached to the disease.
- **Respect for patient's beliefs and values at the end of life**. It is common for the patient and family caregivers to develop or increase their interest in spiritual and religious matters once they perceive that the end of life is approaching. The healthcare providers should respect those beliefs and should not impose personal values and practices that prevent the patient to seek and find comfort in the services delivered by faith-based organizations.

15. MANAGEMENT OF CONTACTS OF MDR/ XDR-TB PATIENTS

Contacts of MDR/XDR-TB patient are defined as people living in the same household, workplace or spending many hours a day together with the index case in the same indoor living space. However there is no universal definition on duration of exposure for close contacts or casual contact. Therefore, the operational definition for MDR/XDR-TB varies between regions, countries and states.

Close contacts are likely to be infected because they have a long and frequent exposure with infectious patient. They are also more likely to develop active TB because of their exposure. The investigation for the contacts of MDR/XDR-TB is to prevent the transmission of the resistant strain either inside or outside the home or at workplace so that they can be treated immediately. It also can provide the opportunity to educate the contacts about issues related to TB and MDR/XDR-TB

Management of MDR/XDR-TB contacts should be integrated into the Programmatic Management of MDR/XDR-TB. General considerations should be given to MDR/XDR-TB contacts:

- Screening for MDR-TB contact should be given high priority
- Screening for XDR-TB contact-should be considered as an emergency situation
- All contacts of MDR/XDR-TB patient should have a proper follow-up

All MDR/XDR-TB cases need urgent attention and therefore a structured programme for management of case and their contacts should be in place to contain the disease (containment phase).

Close contacts of MDR/XDR-TB are at high risk of being infected by the index case and developing active TB.

15.1 Management of contacts of MDR/XDR-TB patients

All contacts of MDR/XDR-TB patients must be identified promptly for evaluation of active TB disease. Close contacts of MDR/XDR-TB should be screened more aggressive than among those contacts of the drugs susceptible cases. Routine symptomatic and physical examination for all MDR/XDR-TB contacts including asking about productive cough, haemoptysis, fever, loss of appetite, loss of weight, night sweat and other sign and symptom of TB. Rapid test for rifampicin resistant (e.g. Xpert MTB/RIF) has a big role in contact management. It should be considered if there is an access to the service because active case can be treated and managed promptly. All close contacts must be followed up at least at intervals of 0, 3, 6, 12 months for two years (refer Figure 8).

Recommendation 18

- All MDR/XDR-TB contacts should be put under surveillance for at least two years and evaluated for active TB regularly (0, 3, 6, 12 months interval).

Recommendation 19

- Rapid test such as Xpert MTB/RIF is recommended for symptomatic MDR/XDR-TB contact as an initial diagnostic test because it provides diagnosis of TB and Rifampicin Resistant rapidly.

15.1.1 Contact screening for symptomatic adult contacts

Screening for MDR/XDR-TB contacts among symptomatic adult include:
- Clinical evaluation by history and physical examination
- Chest x-ray
- Sputum smear microscopy
- Sputum MTB culture & DST
- Rapid test such as Xpert MTB/RIF (if available)

Symptomatic contact with no evidence of active TB in the first screening needs to be referred to specialist for further assessment.

Bacteriological test is often challenging in suspected extrapulmonary TB. However, a chest x-ray and sputum culture and DST should be done if suspected of extrapulmonary TB since the contact may have a concomitant Pulmonary and extrapulmonary TB.

15.1.2 Contact screening for symptomatic paediatric contacts

MDR/XDR-TB close contact among children is at higher risk of infection and developing an active TB. Furthermore, diagnosis of active TB among children is more difficult and challenging because they may have nonspecific symptoms such as failure to thrive and recurrent fever. They must be followed-up for at least two years and treated promptly with recommended regimen if active disease develops *(MOH, 2012)*.
- Clinical evaluation by history and physical examination
- Chest x-ray
- TST
- Sputum smear microscopy
- Sputum MTB culture & DST
- Rapid test such as Xpert MTB/RIF (if available)

Young children often produced insufficient and poor quality of sputum samples. Gastric aspiration and sputum induction are widely used as they are more safe and effective. If any of the recommended tests are not available or the results are not conclusive, clinical judgement can still be used to make a diagnosis of MDR/XDR-TB among children. The presence of three or more symptoms and signs of the following should strongly suggest an active TB:
- Chronic symptoms suggestive of TB\Physical signs highly suggestive of TB
- A positive TST
- Chest x-ray suggestive if active TB

The subsequent follow-up and schedule for contacts among children is similar to an adult.

15.1.3 Contact screening for asymptomatic contacts

All asymptomatic contact should be screened with:
- Chest x-ray
- TST

Subsequent visit for asymptomatic contact with no evidence of active TB in the first screening will include repeat physical examination and chest x-ray at 3, 6, 12 months intervals.

15.2 Empirical treatment of MDR/XDR-TB contacts

Contacts who develop active TB should undergo rapid test such as Xpert MTB/RIF. They should be started on empirical regime that similar to index case or the most common regime in the community while waiting for the culture and DST result.

Recommendation 20
- MDR/XDR-TB contacts with active disease should be treated empirically with same anti-TB regimen as the index case.

15.2.1 Contacts with bacteriologically confirmed TB, without confirmation of MDR/XDR-TB

- MDR/XDR-TB contact may be infected with similar or different strain. However, most of the close contact is infected with the same MDR/XDR strain.
- Rapid molecular test should be performed to all bacteriologically confirmed contacts.
- In the absence of rapid molecular test, confirmation of drug resistance with conventional method may take weeks or months.
- These contacts should be treated empirically with same anti-TB regimen as the index case while pending DST.
- MDR/XDR-TB empirical treatment may include Isoniazide and Rifampicin base on clinical judgement by physician because it is easier to switch to first line anti-TB regimen if DST result showed pan-susceptible.
- However, ineffective regimen at long period may result in amplification of resistance or death.

15.2.2 Extrapulmonary TB contacts

- Certain Extrapulmonary TB is often culture negative. Therefore, contacts with extrapulmonary TB should be started empirically with MDR/XDR-TB regimen as the index case after collecting samples from suspected organs for histopathology examination, culture and DST.
- MDR/XDR-TB empirical treatment may include Isoniazide and Rifampicin base on clinical judgement by physician because it is easier to switch to first line antiTB regimen if DST result showed pan-susceptible.
- This is particularly important for HIV patients where most of the times are smear and culture negative. They are also at risk of developing severe forms of extrapulmonary TB that are highly fatal.

15.2.3 Culture negative TB contacts

- For MDR/XDR-TB contacts under 5 years, most are likely to be infected by same resistant mycobacterium strain of the index case.
- This is particularly important for contacts among children who often, had poor quality sputum samples.
- If the children fulfil the criteria for active TB, they should be considered for second-line treatment of MDR/XDR-TB based on the clinical judgement.

15.3 Chemoprophylaxis of contacts of MDR-TB index case

WHO does not recommend the universal use of second-line anti-TB drugs for chemoprophylaxis of MDR/XDR-TB contacts.

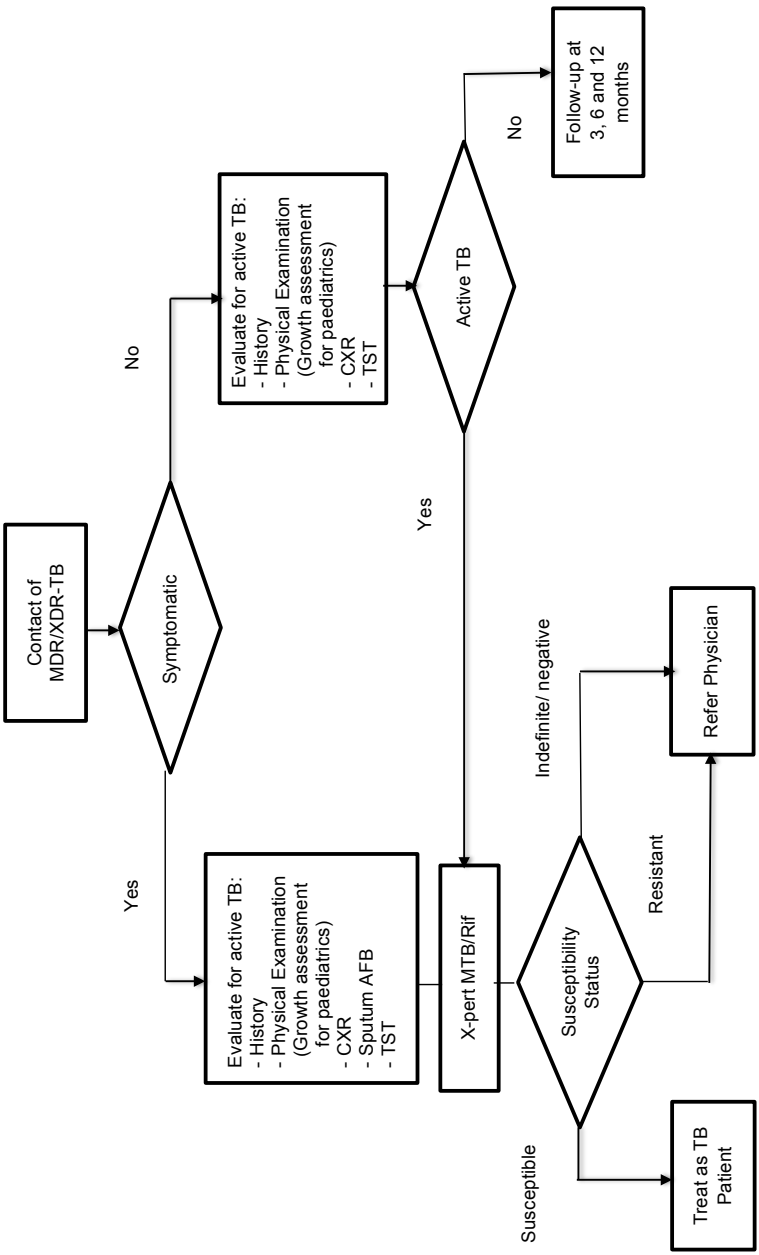


Fig.8. Algorithm for Investigations of MDR/XDRTB contacts

16. DRUG RESISTANCE AND INFECTION CONTROL

TB disease is transmissible, especially among highly vulnerable populations and congregate settings such as shelter home, dormitories, barracks, prison, drug rehabilitation centre, old folks home and immigration depot. MDR/XDR-TB patients may respond slower to treatment and remain sputum positive longer than other drug susceptible TB patients and because of that they may infect more contacts. All services attempting to treat MDR/XDR-TB should be in line with the current policies and strategies. This is to ensure infection control activities are in place to prevent transmission among patients, staff and community.

