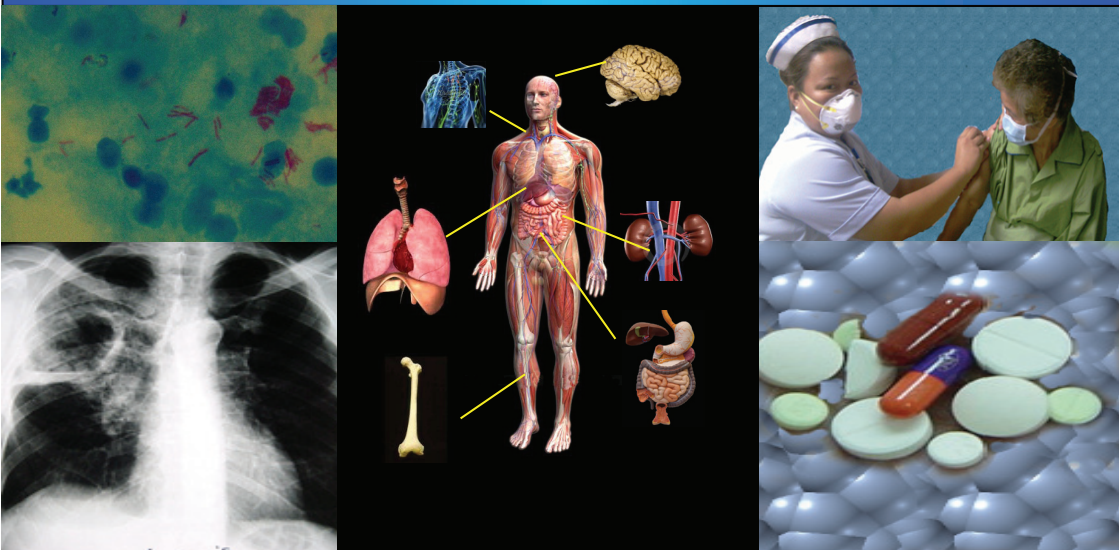


MANAGEMENT OF TUBERCULOSIS (3rd EDITION)



Published by:
Malaysia Health Technology Assessment Section (MaHTAS)
Medical Development Division, Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Federal Government Administrative Centre
62590, Putrajaya, Malaysia

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ISBN: 978-967-0399-39-3

Available on the following websites:

<http://www.moh.gov.my>

<http://www.acadmed.org.my>

<http://mts.org.my>

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 is responsible for the management of his/her unique patient based on the clinical picture presented by the patient and the management options available locally.

These guidelines were issued in 2012 and will be reviewed in 2016 or sooner if new evidence becomes available.

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LEVELS OF EVIDENCE

Level	Study design
I	Evidence from at least one properly randomised controlled trial
II -1	Evidence obtained from well-designed controlled trials without randomisation
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or group
II-3	Evidence from multiple time series with or without intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience; descriptive studies and case reports; or reports of expert committees

SOURCE: US / CANADIAN PREVENTIVE SERVICES TASK FORCE 2001

GRADES OF RECOMMENDATION

A	At least one meta analysis, systematic review, or RCT, or evidence rated as good and directly applicable to the target population
B	Evidence from well conducted clinical trials, directly applicable to the target population, and demonstrating overall consistency of results; or evidence extrapolated from meta analysis, systematic review, or RCT
C	Evidence from expert committee reports, or opinions and /or clinical experiences of respected authorities; indicates absence of directly applicable clinical studies of good quality

SOURCE: MODIFIED FROM THE SCOTTISH INTERCOLLEGIATE GUIDELINES NETWORK (SIGN)

Note: The grades of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

GUIDELINES DEVELOPMENT AND OBJECTIVES

GUIDELINES DEVELOPMENT

The members of the Development Group (DG) for these Clinical Practice Guidelines (CPG) were from the Ministry of Health (MoH), Ministry of Higher Education and the private sector. There was active involvement of a multidisciplinary review committee (RC) during the process of development of these guidelines.