Infection control that consist of administrative, environment or engineering control and personal respiratory protection is a high priority in managing MDR/XDR-TB cases.

16.1 The infection control methods

16.1.1 Administrative control

The administrative control is the most effective and least expensive and therefore have highest priority in resource-constrained settings. These include policies and procedures.

- Development of steering committee for MDR/XDR-TB infection control at national and state level.
- Development of infection control committee representing key departments/ units at health care facilities or congregate settings.
- Ensure adequate budget and personnel is allocated for infection control activities.
- Formulation of a comprehensive infection control plan.
- Prompt identification of infectious cases, separation from other people at well ventilated waiting area, control the spread of microorganism, fast tracked for sputum examination and minimize time contact with health facility. All coughing patients should receive face masks and receive basic education about cough etiquette and hygiene.
- Identify high risk area for MDR/XDR-TB transmission and do the environmental risk assessment.
- Provide a full package of prevention and control intervention for health care providers including chemoprophylaxis for TB and HIV prevention.
- Development of medical surveillance program/ policy for MDR/XDR-TB to ensure environment is safe for health care provider to practice.
- Create a database of TB among Health Care Workers and follow through all cases especially MDR/XDR-TB.
- Training for all staff on infection control policies and procedures. Educating all health care providers and the community on MDR/XDR-TB infection control.
- Provide and encourage structured MDR/XDR-TB infection control advocacy, social mobilization and communication.
- Patients should be encouraged to spend as much time as possible outdoors.
- Encourage operational research.

DR-TB patients should be separated from immunosuppressive patient such as HIV, cancer, SLE, elderly, babies etc. They should be placed in isolation until non-infectious. In resource limited setting where isolation almost impossible, separation of these patients may help to reduce transmission.

16.1.2 Environment and engineering controls

In principle, we must assume that unsuspected, untreated TB patients will enter health facilities despite all efforts to identify them. Engineering control aims to reduce the concentration of infectious droplet nuclei in the air. These include the usage of natural and/or mechanical ventilation. The efficacy of all system, so much depending on number of air exchange and size of the spaces. However, environmental control should never replace administrative controls.

- Identification of most high risk settings: sputum induction rooms, bronchoscopy rooms, emergency department, evaluation rooms for newly admitted patients.
- Rooms/ building for management of MDR/XDR-TB should be designed without interior hallways.
- Waiting areas with natural ventilations should be open at least three sides.
- Air ventilation rate should be at least between six to 12 air changes per hour (ACH). reference
- Supplementation with ultraviolet germicidal irradiation (UVGI), high efficacy particulate air filtration (HEPA Filter) with regular PPM, standing/ wall fans, exhaust/ extraction fan may help when adequate natural ventilation cannot be achieved.

16.1.3 Personal respiratory protection

Administrative and engineering control cannot provide complete protection in most settings. The last line of defence for airborne disease is the use of personal respirators.

- Surgical mask is not adequate for prevention of MDR/XDR-TB infection.
- Masks that prevent TB transmission are known as ‘particulate respirators’ or simply respirators (e.g. N95, N99 or equivalent).
- Respirators should be “fit tested” for individual wearers and being taught how to put on their respirators correctly to prevent leakage/ minimize face-seal-leakage.
- Visitors should be provided with mask while visiting patients if they still infectious.

16.2 Practices at home

Effective infection control activities must also implement while patient at home.

- House should have adequate sunlight and ventilation, particularly where MDR/XDR-TB patient spend most of the time.
- All patients who cough should practice cough etiquette and respiratory hygiene all the time.
- Infectious patients should spend time outdoors as much as they can.
- Infectious patient should sleep in separate well ventilated room from other household members, including their spouse.
- HIV positive person should not provide care to MDR/XDR-TB patients or stay with them. They must wear N95 mask or equivalent if there is no other alternative (carer).

17. MANAGEMENT OF SECOND- LINE ANTITUBERCULOSIS DRUGS

Drug management of second-line anti-TB provides information on the procedures for procurement and management of the second-line drugs used in the treatment of DR-TB.

DR-TB must be managed appropriately in order to ensure that the correct medicines are selected, procured in the right quantities, distributed to treatment centres in a timely manner, handled and stored to maintain quality and availability of sufficient stocks, and used rationally by the health worker and patient alike. Figure 9 shows pharmaceutical management cycle of second-line anti-TB drugs.

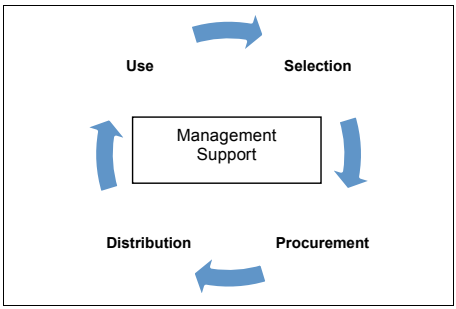


Fig. 9: Pharmaceutical Management Cycle

Description of key functions of the drug management cycle

Quantification: sometimes called forecasting quantification is a process used to estimate the amount of medicines and commodities needed by the national TB control programme for a period of time. Quantification is a key planning step to prepare and justify budgets for procurement. Procurement is timely acquisition of quality-assured anti-TB medicines and commodities at the best possible cost.

Distribution is the process by which medicines are receives at the port of entry, cleared through customs, transported from the central warehouse to storage and health facilities, store and maintained at warehouses and treatment centres.

Rational use refers to proper use of medicines to improve patient safety by providing comprehensive information on the use, dosage, adverse effects, contraindications, warnings and guidance on selecting the right medicines for TB patients.

17.1 Selection of anti-TB drugs for programmatic management of drug-resistant TB

The selection process for MDR-TB medicines differs considerably from the selection of first-line treatment because:

- A number of different regimens and medicines may be prescribed at the start of and within the treatment period due to the drug resistance patterns, availability affordability and long treatment periods (up to 20 months or more);

- The medicines are more toxic to patients, which frequently results in changes made to the original regimen prescribed;
- Only a limited supply of quality assured MDR-TB medicines (according to international Standards or WHO prequalification programme) is available; and medicines are much more expensive (up to 100 times more than drug-susceptible TB).

Factors to be considered when selecting second- line drugs include the efficacy of the drugs, the treatment strategy, possible adverse effects and the cost of the treatment.

17.2 Quantification and procurement

17.2.1 Quantification.

In order to procure appropriate quantities of these medicines, TB managers need to know how many patients are currently under different treatment regimens and how many patients are expected to be enrolled for each treatment regimen during the next planned procurement period.

The following formula is used for quantification for total drug requirement:

Total drug requirement = (consumption of new patients) + (consumption of ongoing patients) – (stock on hand)

Steps in forecasting of second-line anti-TB drug:

1. Obtain the following information and use the formula below to get the drug requirement for new patient enrolment:
   - Number of new patients enrolled
   - Treatment regimen being used and duration of treatment for both intensive and continuation phases (calculated in days per month x months of treatment)
   - Average daily dose per drug
   - Percentage (%) of utilization per drug

17.2.2 Procurement

Effective management of procurement ensures the availability of selected drugs of assured standards of quality, in the right quantities, at the right time and at affordable prices. In instances where an unregistered drug may need to be used, an application will need to be submitted to the Pharmaceutical Services Division for the issuance of an Import Permit before the drug can be imported into the country.

Elements to consider when planning procurement of second-line antituberculosis drugs

- Drug forecast based on treatment regimen, cohort size and pace of patient enrolment
- Drug registration status of products selected
- Drug labeling
- Shelf-life of the products
- Lead-time for delivery of the drug request
- Estimated size of buffer stock (2–3 times the delivery delay)

17.3 Drug distribution, storage and ordering

Distribution is the process by which medicines are received at the port of entry, cleared through customs, transported to the central warehouse and distributed to health centres. During this process, second-line anti-TB drugs can be stored at different warehouses and treatment centres.

Ordering medicines can occur in two ways – *push* and *pull* depending on whether the order is placed by the treatment centre (pull) or whether the order quantities are decided by the TB coordinator (push) at the district or national level. When placing orders, a standardized form should be used so that medicines, strengths and dosage forms are correct for the treatment regimens established by the TB programme.

17.4 Rational medicine use and adherence

In the specific case of DR-TB treatment, the best way to implement a rational use of drugs is to follow the treatment recommendations. This will ensure the maximum benefit to the patients and to the health programme at the same time. This has to be complemented with full adherence to a properly prescribed treatment. From a drug management perspective, the health worker should check that the patient knows at least the following about their treatment:

- Name of their TB medicines
- Number of tablets in one dose
- Number of doses to take per day
- When to return to the TB centre for more medicines
- Need to report to the health care provider any adverse reactions that are encountered while taking second-line anti-TB drugs.

A structured pharmacovigilance system in the programme is encouraged to ensure patients' safety and proper management of any side effects. If adverse reactions are encountered, these should be recorded in the patient's case note and reported using the Adverse Drug Reaction (ADR) form.

18. DR-TB RECORDING AND REPORTING SYSTEM

The organization of information on drug-resistant patients facilitates the:

- standardization of patient data for registration;
- assignment of appropriate treatment regimens;
- monitoring of detection, patient enrolment and treatment and
- surveillance of drug resistance.

The DR-TB information system allows NTP managers to follow trends in the number of DR-TB cases notified and monitor overall programme performance.

Recommendation 21

- A standardised method of recording and reporting should be implemented in DR-TB control programmes.
- DR-TB treatment cards should have an expanded section for information on patients with HIV.

18.1 Registration of information on drug-resistant TB cases

Comprehensive DRTB information system consists of four main forms/registers as follow;

i. Second-line TB treatment card
ii. Second-line TB treatment register
iii. Request for examination of biological specimen for TB
iv. Laboratory register for culture, Xpert MTB/RIF and DST

The details of each forms/ registers which were adapted with slight modification from WHO template (PMDT 2008) and explained in a separate guideline.

18.2 Indicators for monitoring drug-resistant TB programmes

Four sets of indicators on detection, enrolment, interim results and final outcomes are used for programme management.

i. Detection indicators

- TB patients with result for isoniazid and rifampicin DST
- Confirmed MDR-TB cases detected among TB patients tested for susceptibility to isoniazid and rifampicin
- Confirmed MDR-TB cases tested for susceptibility to any fluoroquinolone and any second-line injectable drug
- Confirmed XDR-TB cases detected among MDR-TB patients tested for susceptibility to any fluoroquinolone and any second-line injectable drug
- Interval between presumption of RR-/MDR-TB and DST results

ii. Enrolment indicators

- RR-/MDR-TB cases (presumptive or confirmed) enrolled on MDR-TB treatment
- Confirmed RR-/MDR-TB cases enrolled on MDR-TB treatment regimen
- Confirmed XDR-TB cases enrolled on XDR-TB treatment regimen
- Interval between RR-/MDR-TB diagnosis and start of MDR-TB treatment

iii. Interim results indicators

- RR-/MDR-TB cases on MDR-TB treatment regimen with negative culture by six months.
- RR-/MDR-TB cases on MDR-TB treatment regimen who died by six months.
- RR-/MDR-TB cases on MDR-TB treatment regimen who were lost to follow-up by six months.
- Patients on MDR-TB treatment regimen found not to have RR-/MDR-TB.
- Patients on XDR-TB treatment regimen found not to have XDR-TB.

iv. Final outcomes indicator

- RR-/MDR-TB cases on MDR-TB treatment regimen with an outcome:
  （Cured, treatment completed, treatment failed, died, lost to follow-up, not evaluated)
  (Refer appendix 8).

19. MANAGING DR-TB THROUGH PATIENT-CENTRED CARE

MDR-TB often inflicts the poorest and most marginalized members of a society. Their quality of life and financial situation are further aggravated by the disease, due to the adverse drug reactions produced by its treatment, the catastrophic costs they incur while seeking care and adhering to treatment and the stigma attached to the disease and subsequent discrimination.

The delivery of social support services is important and runs parallel with the efforts to prevent and treat MDR-TB.

Social support may also contribute to improving the quality of life of patients. In many cases it also makes a difference to enable the patient and family to access health care.

In this chapter the patient-centred care approach to directly observation of therapy and the social support framework for programmatic management of drug-resistant TB are discussed.

19.1 Patient-centred care and its role in DOT

Adherence to DR- TB treatment is essential for cure. It is particularly difficult because of the current lengthy recommended treatment regimens, the daily high pill burden, the frequent and serious drug adverse reactions, and the indirect social and economic costs to patients associated with access to care. Thus, MDR-TB patients are at increased risk of poor adherence to treatment.

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

Given that MDR-TB and extensively drug-resistant TB (XDR-TB) treatment are often the last therapeutic option for many patients and that there are serious public health consequences if treatment fails, it is advisable that all patients receive medicines under DOT as a way to ensure full adherence to treatment.

Recommendation 22

- Patient-centred approach to treatment should be developed for all patients in order to promote adherence and improve quality of life. This approach should be based on the patient's needs and mutual respect between the patient and the provider.

19.2 Social support in MDR-TB management

Social support refers to the person's perception and confirmation that he/she is part of a social network that cares for him/her. A large body of evidence has confirmed that social support is a predictor of health status and mortality. Social support is determined by access to four resources:

i. Informational support refers to any useful information that helps a person to solve problems.
ii. Emotional support refers to all expressions of care that contribute to strengthen self-esteem through empathy, trust, encouragement and care, and helps with the psychological challenges in life.
iii. Companionship support refers to the help that makes a person feel that he or she belongs to the social network, and that he or she can rely on it for certain needs.
iv. Financial support as assistance to deal with daily hurdles.

19.2.1 Information support on the disease

All patients and their primary caretaker(s) should receive education about DR-TB and its treatment and the need for adherence to therapy. Information and education interventions should commence as soon as diagnosis is made and continue throughout the course of treatment. Education can be provided by: physicians, nurses, community health workers and other health-care providers. Materials should be appropriate to the literacy levels of the patient and should be gender, age and culturally sensitive.

Tips for delivering key information to the MDR-TB patient

- Always use a venue that guarantees confidentiality in communication.
- Use language that reassures mutual respect and esteem between the patient, caregivers and health-care providers.
- Do not make promises that the health-care service cannot keep.
- Avoid arguments and any discriminatory remarks for whatever conditions the patient has.
- Respect the patient's right to choose.
- Teach the patient how DR-TB can be transmitted (long exposure to contaminated air in crowded conditions), how it cannot be transmitted (sexual relations, kisses, sharing cutlery and clothes, etc.), and teach the essentials about household infection control measures
- While respecting patient's religious beliefs explore proactively and clarify wrong notions the patient may have about the disease and its treatment, especially those that may become barriers to adhere to treatment.
- Enable the patient to counteract stigma and discrimination by reassuring that his/ her disease is not the result of any socially or morally inappropriate behaviour that he/she has made in the past; and that many other patients have passed successfully through a similar experience

19.2.2 Information support on MDR-TB treatment

There should be a well-formulated plan for preparing the patient for treatment. This includes educating the patient and caretaker on the use of drugs, length of treatment, possible side effects, and mechanisms to access support that will be available to the patient. Patient information and education takes place over several visits with different health-care providers (from the DOT provider to the physician). Information and educational pamphlets with reminders of the main points, in the local language, are helpful.

Checklist of information and education issues to provide to patient and family caregivers before starting MDR-TB treatment

- Inform the patient about the length of treatment according to the regimen selected – often at least 20 months, but it may be shorter or longer.
- Discuss where treatment will start. If at a hospital, estimate the approximate length of time. If at home, ask about the home living situation and whether or not the patient feels home treatment will be possible.
- Teach the patient about the drugs in general terms: i.e. there are at least five different anti-TB drugs, which the patient will take, of which one is an injectable agent. Try to teach the names of the drugs and show what the pills look like.
- Teach the patient about possible side effects and the actions to take once detected, including reporting to the DOT provider, especially those with serious consequences like any hearing loss, ringing in the ears or suicidal ideation.
- Teach the patient about monitoring requirements for smear, culture and laboratory tests for early detection of side effects.
- Make sure that patients and caregivers know how to make an appointment if they need to be seen before the next routine visit.
- Make sure they know that the DOT provider can contact a doctor urgently at any time of the day.
- Instruct them what to do in case of an emergency (like severe shortness of breath, seizure, etc.)
- Always provide a copy of the TB Patient Charter, informing the patients about their rights and responsibilities related with the treatment and prevention and control of TB;
- Inform patient and family caregivers on social support and social protection options the patient is eligible for according to the existing law in the country, including palliative and end-of-life care as needed.

19.2.3 Emotional support

Having MDR-TB can be an emotionally devastating experience for patients and their social networks. Considerable stigma is attached to the disease, and this may interfere with adherence to therapy, and may badly affect the quality of life of patients in view of the discrimination that follows stigma.

The provision of emotional support services to patients may increase the likelihood of therapy adherence, and the acquisition of skills to deal with stigma and discrimination. This support may be organized in the form of support groups or in one-to one counselling by trained providers.

Informal support can also be provided by physicians, nurses, DOT providers, drug-resistant TB supporters and family members. The establishment of support groups may allow patients with drug-resistant TB to meet and socialize with other patients and provide emotional support to each other.

Psychological support to MDR-TB patients through peer-to-peer and group support

- A counsellor, social worker or someone trained in facilitating support groups should facilitate the meeting. A trained drug-resistant TB community nurse or health worker may co-facilitate the group
- Clear eligibility criteria should be created for participation in each support group:
- Participation should be generally reserved for patients who are sputum negative and are no longer infectious, especially if the meeting cannot take place in an open space.

- Cured patients may also be invited to support groups, as they provide hope to patients who are still on treatment.
- Some groups may be reserved for patients with serious psychosocial issues and may require a facilitator with psychiatric training.
- Other groups may be largely self-organized and appropriate only for patients without psychiatric issues.
- Support groups may need help in inviting participants, finding a safe meeting place and other organizational issues.
- At the end of each support group meeting, the facilitator and co-facilitator should stay behind to discuss and analyse the lessons learned in the process and plan the next session.

19.2.4 Material support

Poverty, depression, stigmatization, discrimination and perceived isolation are common among drug-resistant TB patients. Socioeconomic problems – not only hunger, homelessness and unemployment, but also family responsibilities – should be addressed to enable patients and their families to adhere to MDR-TB treatment and reduce the impact that the disease and treatment have on their quality of life. Needy patient can be referred to relevant agencies for financial support and assistance.

19.2.5 Companionship support

On-site social support for patients and their support networks through peer counselling can help to contribute to the effectiveness of TB programmes. These “community champions/expert patients” would follow each patient from diagnosis through to cure, and they would act as both “friend” and educator. From the patient’s perspective, having this companion available greatly reduces the psychological burden of the long duration of treatment and provides them with skills to cope with TB stigma and discrimination.

19.3 Planning and managing social support for MDR-TB patients

In order to support people with drug-resistant TB during their treatment, health policy and practice must appreciate that TB affects all aspects of patients’ lives. A focus on caring for each patient as an individual should underlie all aspects of treatment and care. Overall, the following principles can be followed for good care and support:

i. Develop a treatment partnership with your patient.
ii. Focus on your patient’s concerns and priorities.
iii. Use the 5 A’s: Assess, Advise, Agree, Assist and Arrange
iv. Link the patient with a “DOT provider” for MDR-TB regimens supporter.
v. Support patient self-management, as it relates to personal care and needs.
vi. Organize proactive follow-up care.
vii. Involve “expert patients,” peer educators and support staff in your health facility.
viii. Link the patient to community-based resources and support.
ix. Use written information – registers, treatment plans, treatment cards and written Information for patients – for documenting, monitoring and reminding.
x. Work as a team.
xi. Assure continuity of care.