The previous CPG entitled Control and Prevention of Tuberculosis (2nd Edition) 2002 was used as the basis for the development of the present guidelines. Literature search was carried out using the following electronic databases: Guidelines International Network (G-I-N); World Health Organization (WHO), Medline via Ovid, Pubmed, Cochrane Database of Systemic Reviews (CDSR) and International Health Technology Assessment websites (refer to **Appendix 1 for Search Terms**). The search was limited to literature published in the last ten years and in English. If the evidence was insufficient, the period of publication was extended for another ten years. In addition, the reference lists of all retrieved literature and guidelines were searched to further identify relevant studies. Experts in the field were also contacted to identify further studies. All searches were conducted between 9 May 2011 - 29 March 2012. Literature searches were repeated for all clinical questions at the end of the CPG development process allowing any relevant papers published before 31 August 2012 to be included. Future CPG update will consider evidence published after this cut-off date. The details of the search strategy can be obtained upon request from the CPG Secretariat.

Reference was also made to other CPGs on tuberculosis such as the World Health Organization (2010) – Treatment of Tuberculosis Guidelines, The National Collaborating Centre for Chronic Conditions (2006) & National Institute for Health and Clinical Excellence (2011) – Clinical Diagnosis and Management of Tuberculosis, and Measures for Its Prevention and Control, and MoH New Zealand (2010) – Guidelines for Tuberculosis Control in New Zealand. The CPGs were evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE) II prior to them being used as references.

A total of 42 clinical questions were developed under different sections. Members of the DG were assigned individual questions within these sections (refer to **Appendix 2 for Clinical Questions**). The DG members had met 20 times throughout the development of these guidelines. All literature retrieved were appraised by at least two DG members using Critical Appraisal Skill Programme checklist, presented in evidence tables and further discussed in each DG meeting. All statements and recommendations formulated after that were agreed upon by both the DG and RC. Where evidence was insufficient, the recommendations were made by consensus of the DG and RC. This CPG is based largely on the findings of systematic reviews, meta-analyses and clinical trials, with local practices taken into consideration.

The literature used in these guidelines were graded using the US/Canadian Preventive Services Task Force Level of Evidence (2001), while the grading of recommendation was modified from grades of recommendation of the Scottish Intercollegiate Guidelines Network. On completion, the draft guidelines were sent for review by 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 review and approval.

OBJECTIVES

The aim of these guidelines is to assist clinicians and other healthcare providers in making evidence-based decisions about appropriate management and treatment of tuberculosis (TB) specifically:-

- i. Screening and diagnosis,
- ii. Treatment,
- iii. Follow-up, prevention and referral.

CLINICAL QUESTIONS

Refer to **Appendix 2**

TARGET POPULATION

Patients with TB (confirmed TB, suspected TB and latent TB infection)

TARGET GROUP/USER

This document is intended to guide healthcare professionals and relevant stakeholders in all healthcare settings including:

- i. Doctors
- ii. Pharmacists
- iii. Allied health professionals
- iv. Medical students and trainees
- v. Tuberculosis programme managers
- vi. Patients and carers/non-governmental organisations

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Outpatient, inpatient and community settings

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1. INTRODUCTION

The number of tuberculosis (TB) cases in Malaysia continues to rise unabated leading to high rates of morbidity and mortality. This problem has been compounded by the HIV pandemic, complacency, neglect towards the disease and international movement. In Malaysia, although the incidence of multidrug-resistant TB (MDR-TB) is still under control, extensively drug-resistant TB (XDR-TB) has been detected.

Delayed presentation, inaccurate diagnosis, inappropriate empirical treatment, high treatment default rates in some settings e.g. in immigrants and TB in children are just some of the issues in the management of TB in the local context. It is very important for the non-specialist doctors to know when to refer and who to refer to when in doubt. Empirical treatment must be avoided where possible and referral to doctors with experience in TB is encouraged.

This third edition is the first evidence-based TB CPG in Malaysia in contrast to the previous TB CPG which was consensus-based. This is consistent with current evidence-based medicine practised around the globe. Not all recommendations in the current CPG are evidence-based since certain papers were excluded due to poor study design. This should spur our doctors to do local research in order to get more evidence for the next CPG update. Many newer diagnostic tools are now available or will be made available in Malaysia. New chapters such as latent TB and indications for specialist referral have been added in keeping with the latest practice in TB management.