19.4 Adherence monitoring and the follow-up of the non-adherent patient

When a patient fails to attend a DOT appointment or refuses to take their medicines, a system should be in place that allows prompt patient follow-up. Most commonly, this system will involve the drug-resistant TB clinic or community nurse, doctor or supervisor assisting the drug-resistant TB DOT supporter by visiting the patient's home the same day to find out why the patient has defaulted and ensure that treatment is resumed promptly and effectively. The situation should be addressed in a sympathetic, friendly and non-judgmental manner. Every effort should be made to listen to the patient's reasons for missing a dose(s) and to work with the patient and the family to ensure continuation of treatment.

The following steps should be taken for patients showing any signs of possible poor adherence:

- Home visit by the health-care provider involved in the drug-resistant TB programme: The drug-resistant TB clinic or community nurse, doctor or supervisor should visit the home of the patient together with, or in addition to, the drug-resistant TB DOT supporter, as during the home visit it may be possible to identify more clinical problems than during the monthly clinic evaluation.
- Manage side effects: This is one of the most common reasons for the MDR-TB patient to be lost to follow-up.
- Counselling: The patient may no longer want to continue treatment because he/she feels better, and therefore, feels treatment is no longer necessary. Additionally, the patient's perspective about his/her care should be assessed. The patient may have greater confidence in alternative or folk medicine. If this is the case, the drug-resistant TB DOT supporter, along with a nurse, doctor or community supervisor, should explore ways in which to meet the patient's needs, all the while putting them back on treatment.
- Address economic problems: Many patients are unable to work when they are ill, and may be the primary wage earners for their family. An assessment related to basic housing, food and clothing needs should be explored and ways to assist with these issues addressed.
- Address addiction or other social problems: Alcohol consumption and drug abuse are known issues, which affect treatment adherence. Patients should be encouraged to stop or decrease consumption.
- Involve the family: Family is the most important source of psychosocial support for the patient. When a patient has no family, have the patient identify a person who can act as a caregiver.
- Involve community leaders: Community and religious leaders can be helpful if there are community-wide issues, such as stigma towards drug-resistant TB patients. This option is not always available if the patient desires to keep his or her health status confidential.

20. IMPLEMENTING THE GUIDELINES

Implementation of CPG is important as it helps in providing quality healthcare services based on best available evidence applied to local scenario and expertise. Various factors and resource implications should be considered for the success of the uptake in the CPG recommendations.

20.1 Facilitating and Limiting Factors

The facilitating factors in implementing the CPG are:
- availability of CPG to healthcare providers (hardcopies and softcopies)
- regular conferences and updates on management of DR-TB

Limiting factors in the CPG implementation include:
- limited awareness in management and referral of DR-TB among healthcare providers
- inadequate DR-TB training at all levels of healthcare providers
- variation in DR-TB treatment at different levels of care due to administrative and financial constraints

20.2 Potential Resource Implications

To implement the CPG, there must be strong commitments to:
- ensure widespread distribution of CPG to healthcare providers via printed copies and online accessibility
- reinforce training of healthcare providers via regular seminars and workshops
- involve multidisciplinary team at all levels
- improve the diagnostic and therapeutic facilities, and trained experts
- strengthen the DR-TBIS registry

To assist in the implementation of the CPG, the following is indicator for monitoring of DR-TB control programme:

'Treatment success rate, laboratory confirmed MDR-TB cases whom started 2nd line TB treatment: 80%'. The formula is as below;

$$\left(\frac{\text{No of MDR-TB cases with treatment outcome cured and completed treatment}}{\text{No of MDR-TB cases}} \times 100 \right)$$

Implementation strategies will be developed following the approval of the CPG by MOH, which include Quick Reference and Training Module.

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APPENDIX 1

CLINICAL QUESTIONS

1. Who are at high risk for DR TB?
2. Who should undergo rapid drug susceptibility testing?
3. What are the effective and safe treatment strategies in DR TB?
4. What are the key components in designing a treatment regimen in DR TB?
5. What is the effective and safe treatment option of MDR TB and XDR TB?
6. What is the effective and safe (optimum) duration of MDR TB and XDR TB treatment?
7. What is the effective method to monitor patients on MDRTB and XDR TB treatment?
8. Can MDRTB and XDR TB patients be managed effectively in the ambulatory setting?
9. How should contacts of patients with MDR/XDR TB be screened and managed effectively?
10. What are the effective and safe treatment regimens for mono and poly-drug-resistant TB?
11. What is the optimal management of DR TB in special situation?
    a) Children
    b) Pregnancy and breastfeeding
    c) Renal Insufficiencies
    d) Liver disorders
12. How to treat patients with HIV and DR TB receiving HAART effectively?
13. How to identify and manage MDRTB and XDR TB treatment failure effectively?
14. What is the effective surveillance system for DR TB?

APPENDIX 2

Cost Comparison for MDR-TB treatment

Conventional Treatment-20 months (609 days) 8 months intensive, 12 months maintenance				
Name	**Dose and frequency**	**Price /tab (RM)**	**Cost /patient (RM)**	**Note**
IVKanamycin 1g	900mg od	4.76	1113.84	234 days for 8months (5x/ week) -Intensive phase
T. Ethionamide 250mg	250mg bd	2.1	2557.8	
T.Cycloserine 250mg	250mg bd	6.35	7734.3	
T.Levofloxacin 500mg	750mg od	0.93	849.6	
T.Pyrazinamide 500mg	1500mg od	0.16	292.32	
T.Pyridoxine 10mg	50mg od	0.024	73.08	
TOTAL			**12,620.94**	
Short Course MDRTB Regimen-9 months (274 days) 5 months intensive. 4 months maintenance				
Intensive phase (5 months -152days)				
Name	**Dose and frequency**	**Price /tab (RM)**	**Cost /patient (RM)**	**Note**
T.Moxifloxacin 400mg	400mg od	7.96	1209.92	
T.Pyrazinamide 500mg	1500mg od	0.16	72.96	
IM Kanamycin 1g od	900mg od	4.76	523.6	110 days for 5 months (5x /week)
High dose Isoniazid 100mg	1000mg od	0.2	304	
T.Ethionamide 250mg	500mg om 250 on	2.1	957.6	
T.Clofazimine 50mg	200mg od	1.5	630	200mg x2/12 then 100mg od 3/12
T.Cycloserine 250mg	500mg 250mg	6.35	2895.6	
T.Pyridoxine 10mg	100mg od	0.024	36.48	
TOTAL			**6,630.16**	
Maintenance Phase (4 months-122days)				
Name	**Dose and frequency**	**Price /tab (RM)**	**Cost /patient (RM)**	**Note**
T.Moxifloxacin 400mg	400mg od	7.96	971.12	
T.Pyrazinamide 500mg	1500mg od	0.16	58.56	
T.Clofazimine 50mg	100mg od	1.5	360	4 months
T.Ethambutol 400mg	1000mg od	0.5	152.5	
TOTAL			**1,542.18**	
GRAND TOTAL			**8,172.34**	

Cost Saved with Short Course MDRTB treatment = RM 4449.60

APPENDIX 3

Indication for GeneXpert MTB/RIF Test (WHO, 2013)

No	Indication for GeneXpert MTB/RIF Test	Remark
1.	GeneXpert MTB/RIF **should** be used rather than conventional microscopy, culture and DST as the initial diagnostic test in adults suspected of having MDR-TB or HIV-associated TB	Strong recommendation, high- quality evidence
2.	GeneXpert MTB/RIF **should** be used rather than conventional microscopy, culture and DST as the initial diagnostic test in children suspected of having MDR-TB or HIV-associated TB	Strong recommendation, very low- quality evidence
3.	GeneXpert MTB/RIF **may** be used rather than conventional microscopy and culture as the initial diagnostic test in all adults suspected of having TB	Conditional recommendation, if resources are available, high-quality evidence
4.	GeneXpert MTB/RIF **may** be used rather than conventional microscopy and culture as the initial diagnostic test in all children suspected of having TB	Conditional recommendation, if resources are available, very low-quality evidence
5.	GeneXpert MTB/RIF **may** be used as a follow-on test to microscopy in adults suspected of having TB who are not at risk of MDR-TB or HIV-associated TB, especially when further testing of smear-negative specimens is necessary	Conditional recommendation, if resources are available, high-quality evidence
6.	GeneXpert MTB/RIF **should** be used in preference to conventional microscopy and culture as the initial diagnostic test for cerebrospinal fluid (CSF) specimens from patients suspected of having TB meningitis	Strong recommendation given the urgency of rapid diagnosis, very low - quality evidence
7.	GeneXpert MTB/RIF **may** be used as a replacement test for the usual practice (including conventional microscopy, culture or histopathology) for testing specific non-respiratory specimens (lymph nodes and other tissues) from patients suspected of having extrapulmonary TB)	Conditional recommendation, if resources are available, very low-quality evidence

APPENDIX 4

WEIGHT-BASED DOSING FOR ADULTS

Weight-based oral anti-TB drug daily dosing in adults ≥30 kg

DRUGS	DAILY DOSE	30–35 KG	36–45 KG	46–55 KG	56–70 KG	>70 KG
Isoniazid	4–6 mg/kg once daily	150 mg	200 mg	300 mg	300 mg	300 mg
High-dose isoniazid	16–20 mg/kg once daily	600–1000 mg	1000– 1500 mg	1500 mg	1500 mg	1500 mg
Rifampicin	8–12 mg/kg once daily	300 mg	450 mg	450 mg	600 mg	600 mg
Pyrazinamide	20–30 mg/kg once daily	800 mg	1000 mg	1200 mg	1600 mg	2000 mg
Ethambutol	15–25 mg/kg once daily	600 mg	800 mg	1000 mg	1200 mg	1200 mg
Rifabutin	5–10 mg/kg once daily	300 mg	300 mg	300 mg	300 mg	300 mg
Levofloxacin	750–1000 mg once daily	750 mg	750 mg	1000 mg	1000 mg	1000 mg
Moxifloxacin	400 mg once daily	400 mg	400 mg	400 mg	400 mg	400 mg
Ethionamide	500–750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750 mg	1000 mg
Prothionamide	500–750 mg/day in 2 divided doses	500 mg	500 mg	750 mg	750 mg	1000 mg
Cycloserine	500–750 mg/day in 2 divided doses	500 mg	500 mg	500 mg	750 mg	750 mg
p-aminosalicylic acid	8 g/day in 2 divided doses	8 g	8 g	8 g	8 g	8–12 g
Bedaquiline	400 mg once daily for 2 weeks then 200 mg 3 times per week					
Clofazimine	200–300 mg (2 first months) then 100 mg					
Linezolid	600 mg once daily	600 mg	600 mg	600 mg	600 mg	600 mg