The management of TB needs to be standardised to improve patient outcomes, assist monitoring and evaluation efforts and prevent the emergence of MDR-TB. Preventing MDR-TB is critically important since chemotherapy for MDR-TB is fraught with side effects, is expensive and requires a longer duration of treatment. Prevention of MDR-TB can be achieved if health care providers manage TB appropriately and ensure optimal adherence to first-line therapy.

Although several international TB CPGs are available, there is a need to provide local guidance that considers its application within our context and addresses issues that are unique to Malaysia. Therefore, the need for a local evidence-based TB CPG is timely and long overdue. It is mainly aimed at health care providers in primary care but it should also be useful to those in the secondary/tertiary care.

The aim of the TB CPG is to standardise the management of TB at all levels of care in Malaysia with a view to improving patient care and preventing the emergence of MDR-TB and XDR-TB.

2. EPIDEMIOLOGY & HIGH RISK GROUPS

TB continues to be an important disease both globally and in Malaysia. In 2010, there were an estimated 8.8 million new cases of TB globally with 1.1 million deaths among HIV-negative cases of TB and an additional 0.35 million deaths among people who were HIV-positive.^{1, level III} Locally, the incidence was 81.4 per 100,000 population in year 2010.^{2, level III} The number of new TB cases in the country increased from 15,000 in 2005 to 19,251 in 2011 as shown in **Fig. 1**. While PTB was the commonest form of TB in Malaysia, extrapulmonary TB (EPTB) still posed a threat.^{2, level III}

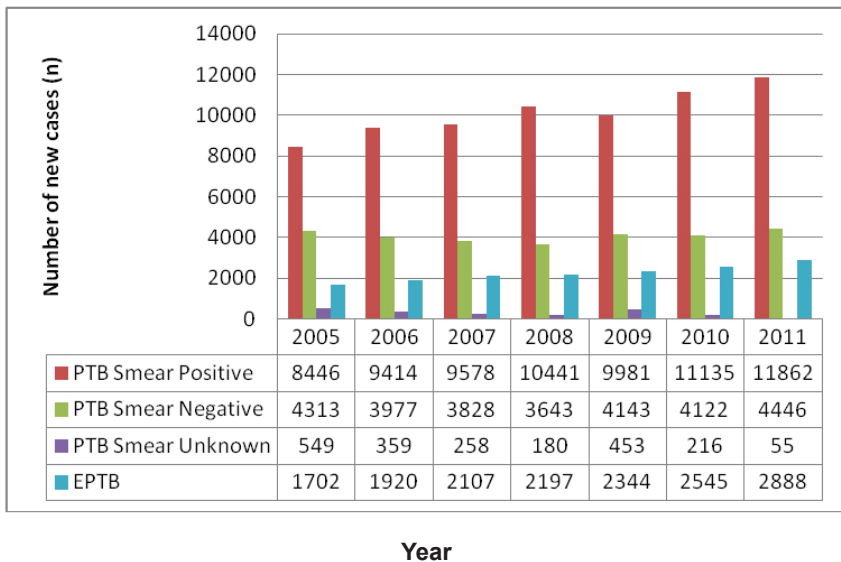


Fig. 1: Notification of new TB cases in Malaysia 2005 - 2011

The incidence and prevalence of TB varies in different age groups. The majority of patients are in the 21 - 60 years age group (69.5%) and there is a male predominance (65%).^{3, level III} In 2011, 2.7% of TB cases in Malaysia were in the age group ≤ 14 years while 12.3% were those aged ≥ 65 years. Among all TB cases, 13.9% were foreigners. The smear positive rate among new pulmonary tuberculosis (PTB) patients was 72% (refer to **Fig. 1**). The rate of MDR-TB cultures had increased from 0.3% in 2005 to 1.3% in 2011 of all AFB cultures positive for MDR-TB.^{2, level III level III}