Amoxicillin/clavulanic acid 7/1	80 mg/kg/day in 2 divided doses	2600 mg	2600 mg	2600 mg	2600 mg	2600 mg
Amoxicillin/clavulanic Acid 8/1	80 mg/kg/day in 2 divided doses	3000 mg	3000 mg	3000 mg	3000 mg	3000 mg
Imipenem/cilastatin	1000 imipenem/1000 mg cilastatin twice daily					
Meropenem	1000 mg three times daily (alternative dosing is 2000 mg twice daily)					

Weight-based injectable anti-TB daily dosing in adults ≥30 kg

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

APPENDIX 5

Important drug–drug interactions in the treatment of HIV and DR-TB

Drugs implicated	Drug-drug Interaction
Rifamycin derivatives	Interaction with ART (including protease inhibitor-based regimens)
Bedaquiline	Multiple drug interactions with protease inhibitors and NNRTI
Quinolones and buffered didanosine	decreased fluoroquinolone absorption
Ehionamide/protionamide	May have interactions with ART
Clarithromycin	Multiple drug interactions with protease inhibitors and NNRTI

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

Toxicity	Antiretroviral Agent	Anti-TB Agent	Comments
Peripheral neuropathy	d4T, ddI	Lzd, Cs, H, aminoglycosides Eto/Pto, E	Avoid use of d4T or ddI in combination with Cs or Lzd because of an increased risk of peripheral neuropathy; If these agents must be used in combination and peripheral neuropathy does develop, replace antiretrovirals with a less neurotoxic agent. Patients taking H, Cs or Lzd should receive prophylactic pyridoxine.
Central nervous system (CNS) toxicity	EFV	Cs, H, Eto/Pto, FQ	EFV has a high rate of CNS side effects (dizziness, impaired concentration, depersonalization, abnormal dreams, insomnia and confusion) in the first 2–3 weeks of use, but typically resolve on their own. If these effects do not resolve, consider substitution of the agent. At present, there are limited data on the use of EFV with Cs; concurrent use is the accepted practice as long as there is frequent monitoring for central nervous system toxicity. Frank psychosis can occur with Cs but is rare with EFV alone; other causes should always be ruled out.
Depression	EFV	Cs, FQ, H, Eto/ Pto	Severe depression can be seen in 2.4% of patients receiving EFV. Consider substitution of EFV if severe depression develops.

Headache	AZT, EFV	Cs, Bdq	Rule out more serious causes of headache, such as bacterial meningitis, cryptococcal meningitis, central nervous system toxoplasmosis, etc. Use of analgesics (ibuprofen, paracetamol) and good hydration may help. Headaches secondary to AZT, EFV and Cs are usually self-limited.
Nausea and vomiting	RTV, d4T, NVP, and most others	Eto/Pto, PAS, H, Bdq, E, Z and others	Persistent vomiting and abdominal pain may be a result of developing lactic acidosis (especially common with long-term d4T use) and/or hepatitis secondary to medications.
Abdominal pain	All antiretrovirals have been associated with abdominal pain	Eto/Pto, PAS	Abdominal pain is a common adverse effect and often benign; however, abdominal pain may be an early symptom of severe side effects, such as pancreatitis, hepatitis or lactic acidosis (especially common with long-term d4T use.
Pancreatitis	d4T, ddI	Lzd	Avoid use of these agents together. If an agent causes pancreatitis, suspend it permanently and do not use any of the potentially pancreatitis-producing antiretrovirals (d4T or ddI) in the future. Also consider gallstones or excessive alcohol use as potential causes of pancreatitis.
Diarrhoea	All protease inhibitors, ddI (buffered formulation)	Eto/Pto, PAS, FQ	Diarrhoea is a common adverse effect. Also consider opportunistic infections as a cause of diarrhoea, or C*lostridium difficile* (pseudomembranous colitis).
Hepatotoxicity	NVP, EFV, all protease inhibitors (RTV > others), all NRTIs	H, R, E, Z, Bdq, PAS, Eto/ Pto, FQ	Also see Section on hepatotoxicity treatment related to second-line anti-TB drugs. When severe, stop both the ART and TB medications, and restart the TB medications first. (Also see Chapter 9 on managing drug-induced hepatotoxicity). Also consider co-trimoxazole as a cause of hepatotoxicity if the patient is receiving this medication. Also rule out viral aetiologies as cause of hepatitis (hepatitis A, B, C, and CMV).

Lactic acidosis	d4T, ddI, AZT, 3TC	Lzd	If an agent has caused hyperlactataemia (i.e. high lactate) or lactic acidosis, replace it with an agent less likely to cause lactic acidosis. Note: the goal should always be early detection and management of hyperlactataemia to prevent development of lactic acidosis.
Renal toxicity	TDF (rare)	Aminoglycosides, Cm	TDF may cause renal injury with the characteristic features of Fanconi syndrome, hypophosphataemia, hypouricaemia, proteinuria, normoglycaemic glycosuria and, in some cases, acute renal failure. **Avoid TDF in patients receiving aminoglycosides or Cm. If TDF is absolutely necessary, serum creatinine and electrolytes should be monitored frequently (at least every two weeks).** Even without the concurrent use of TDF, HIV-infected patients have an increased risk of renal toxicity secondary to aminoglycosides and Cm. Frequent creatinine and electrolyte monitoring is recommended. In the presence of renal insufficiency, antiretrovirals and anti-TB medications need to have their doses adjusted.
Electrolyte disturbances	TDF (rare)	Cm, aminoglycosides	Diarrhoea and/or vomiting can contribute to electrolyte disturbances. Even without the concurrent use of TDF, HIV-infected patients have an increased risk of both renal toxicity and electrolyte disturbances secondary to aminoglycosides and Cm.
Bone marrow suppression	AZT	Lzd, R, Rfb, H	Monitor blood counts regularly. Replace AZT if bone marrow suppression develops. Consider suspension of Lzd. Also consider co-trimoxazole as a cause if the patient is receiving this medication. Consider adding folinic acid supplements, especially if the patient is receiving co-trimoxazole.

Dysglycaemia (disturbed blood sugar regulation)	Protease inhibitors	Gfx, Eto/Pto	Protease inhibitors tend to cause insulin resistance and hyperglycaemia. Eto/Pto tends to make insulin control in diabetics more difficult, and can result in hypoglycaemia and poor glucose regulation.
Hypothyroidism	d4T	Eto/Pto, PAS	There is potential for overlying toxicity, but evidence is mixed. Several studies show subclinical hypothyroidism associated with some antiretrovirals, particularly d4T. PAS and Eto/ Pto, especially in combination, can commonly cause hypothyroidism.
Arthralgia	Indinavir, other protease inhibitors	Z, BDQ	Protease inhibitors can cause arthralgia and there have been case reports of more severe rheumatologic pathology. Arthralgias are very common with Z and has been reported as one of the most frequent adverse effects (>10%) in controlled clinical trials with Bdq.
QT Prolongation	ART has been associated with QTc prolongation	Bdq, Mfx, Gfx, Cfz, Lfx, Ofx	ARV therapy does appear to confer a significant increased risk of QTc prolongation in HIV-positive patients but data is sparse. The additive effects of combining ART with the known second-line anti-TB drugs in respect to QTc prolongation is not known.

APPENDIX 6

MDRTB TREATMENT CHART

	Year	2014											
	Jan - 14	Feb - 14	Mar - 14	Apr - 14	May - 14								
SmearAFB	3+	2+	negative										
Culture	Positive	Positive	negative										
INH													
RMP													
EMB													
PZA	1500mg	1500mg	1500mg										
Ofloxacin													
Levofloxacin	750mg	750mg	750mg										
Ethionamide	750mg	750mg	750mg										
Kanamycin	750mg	750mg	750mg										
Cycloserine	750mg	750mg	750mg										
PAS													
Clofazimine													
Pyridoxine%	50mg	50mg	50mg										
DST													
INHinh-A/KatG)	R												
RMP	R												
EMB	R												
SM	S												
Ofloxacin	S												
Ethionamide	ND												
Amikacin	S												
PZA	S												
weight													

Notes: drug dosage represent the total daily dose given. R:Resistant, S:Sensitive, ND: Not Done

Common adverse effects, the likely responsible anti-TB drugs and the suggested management strategies

Adverse effect	Suspected agent(s)[b]	Suggested management strategies	Comments
Rash, allergic reaction and anaphylaxis	Any drug	1. For serious allergic reactions, stop all therapy pending resolution of reaction. 2. Eliminate other potential causes of allergic skin reactions. 3. For minor dermatologic reactions, various agents may be helpful and allow continuation of the medication. They include; • Antihistamines • Hydrocortisone cream for localized rash Prednisone in a low dose of 10 to 20 mg per day for several weeks can be tried if other measures are not helpful. • Phototoxicity may respond to sunscreens, but these can also cause rash. • Dry skin may cause itching, liberal use of moisturizing lotion is recommended. Dry skin is a common and significant problem with clofazimine. 4. Once the rash resolves, reintroduce remaining drugs, one at a time with the one most likely to cause the reaction last. Consider not reintroducing even as a challenge any drug that is highly likely to be the cause. 5. Suspend permanently any drug identified to be the cause of a serious reaction.	1. History of previous drug allergies should be carefully reviewed. Any known drug allergies should be noted on the treatment card. 2. Flushing reaction to rifampicin or pyrazinamide is usually mild and resolves with time. Antihistamines can be used. Hot flushes, itching, palpitations can be caused with isoniazid and tyramine containing foods (cheese, red wine). If this occurs advise patients to avoid foods that precipitate the reaction. 3. Any drug that resulted in anaphylaxis or Stevens– Johnson syndrome should never be reintroduced, not even as a challenge.
Nausea and vomiting	Eto, Pto, PAS, Bdq H, E, Z, Amx/ Clv, Cfz	1. Assess for danger signs including dehydration, electrolyte disturbances and hepatitis. Initiate rehydration therapy if indicated and correct any electrolyte disturbances.	1. Nausea and vomiting are universal in early weeks of therapy and usually abate with time on treatment and adjunctive therapy. Some nausea and even vomiting

		2. Initiate a stepwise approach to manage nausea and vomiting. **Phase 1: Adjust medications and conditions without lowering the overall dose:** - Give Eto/Pto at night - Give Eto or PAS twice or thrice daily - Give a light snack (biscuits, bread, rice, tea) before the medications - Give PAS two hours after other anti-TB drugs. **Phase 2: Start antiemetic(s):** - Metoclopramide 10 mg, 30 minutes before anti-TB medications. - Ondansetron 8 mg, 30 minutes before the anti-TB drugs and again eight hours after. Ondansetron can either be used on its own or with metoclopramide. **Phase 3: Decrease dose of the suspected drug** by one weight class if this can be done without compromising the regimen.	may need to be tolerated at least in the initial period. 2. Creatinine and electrolytes should be checked if vomiting is severe. Give intravenous fluids and replace electrolytes as needed. 3. Another strategy is to stop the responsible medicine for two or three days and then add it back gradually increasing the dose (advise the patient that the medicine will be increased back to a therapeutic dose in a manner that will be better tolerated).