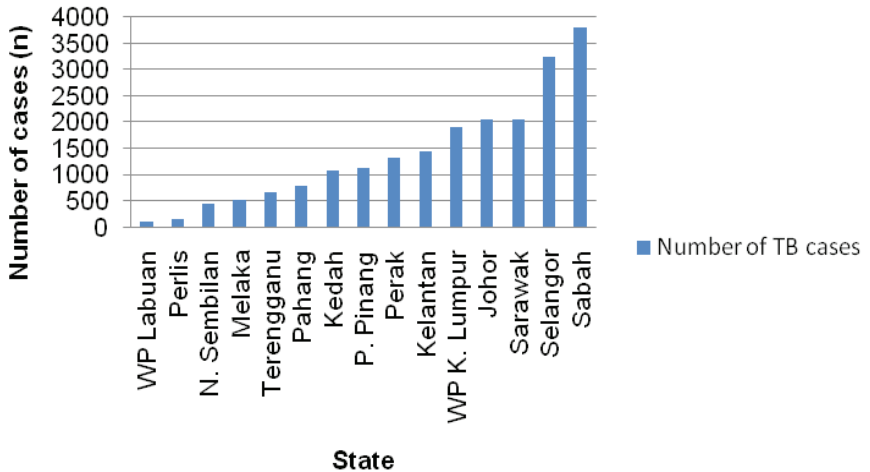


Fig. 2: Notification of new TB cases in Malaysia 2005 - 2011

Based on different sources, Sabah was noted to have the highest prevalence of TB cases.^{2, level III; 4 - 5, level III} In 2011, the other two states with a high number of TB cases were Selangor and Sarawak as shown in **Fig. 2** below.^{2, level III}

Important high risk groups include:-

- a. Close TB contacts [household contacts with HR=9.6 (95% CI 6.7 to 13.8) and non-household contact with HR=2.5 (95% CI 1.6 to 3.9)]^{6, level II-2}
- b. Immunocompromised patients:-
 - Diabetes mellitus (RR=3.1, 95% CI 2.3 to 4.3)^{7, level II-2}
 - Human Immunodeficiency Virus infection (OR=2.3, 95% CI 1.3 to 3.5)^{8, level II-2}
 - Chronic obstructive pulmonary disease (HR=3.0, 95% CI 2.4 to 4.0)^{9, level II-2}
 - End-stage renal disease (RR=4.5)^{10, level II-2}
 - Malignancy (HR=3.7, 95% CI 1.2 to 11.1)^{6, level II-2}
 - Malnutrition (HR=37.5, 95% CI 12.7 to 111.4)^{6, level II-2}
 - Use of immunosuppressant drugs in rheumatoid arthritis i.e. TNF blockers (RR=12.5, 95% CI 3.5 to 44.7) and prednisolone > 10 mg per day (RR=4.4, 95% CI 1.5 to 13.6)^{11, level II-2}
- c. Substance abusers and cigarette smokers
 - Drug user (illicit drugs, intravenous drugs and hard drugs) (OR=3.0, 95% CI 2.1 to 4.2)^{12, level III}
 - Intravenous drug users (HR=6.0, 95% CI 2.5 to 14.6)^{6, level II-2}
 - Excessive alcohol consumption i.e. ≥40 g alcohol per day (RR=2.3, 95% CI 1.9 to 4.6)^{13, level II-2}
 - Current smoker (OR=3.1, 95% CI 2.4 to 4.2)^{8, level II-2}

- d. People living in overcrowded conditions
 - Homelessness (OR=2.9, 95% CI 2.0 to 4.0)^{12, level III}
 - History of incarceration (OR=2.2, 95% CI 1.7 to 2.9)^{12, level III}
 - Institutionalisation (such as homes for the elderly and shelters) (OR=3.6, 95% CI 1.7 to 7.65)^{14, level II-2}
 - Prison (IRR=23.0, IQR 11.7 - 36.1)^{15, level II-2}

Recommendation 1

- High risk groups* should be considered to be screened for active tuberculosis. **(Grade C)**
- HIV screening should be offered to all patients with tuberculosis. **(Grade C)**

*Refer to the preceding paragraphs

Clinical Features

Adult patients with active PTB typically presents with a history of chest symptoms such as productive cough, haemoptysis and chest pain and also nonspecific constitutional symptoms such as loss of appetite, unexplained weight loss, fever, night sweats and fatigue.

Adult patients presenting with unexplained cough lasting more than two weeks with or without constitutional symptoms should be investigated for PTB. However, the typical symptoms may be absent in the immunocompromised or elderly patients.