Gastritis and abdominal pain	PAS, Eto, Pto, Cfz, FQs, H, E, and Z	1. Abdominal pain can also be associated with serious adverse effects, such as pancreatitis, lactic acidosis and hepatitis. If any of these are suspected, obtain appropriate laboratory tests to confirm and suspend the suspected agent. 2. If symptoms are associated consistent with gastritis (epigastric burning or discomfort, a sour taste in mouth associated with reflux) initiate medical therapy with the use of H2-blockers or proton-pump inhibitors. Avoid the use of antacids as they decrease absorption of fluoroquinolones. 3. For severe abdominal pain stop suspected agent(s) for short periods of time (one to seven days). 4. Lower the dose of the suspected agent, if this can be done without compromising the regimen. 5. Discontinue the suspected agent if this can be done without compromising the regimen.	1. If antacids must be used, they should be carefully timed so as to not interfere with the absorption of fluoroquinolones (take two hours before or three hours after anti-TB drugs). 2. Stop any nonsteroidal anti-inflammatory drugs that patient may be taking. 3. Diagnose and treat for *Helicobacter pylori* infections.
Diarrhoea and/ or flatulence	PAS, Eto/Pto	1. Encourage patients to tolerate some degree of loose stools and flatulence. 2. Encourage fluid intake. 3. Treat uncomplicated diarrhoea (no blood in stool and no fever) with loperamide 4 mg by mouth initially followed by 2 mg after each loose stool to a maximum of 10 mg per 24hours. 4. Check serum electrolytes (especially potassium) and dehydration status if diarrhoea is severe. 5. Fever and diarrhoea and/or blood in the stools indicate that diarrhoea may be secondary to something other than the simple adverse effect of anti-TB drugs.	1. Consider other causes of diarrhoea: • pseudo-membranous colitis related to broad-spectrum antibiotics (such as the fluoroquinolones) is a serious and even life threatening condition. Fever, bloody diarrhoea, intense abdominal pain and increased white blood cells are warning signs of possible pseudomembranous colitis.

Hepatitis	Z, H, R, Pto / Eto, and PAS	1. If enzymes are more than five times the upper limit of normal, stop all hepatotoxic drugs and continue with at least three non hepatotoxic medications (for example, the injectable agent, fluoroquinolone and cycloserine). If hepatitis worsens or does not resolve with the three-drug regimen, then stop all drugs. 2. Eliminate other potential causes of hepatitis (viral hepatitis and alcohol induced hepatitis being the two most common causes) and treat any that is identified. 3. Consider suspending the most likely agent permanently. Reintroduce remaining drugs, one at a time with the least hepatotoxic agents first, while monitoring liver function by testing the enzymes every three days, and if the most likely agent is not essential consider not reintroducing it.	1. History of previous drug hepatitis should be carefully analysed to determine the most likely causative agent(s); these drugs should be avoided in future regimens. 2. Viral serology should be done to rule out other aetiologies of hepatitis if available, especially to hepatitis A, B and C. 3. Alcohol use should be investigated and alcoholism addressed. 4. Generally, hepatitis due to medications resolves upon discontinuation of the suspected drug.
Hypo-thyroidism	Eto/Pto, PAS	1. Most adults will require 100–150 mcg of levothyroxine daily. Start levothyroxine in the following manner: • Young healthy adults can be started on 75–100 mcg daily • Older patients should begin treatment with 50 mcg daily • Patients with significant cardiovascular disease should start at 25 mcg daily. 2. Monitor TSH every one to two months and increase the dose by 12.5–25 mcg until TSH normalizes. Adjust the dose more slowly in the elderly and in patients with cardiac conditions.	1. Symptoms of hypothyroidism include fatigue, somnolence, cold intolerance, dry skin, coarse hair, and constipation, as well as occasional depression and inability to concentrate. 2. Do not start treatment unless TSH is above 1.5– 2.0 times of the upper normal limit. 3. It is completely reversible upon discontinuation of PAS and/or ethionamide/ protionamide. 4. The combination of ethionamide/ protionamide with PAS is more frequently associated with hypothyroidism than when each individual drug is used.

Arthralgia	Z, Bdq, Fluoroquinolones	1. Initiate therapy with nonsteroidal anti-inflammatory drugs (indomethacin 50 mg twice daily or ibuprofen 400 to 800 mg three times a day). 2. Lower the dose of the suspected agent (most commonly pyrazinamide) if this can be done without compromising the regimen. 3. Discontinue the suspected agent if this can be done without compromising the regimen.	1. Symptoms of arthralgia generally diminish over time, even without intervention. 2. Uric acid levels may be elevated in patients on pyrazinamide. There is little evidence to support the addition of allopurinol for arthralgias, although if gout is present it should be used. 3. If acute swelling, redness and warmth are present in a joint, consider aspiration for diagnosis of gout, infections, autoimmune diseases, etc.
Tendonitis and tendon rupture	Fluoroquinolones	1. If significant inflammation of tendons or tendon sheaths occur: • Consider stopping fluoroquinolones • Give a non-steroidal anti-inflammatory drug (ibuprofen 400 mg four times daily) • Rest the joint. 2. If treatment failure is likely without the fluoroquinolone • Reduce dose if possible • Ensure joint is strictly rested • Inform patient of the possible risk of tendon rupture and discuss the risks and benefits of ongoing use of the fluoroquinolone.	1. Tendon rupture with fluoroquinolone use is more likely in patients doing new physical activities and more common among older patients and diabetics. 2. Tendon rupture is relatively rare in patients on MDR-TB regimens with fluoroquinolones.
Electrolyte disturbances (hypokalaemia and hypomagnesaemia)	Cm, Km, Am, S	1. Check potassium. 2. If potassium is low, also check for magnesium and calcium. 3. Replace electrolytes as needed. Dose oral electrolytes apart from fluoroquinolone as they can interfere with fluoroquinolone absorption	1. If severe hypokalaemia is present, consider hospitalization. 2. Amiloride, 5–10 mg daily, or spironolactone, 25 mg daily, may decrease potassium and magnesium wasting, and thus useful in refractory cases

Nephrotoxicity (renal toxicity)	S, Km, Am, Cm	1. Discontinue the suspected agent. 2. Consider using capreomycin if an aminoglycoside had been the prior injectable drug in the regimen. 3. Consider other contributing aetiologies and address as indicated. 4. Follow creatinine (and electrolyte) levels closely, every one to two weeks. 5. Consider dosing the injectable agent two to three times a week if the drug is essential to the regimen and the patient can tolerate. If the creatinine continues to rise despite twice/thrice a week dosing, suspend the injectable agent. 6. Adjust all TB medications according to the creatinine clearance.	1. History of diabetes or renal disease is not a contraindication to the use of agents listed here, although patients with these comorbidities may be at increased risk for developing renal failure. 2. Renal impairment may be permanent.
Vestibular toxicity (tinnitus and dizziness)	S, Km, Am, Cm, Cs, FQs, H Eto, Lzd	1. If early symptoms of vestibular toxicity appear, change the dosing of the injectable agent to twice/thrice a week. Also, consider using capreomycin if an aminoglycoside had been the prior injectable in the regimen. 2. If tinnitus and unsteadiness worsen with the above adjustment, stop the injectable agent. *This is one of the few adverse reactions that cause permanent intolerable toxicity and can necessitate discontinuation of a class of agents.*	1. Ask the patient about tinnitus and unsteadiness every week. 2. Fullness in the ears and intermittent ringing are early symptoms of vestibular toxicity. 3. A degree of disequilibrium can be caused by Cs, FQs, Eto/Pto, INH or linezolid. Some clinicians will stop all drugs for several days to see if symptoms are attributed to these drugs. Symptoms of vestibular toxicity generally do not improve on withholding medications.
Hearing loss (also see vestibular toxicity above)	S, Km, Am, Cm, Clr	1. Document hearing loss and compare with baseline audiogram if available. (Some degree of hearing loss occurs with most patients starting with high frequency loss.) 2. If early symptoms of hearing loss are documented, change the dosing of the injectable agent to twice/thrice a week. Also, consider using capreomycin if an	1. Patients with previous exposure to aminoglycosides may have baseline hearing loss. In such patients, audiometry may be helpful at the start of MDR-TB therapy. 2. Hearing loss is almost always permanent. *Continuing the injectable agent*

		aminoglycoside had been the prior injectable in the regimen. **3.** Discontinue the injectable agent if hearing loss continues despite dose adjustment and add additional drugs to reinforce the regimen.	*despite hearing loss almost always results in irreversible deafness.*
Peripheral neuropathy	Cs, Lzd, H, S, Km, Amk, Cm, H, Fluoroquinolones, rarely Pto/Eto, E	1. Correct any vitamin or nutritional deficiencies. Increase pyridoxine to the maximum daily dose (200 mg per day). 2. Consider whether the dose of cycloserine can be reduced without compromising the regimen. If isoniazid is being used (especially high dose isoniazid), consider stopping it. If possible, switching the aminoglycoside to capreomycin may also be helpful. 3. Initiate medical therapy for example nonsteroidal anti-inflammatory drugs or acetaminophen, tricyclic antidepressants, carbamazepine or gabapentin can be used. 4. Rarely, medication may be discontinued, but only if an alternative drug is available and the regimen is not compromised.	1. Patients with comorbid disease (e.g. diabetes, HIV, alcohol dependence) may be more likely to develop peripheral neuropathy. 2. Neuropathy may be irreversible but many patients experience improvement when the offending agents are suspended. 3. The neuropathy associated with linezolid is common after prolonged use and often permanent. For this reason, suspension of this drug should be strongly considered when neuropathy develops due to linezolid.
Headache	Cs, Bdq,	Rule out more serious causes of headache including meningitis, and other infections of the central nervous system. (HIV coinfected patients should receive a head computed tomography scan and cerebrospinal fluid analysis.) Start analgesics like ibuprofen or paracetamol.	1. Headaches are common during the initial months of MDR-TB therapy. They can present as migraine or cluster headaches. 2. To minimize headaches at the start of therapy, cycloserine can be started at lower doses of 250– 500 mg and gradually increased over one to two weeks to achieve the target dose. 3. Headaches due to cycloserine and bedaquiline are usually self-limited.