Symptoms and signs due to EPTB vary according to the organs involved and may be non-specific. For example, patients with TB meningitis may present with intermittent or persistent headaches for a few weeks and subtle mental status changes, which may progress to coma over a period of days to weeks.

Common clinical features suggestive of TB in children are prolonged fever, failure to thrive, unresolving pneumonia, loss of weight and persistent lymphadenopathy. TB should be suspected in a symptomatic child having history of contact with active TB.

3. INVESTIGATIONS

The diagnosis of TB is supported by imaging and laboratory tests. However, diagnosis is confirmed by isolating *Mycobacterium tuberculosis* from clinical samples. In situations where clinical samples are difficult to obtain and in extrapulmonary TB (EPTB), certain procedures should be performed in order to establish the diagnosis of TB.

3.1 Laboratory Investigations

Diagnosis of TB is based on the detection of acid fast bacilli (AFB) on smears and cultures from clinical specimens. All patients suspected of having PTB should submit at least two sputum specimens for microscopic examination in a quality-assured laboratory. When possible, at least one early morning specimen should be obtained, as sputum collected at this time has the highest yield.^{1, level III} These techniques while remaining an important baseline modality of investigations currently, they lack the desired sensitivity or are time consuming. Hence, Nucleic Acid Amplification Tests for the detection of *Mycobacterium tuberculosis* are useful tools for rapid diagnosis of TB, both pulmonary and extrapulmonary. These tests are also useful for the rapid screening of patients suspected of MDR-TB.

a. Fluorescence Microscopy (FM)

Microscopic examination of sputum using conventional light microscopy is a common method used in diagnosing PTB. However, the disadvantage of this method is its relatively low sensitivity (20 - 60%).^{16, level III}

A systematic review (SR) by Steingart KR et al. showed that FM was 10% (95% CI 5 to 15) more sensitive compared to conventional microscopy. Its implementation in TB endemic countries would be able to improve TB case-finding through increase in direct smear sensitivity. The other advantage of this method is the shorter time spent on microscopic examination resulting in a quicker turnaround time for smear results and reduce patient drop-out from the diagnostic process.^{16, level III}

Light emitting diode-based fluorescence microscopy (LED FM) has benefits over conventional FM in terms of being less expensive, having lower maintenance requirement and not requiring a dark room. In a study evaluating the performance of LED FM vs Ziehl-Neelson microscopic examination using mycobacterial culture as reference standard, the sensitivity and specificity of LED FM on pulmonary specimens were 78.3% and 92.0% respectively. The mean time per smear examination was only 1.41 minutes for LED FM compared to 2.48 minutes for Ziehl-Neelson microscopic examination.^{17, level III}

The World Health Organization (WHO) recommends that conventional FM to be replaced by LED FM and carried out through carefully phasing in implementation plans.^{18 - 19, level III}

Recommendation 2

- Light emitting diode-based fluorescence microscopy (LED FM) should be used as the preferred method over the conventional Ziehl-Neelsen light microscopy in diagnosing pulmonary tuberculosis in both high and low volume laboratories. **(Grade C)**
- In implementing LED FM, the need of laboratory staff training, standard operating procedures and appropriate quality assurance should be addressed. **(Grade C)**

b. Molecular Methods

Nucleic Acid Amplification Tests (NAAT) provide rapid results within 24 - 48 hours and has greater PPV (>95%) with AFB smear positive specimens. They have the ability to confirm rapidly the presence of *Mycobacterium* in 50 - 80% AFB smear negative, culture positive specimens.^{20 - 21, level III}

NAAT can detect the presence of *Mycobacterium* in specimens weeks earlier than culture for 80 - 90% patients suspected of having PTB, hence having a positive impact on TB control efforts.^{20, level III}

Interferon Gamma Release Assay, an immunological test, is addressed in other sections of the CPG especially on Latent TB Infection.

Recommendation 3

- Nucleic Acid Amplification Tests (molecular methods endorsed by World Health Organization) can be performed for the detection of *Mycobacterium tuberculosis* from clinical specimens. **(Grade C)**

c. Optimal Methods To Rapidly Detect Drug-Resistant TB

Current methods utilised for routine drug susceptibility testing include the use of commercial liquid medium and the proportion method on conventional agar medium. The notable advantage of incorporating molecular tests such as the Line Probe Assay (LPA) in the routine TB diagnostic algorithm is its rapid turnaround time which has a direct impact on patient management and ultimately the transmission of TB. Moreover, the direct use of LPA on smear positive sputum specimens or on cultures of smear negative specimens confirms their value in the rapid screening of patients suspected of having MDR-TB infection.