Depression	Socioeconomiccirc umstances, Chronic disease, Cs, fluoroquinolones, H, Eto/Pto	1. Assess and address underlying socioeconomic issues 2. Assess patients for coexisting substance abuse and refer to treatment if appropriate. 3. Initiate individual counselling (or group counselling if the patient is sputum smear and culture negative). 4. When depression is more significant, initiate antidepressant therapy. 5. Lower the dose of the suspected agent if this can be done without compromising the regimen. 6. Discontinue the suspected agent if this can be done without compromising the regimen.	1. Socioeconomic conditions and chronic illness should not be underestimated as contributing factors to depression. 2. Depressive symptoms may fluctuate during therapy and may improve as illness is successfully treated. 3. History of previous depression is not a contraindication to the use of agents listed but may increase the likelihood of depression developing during treatment. If significant depression is present at the start of treatment, avoid a regimen with cycloserine, if possible. 4. Question the patient regarding suicidal ideation any time the depression is judged to be more than mild.
Suicidal ideation	CS, H, Eto/Pto	1. Hospitalize the patient and put under 24-hour surveillance. 2. Discontinue cycloserine. 3. Request psychiatric consultation. 4. nitiate antidepressant therapy. 5. Lower the dose of Eto/Pto to 500 mg daily until the patient is stable.	1. Keep the patient in the hospital until risk of suicide has passed. 2. If no improvement occurs after holding cycloserine, hold H and/or Eto/Pto.
Psychotic symptoms	Cs, H, fluoroquinolones	1. Stop the suspected agent for a short period of time (1–4 weeks) while psychotic symptoms are brought under control. The most likely drug is cycloserine followed by high dose isonizaid. 2. If moderate to severe symptoms persist, initiate antipsychotic therapy (haloperidol). 3. Hospitalize in a ward with psychiatric expertise	1. Some patients will need to continue antipsychotic treatment throughout MDR-TB treatment (and discontinued upon completion of treatment). 2. Previous history of psychiatric disease is not a contraindication to cycloserine, but its use may

		if patient is at risk to himself/herself or others. 4. Increase pyridoxine to the maximum daily dose (200 mg per day). 5. Lower the dose of the suspected agent (most commonly cycloserine to 500 mg a day) if this can be done without compromising the regimen. 6. Discontinue the suspected agent if this can be done without compromising the regimen. 7. Once all symptoms resolve and patient is off cycloserine, antipsychotic therapy can be tapered off. If cycloserine iscontinued at a lower dose, antipsychotic therapy may need to be continued and any attempts of tapering off should be done after referring to a psychiatrist trained in the adverse effects of second-line anti-TB drugs.	increase the likelihood of psychotic symptoms developing during treatment. 3. Some patients will tolerate cycloserine with an antipsychotic drug but this should be done in consultation with a psychiatrist, as these patients will need to be under special observation; this should only be done when there is no other alternative. 4. Psychotic symptoms are generally reversible upon completion of MDR-TB treatment or cessation of the offending agent. 5. Always check creatinine in patients with new onset psychosis. A decrease in renal function can result in high blood levels of cycloserine, which can cause psychosis.
Seizures	Cs, H, fluoro-quinolones	1. Hold cycloserine, fluoroquinolones and isoniazid pending resolution of seizures. 2. Initiate anticonvulsant therapy (carbamazepine, phenytoin or valproic acid are most commonly used). 3. Increase pyridoxine to the maximum daily dose (200 mg per day). 4. Check serum electrolytes including potassium, sodium, bicarbonate, calcium, magnesium and chloride. 5. When seizures have resolved, restart medications one at a time. Cycloserine should not be restarted unless itis absolutely essential to the regimen. If cycloserine is reinitiated, start a dose one weight band lower.	1. An anticonvulsant is generally continued until MDR-TB treatment is completed or suspected agentis discontinued. 2. History of previous seizure disorder is not a contraindication to the use of agents listed here if a patient's seizures are well controlled and/ or the patient is receiving anticonvulsant therapy.(Do not include cycloserine if an alternative drug is available.) 3. Patients with history of previous seizures may be at increased risk for development of seizures during

			MDR-TB therapy. 4. Always check creatinine in patients with new onset seizures. A decrease in renal function can result in high blood levels of cycloserine, which can cause seizures. Adjusting the dose of cycloserine in the presence of low creatinine may be all that is needed to control the seizures.
Optic neuritis	E, Eto/Pto, Lzd, Cfz, rifabutin, H, S	1. Stop ethambutol. Do not restart. 2. Refer patient to an ophthalmologist.	1. The most common drug responsible is ethambutol and it usually reverses with cessation of the drug. 2. Improve diabetes control in diabetic patients.
Metallic taste	Eto/Pto, Clr, FQs	1. Encourage the patient to tolerate this side effect. 2. Sucking hard candy or chewing gum can be helpful.	1. Normal taste returns when treatment is stopped.
Gynaecomastia	Eto/Pto	1. Breast enlargement can be a troublesome side effect of Eto/Pto therapy, especially for male patients. Galactorrhoea has also been reported. 2. Encourage patients to tolerate this side effect.	1. Resolution occurs after treatment is stopped.
Alopecia	H, Eto/Pto	1. Hair loss can occur or there can be significant thinning of the hair, but this is temporary and not progressive during treatment. 2. Encourage patients to tolerate this side effect.	1. Significant cosmetic change has not been reported.

Superficial fungal infection and thrush	Fluoroquinolones and other antibiotics with antibacterial properties	1. Topical antifungal agents or short-course oral antifungal drugs are helpful. 2. Exclude other diseases if response to treatment is not prompt (such as HIV).	1. Vaginal or penile candidiasis, oral thrush or cutaneous candidiasis in skin folds may occur with antibiotic treatment.
Lactic acidosis	Lzd	1. Stop linezolid if lactic acidosis occurs.	1. Lactic acidosis can be monitored with a blood test that measures lactic acid.
Dysglycaemia and hyperglycaemia	Gfx, Eto/Pto	1. Stop gatifloxacin and replace with different latergeneration fluoroquinolone like moxifloxacin. 2. Treat diabetes as needed. Good glucose control is important during treatment.	
QT prolongation	Bdq, fluoroquinolones, clarithromycin clofazimine	Any patient found to have a QTc value greater than 500 ms should be managed carefully. • Repeat ECG and confirm the prolongation. • Bedaquiline should be stopped for QTc value greater than 500 ms. Consider stopping other drugs that prolong the QT interval. • Check potassium, calcium and magnesium levels. Electrolyte levels should be maintained in the normal range. • It is suggested to maintain potassium levels of more than 4 mEq/l and magnesium levels of more than 1.8 mg/dl. • Avoid other drugs that increase the QT interval. Monitor the patient's renal and hepatic function and adjust the dose of fluoroquinolones if impairment is present. Consider suspension of fluoroquinolone if risk of torsades de pointes outweighs the benefits of the drug.	1. The QT interval is measured from the end of the QRS complex to the beginning of the T wave on a standard ECG. The QT is corrected for heart rate, which is referred to as the QTc and calculated by most ECG machines. A normal QTc is generally <440 ms. 2. Values above QTc 440 ms are referred to as prolonged. Patients with prolonged QTc are at risk for developing cardiac arrhythmias like torsades de pointes, which can be life threatening. Patients with QTc greater than 500 ms are at the greatest risk for developing these arrhythmias. 3. The fluoroquinolones cause prolongation of the QTc. Moxifloxacin and gatifloxacin cause the greatest QTc prolongation, while levofloxacin and ofloxacin

			have a lower risk. 4. Currently, ECG monitoring prior to initiation and during MDR-TB therapy is only required with the use of bedaquiline.
Haematological abnormalities	Lzd	Stop linezolid if myelosuppression (suppression of white blood cells, red blood cells or platelets) occurs. Consider restarting with a lower dose of linezolid (300 mg instead of 600 mg) if myelosupression resolves and if linezolid is considered essential to the regimen. Consider nondrug related causes of the haematological abnormality. Consider blood transfusion for severe anaemia.	1. Haematological abnormalities (leukopenia, thrombocytopenia, anaemia, red cell aplasia, coagulation abnormalities, and eosinophilia) can rarely occur with a number of other anti-TB drugs. 2. There is little experience with prolonged use of linezolid.

a Adapted from *(5)* and *(6)*.

APPENDIX 8

Definition of DRTB indicators

1. DETECTION INDICATORS	Definition
1.1 TB patients with result for isoniazid and rifampicin DST	**Numerator**: Number of TB cases with DST result for both isoniazid and rifampicin by each risk category specified in the national policy during the period of assessment. **Denominator**: Number of TB cases identified in each respective risk category during the period of assessment.
1.2 Confirmed MDR-TB cases detected among TB patients tested for susceptibility to isoniazid and rifampicin	**Numerator**: Number of confirmed MDR-TB cases by each risk category specified in the national policy during the period of assessment. **Denominator**: Number of TB cases in each risk category with DST result for both isoniazid and rifampicin during the period of assessment.
1.3 Confirmed MDR-TB cases tested for susceptibility to any fluoroquinolone and any second-line injectable drug	**Numerator**: Number of confirmed MDR-TB cases tested for susceptibility to a fluoroquinolone and a second-line injectable anti-TB medication during the period of assessment. **Denominator**: Number of confirmed MDR-TB cases during the period of assessment
1.4 Confirmed XDR-TB cases detected among MDR-TB patients tested for susceptibility to any fluoroquinolone and any second-line injectable drug	**Numerator**: Number of confirmed XDR-TB cases detected during the period of assessment. **Denominator**: Number of confirmed MDR-TB cases tested for susceptibility to a fluoroquinolone and a second-line injectable anti-TB medication during the period of assessment.
1.5 Interval between presumption of RR-/MDR-TB and DST results	The duration in days between the date when the TB patient was identified as being in a risk category as per the national policy and the dates of the DST results for isoniazid and rifampicin as recorded in the Laboratory register. The first date is determined by type of risk category. This date may correspond to when TB is diagnosed if universal DST is practised, or when a laboratory result indicates treatment failure or persistent sputum smear positivity during the course of TB treatment, or when HIV-associated TB is detected. In the

	case of a contact with TB, this would be when the laboratory confirms MDR in the source case, which may precede or occur after the diagnosis of TB in the contact (information as in the Laboratory register). In sites testing with Xpert MTB/RIF alone, the indicator can be modified to include all cases with a rifampicin test result and the date of the first result showing rifampicin resistance is used, regardless of whether the same patient was confirmed to be MDR-TB or not subsequently. The calculation is done on all cases with DST results for isoniazid and rifampicin (sensitive or resistant) entered in the Laboratory register during the six-month period of assessment. The difference in days between the two dates is summed up for all patients and divided by the number of cases with test results. The indicator is expressed as the arithmetic mean number of days with the minimum and maximum ranges for the episodes included in the calculation. The number of episodes included in the calculation should be indicated.
2. ENROLMENT INDICATORS	
2.1 RR-/MDR-TB cases (presumptive or confirmed) enrolled on MDR-TB treatment	Number of RR-/MDR-TB cases (presumptive or confirmed) registered and started on a prescribed MDR-TB treatment regimen during the period of assessment. **Comparator**: Number of RR-/MDR-TB cases (presumptive or confirmed) eligible for second-line drugs treatment during the period of assessment.
2.2 Confirmed RR-/MDR-TB cases enrolled on MDR-TB treatment regimen	Number of confirmed MDR-TB cases registered and started on a prescribed MDR-TB treatment regimen during the period of assessment. **Comparator**: Number of confirmed MDR-TB cases detected during the period of assessment.
2.3 Confirmed XDR-TB cases enrolled on XDR-TB treatment regimen	Number of confirmed XDR-TB cases registered and started on a prescribed XDR-TB treatment regimen during the period of assessment. Comparator: Number of confirmed XDR-TB cases detected during the period of assessment.
2.4 Interval between RR-/MDR-TB diagnosis and start of MDR-TB treatment	The duration in days between the date of RR-/MDR-TB confirmation (DST results showing resistance to both isoniazid and rifampicin in the Laboratory register) and the date when the patient started a prescribed second-line drug regimen as per the Second-line TB treatment register; in sites testing with Xpert MTB/RIF alone, the

	indicator is modified to include all confirmed RR-TB cases and the date of the first result showing rifampicin resistance is used regardless of whether the same patient was confirmed with MDR-TB or not subsequently (i.e. the date when the patient was first found to be eligible for a MDR-TB regimen). The calculation is done on all confirmed RR-/MDR-TB cases recorded on the Second-line TB treatment register during the six-month period of assessment. The difference in days between the date of confirmation and start of treatment is summed up for all patients and divided by the number of treatment episodes. The indicator is expressed as the arithmetic mean number of days with the minimum and maximum ranges for all episodes included in the calculation. If treatment was started before the confirmatory DST was reported then the interval is marked as zero days. The number of episodes included in the calculation should be indicated.
3. INTERIM RESULTS INDICATORS	
3.1 RR-/MDR-TB cases on MDR-TB treatment regimen with negative culture by six months	**Numerator:** Number of confirmed pulmonary RR-/MDR-TB cases registered and started on a prescribed MDR-TB treatment with negative results for culture in month six of their treatment. **Denominator**: Number of confirmed RR-/MDR-TB cases registered and started on treatment for MDR-TB during the period of assessment.
3.2 RR-/MDR-TB cases on MDR-TB treatment regimen who died by six months	**Numerator**: Number of confirmed RR-/MDR-TB cases registered and started on a prescribed MDR-TB treatment who died of any cause by the end of month six of their treatment. **Denominator**: Number of confirmed RR-/MDR-TB cases registered and started on treatment for MDR-TB during the period of assessment.
3.3 RR-/MDR-TB cases on MDR-TB treatment regimen who were lost to follow-up by six months	**Numerator**: Number of confirmed RR-/MDR-TB cases registered and started on a prescribed MDR-TB treatment who were lost to follow-up by the end of month six of their treatment **Denominator**: Number of confirmed RR-/MDR-TB cases registered and started on treatment for MDR-TB during the period of assessment. *The three indicators (3.1, 3.2, and 3.3) should include XDR-TB cases started on prescribed treatment with second-line drugs.*

3.4 Patients on MDR-TB treatment regimen found not to have RR-/MDR-TB	Number of patients started on a prescribed MDR-TB treatment regimen during the period of assessment and later found not to have RR-/MDR-TB.
3.5 Patients on XDR-TB treatment regimen found not to have XDR-TB	Number of patients started on a prescribed XDR-TB treatment regimen during the period of assessment and later found not to be XDR-TB.
4. OUTCOME INDICATOR	
4.1 RR-/MDR-TB cases on MDR-TB treatment regimen with an outcome.	Numerator: The number of confirmed RR-/MDR-TB cases registered for MDR-TB treatment during the period of assessment assigned one of the six outcomes i.e. i. Cured, ii. Treatment completed, iii. Treatment failed, iv. Died, v. Lost to follow-up, and vi. Not evaluated. Denominator: Number of confirmed RR-/MDR-TB cases registered for treatment and starting a prescribed MDR-TB treatment regimen during the period of assessment.

LIST OF ABBREVIATIONS

ACH	Air change per hour
ADR	Adverse drug reaction
AFB	Acid Fast Bacilli
Am	Amikacin
Amx/Clv	Amoxicillin/ clavulanate
ART	Anti-Retro viral Treatment
AZT	Azhitromycin
anti-TB	anti-tuberculous
Bdq	Bedaquiline
BMI	Body Mass Index
CBC	Complete Blood Count
Cfz	Clofazimine
Clr	Clarithromycin
CMV	Cytomegalovirus
Cm	Capreomycin
CPT	Co-trimoxazole Preventive Therapy
Cs	Cycloserine
Cr	Creatinine
CHW	Community health workers
Dlm	Delamanid
DOT	Direct Observe Treatment
DOTS	Direct Observe Treatment Short-course
DR-TB	Drug Resistant Tuberculosis
DRS	Drug Resistance Surveillance
DST	Drug Susceptibility Testing
E	Ethambutol
ECG	Electrocardiogram
Eto	Ethionamide
FQ	Fluorquinolone
Gfx	Gatifloxacin
GFR	Glomerulal Filtration Rate
GMP	Good manufacturing practices
H	Isoniazid
HAART	Highly active anti-retroviral therapy
HE	Isoniazid + Ethambutol
Hepa Filter	High efficacy particulate air filtration
HIV	Human Immunodeficiency Virus
High dose H	High-dose Isoniazid
HR	Isoniazid + Rifampicin
HREZ	Isoniazid + Rifampicin + Ethambutol + Pyrazinamide
HRZE	Isoniazid + Rifampicin + Pyrazinamide + Ethambutol
HZE	Isoniazid + Pyrazinamide + Ethambutol
HCW	Healthcare worker
ICA	Immuno chromatographic Assay

INJ	Injectable
Ipm/Cln	Imipenem/cilastatin
IRIS	Immune Reconstitute Inflammatory Syndrome
K	Potassium
Km	Kanamycin
LED	Light Emitting Diode
LPA	Line Probe Assay
LFT	Liver Function Test
Lzd	Linezolid
MDR-TB	Multi Drug Resistant Tuberculosis
Mfx	Moxifloxacin
MTB	Mycobacterium Tuberculosis
MTB/RIF	Mycobacterium Tuberculosis / Rifampicin
MTBc	Mycobacterium Tuberculosis Complex
Mpm	Meropenem
mg	miligram
mcg	microgram
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NTM	Non Tuberculosis Mycobacterium
NTP	National Tuberculosis Programme
NGO	Non-governmental organization
PAS	Para-aminosalicylic acid
PAS-Na	Para-aminosalicylate sodium
PCR	Polimerase Chain Reaction
POS	Positive
PPE	Personal Protective Equipment
PPM	Public Private Mix
Pto	Prothionamide
QMS	Quality Management System
QTcF	QT interval corrected for heart rate (Fridericia method)
R	Rifampicin
Rfb	Rifabutin
Rpt	Rifapentine
RR	Rifampicin Resistance – Multiple Drug Resistance Tuberculsis
RR-/MDR-TB	Rifamoicin
S	Streptomycin
SHREZ	Steptomycin + Isoniazid + Rifampicin + Ethambutol + Pyrazinamid
SRL	Supranational reference laboratory
SLE	Systematic Lupus Erythematosus
SOPs	Standard Operating Procedures
SRL	Supranational Reference Laboratory
T	Thioacetazone
TB	Tuberculosis
Trd	Terizidone
TSH	Thyroid Stimulating Hormone
TST	Tuberculin Skin Test
UVGI	Ultraviolet germicidal irradition

WHO	World Health Organization
XDR-TB	Extensive Drug Resistant Tuberculosis
Xpert MTB/RIF	Xpert Mycobacterium Tuberculosis/Rifampicin
Z	Pyrazinamide

LIST OF TABLE

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