The pooled sensitivity and specificity for LPA rifampicin resistance demonstrates an excellent accuracy of 98.1% (95% CI 95.9 to 99.1) and 98.7% (95% CI 97.3 to 99.4) respectively whilst for isoniazid resistance, the pooled sensitivity and specificity of 88.7% (95% CI 82.4 to 92.8) and 99.2% (95% CI 95.4 to 99.8).^{22 - 23, level III} These assays can be used to detect rifampicin resistance alone (as rifampicin resistance is accepted as a valid and reliable indicator or proxy of MDR-TB) or in combination with isoniazid resistance.

Molecular assays supplement but cannot replace conventional methods for culture and sensitivity. Moreover their high cost and requirement for sophisticated laboratory infrastructure (TB risk level 2) limit their use in routine diagnosis. Laboratories with such infrastructure are limited in our country.

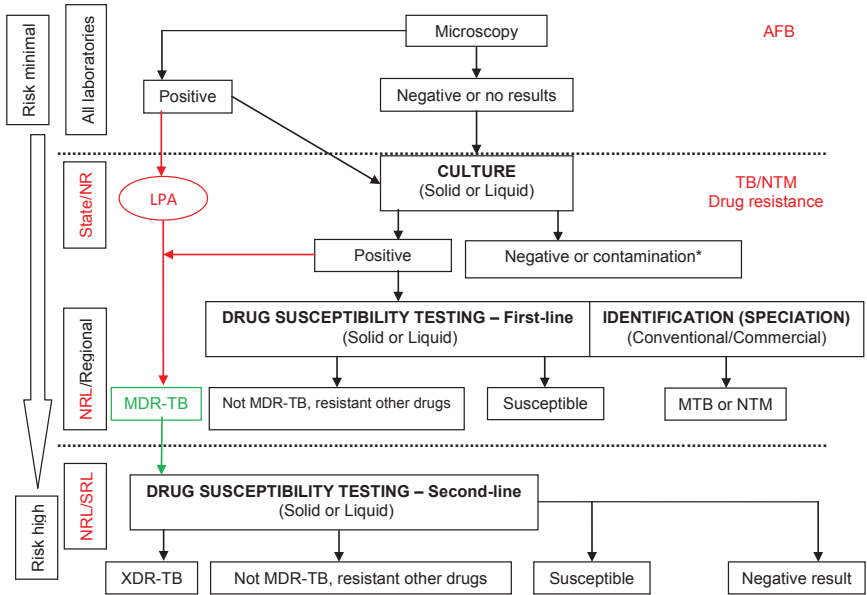
To balance the lack of sophisticated laboratory infrastructure for performing TB identification and sensitivity (conventional or molecular based) in laboratories outside of Klang Valley and the need to detect cases of MDR-TB with speed and accuracy, another molecular platform endorsed by WHO is recommended. A fully integrated and automated on-demand molecular diagnostic system referred to as the Xpert MTB/RIF can bring incremental improvement to detection and drug susceptibility testing with speed and accuracy at the peripheral laboratories.^{19, level III; 24 - 25, level III} The following are its characteristics:-

- fully automated
- near the patient
- uses a robust system
- technically simple, allowing a relatively untrained operator to detect TB and genetic mutation associated with rifampicin resistance

- results can be made available while patient waits in the clinic (within 2 hours)
- has overall sensitivity of 98% to 100% and specificity of 100%

The use of LPA to rapidly detect drug resistant TB is shown in **Algorithm 1** below.

Algorithm 1: Laboratory Diagnosis of *Mycobacterium tuberculosis*



*Repeat if clinically indicated

Adopted from: World Health Organization. Policy Framework for Implementing New Tuberculosis Diagnostics. Geneva: WHO; 2010

Recommendation 4

- Line Probe Assay should be performed to detect rifampicin and isoniazid resistance in smear positive sputum specimens or culture isolates from smear positive and negative specimens. It should be carried out in a tuberculosis (TB) risk level 2 laboratory. **(Grade C)**
- Xpert MTB/RIF can be deployed in state laboratories to scale up the detection of drug resistant tuberculosis for which a TB risk level 1 laboratory will suffice. **(Grade C)**

• **TB risk level 2**

Minimum requirements:

- ▶ Laboratory separated from other areas
- ▶ Access to the laboratory restricted to authorised persons
- ▶ Floors, walls, ceilings and benches with impervious surfaces
- ▶ Windows permanently closed, air supply without circulation
- ▶ Centrifuge with aerosol tight buckets
- ▶ Handling of samples in appropriate biological safety cabinets equipped with H14 high efficiency particulate air filters
- ▶ Biological safety cabinets designed by certified manufactures, properly installed, regularly maintained and re-certified at least annually on site
- ▶ A controlled ventilation system that maintains a directional airflow into the laboratory from functionally clean to dirty areas, with a minimum of 6 and up to 12 air changes per hour*.

*Installation of a controlled ventilation system should be planned with engineering specialist.

• **TB risk level 1**

Minimum requirements:

- ▶ Adequate ventilation*
- ▶ Laboratory separated from other areas
- ▶ Access to the laboratory restricted to authorised persons

*Adequate ventilation can be ensured by opening windows if local climatic conditions allow. An exhaust fan can be used to ensure adequate room air exchanges. When climatic conditions obviate opening of windows, consideration should be given to mechanical ventilation systems that provide an inward flow of air without recirculation in the room.

d. Rapid Methods (Serology Assays)

Current diagnostic methods such as slide smears may not detect a large number of cases (sensitivity between 40% and 75%) and cultures may yield results in 4 - 8 weeks resulting in many cases being treated based on clinical judgement. The emergence of multidrug-resistant *Mycobacterium tuberculosis* has prompted interest in the use of molecular test to “speed” up the diagnosis of TB (especially in sputum positive cases). However, molecular tests are expensive and require expertise, specialised equipment and infrastructure. Hence, they are not routinely and widely available.

In view of the above setbacks, there is an urgent need for a readily available, simple, reliable and cost-effective rapid diagnostic test for TB which can be applied to a clinically diverse patient population. For example, an antibody-based test which can potentially aid in rapid TB diagnosis even at the lower levels of the health services. However, serologic TB tests are beset by challenges, including inability to avoid cross reactivity to Bacille Calmette-Guérin (BCG) or nontuberculous mycobacteria (NTM) and to discriminate active from latent infection. These tests have also not been shown to perform consistently in genetically and immunologically diverse groups.

A recent meta-analysis of 67 studies on commercial serological tests (48% from low- and middle-income countries) which included revealed that all commercial tests for active PTB had highly variable sensitivity (0% to 100%) and specificity (31% to 100%). The most commonly evaluated test was Anda-TB IgG with a pooled sensitivity of 76% (95% CI 63% to 87%) in smear positive cases and 59% (95% CI 10% to 96%) in smear negative patients. The pooled specificity was 92% (95% CI 74% to 98%) and 91% (95% CI 79% to 96%) respectively.^{26, level III}

In the same meta-analysis on active EPTB, 25 studies were identified. The results showed that all commercial tests had highly variable sensitivity (0% to 100%) and specificity (59% to 100%). Pooled sensitivity was 64% (95 CI 28% to 92%) for lymph node TB and 46% (95% CI 29% to 63%) for pleural TB. For Anda-TB IgG, the pooled sensitivity and specificity were 81% (95% CI 49% to 97%) and 85% (95% CI 77% to 92%) respectively.^{26, level III}

WHO published a policy statement in 2011 stating that commercial serological tests for TB provides inconsistent and imprecise estimates of sensitivity and specificity which can adversely impact patient safety.^{27, level III}

Recommendation 5

- Commercial serological assay **should not be used** to diagnose pulmonary and extrapulmonary TB. **(Grade C)**

3.2 Additional Procedures/Diagnostic Tests

a. PTB

Sputum induction with nebulised hypertonic saline, fiberoptic bronchoscopy with bronchoalveolar lavage and gastric lavage are established techniques for patients who are unable to spontaneously expectorate adequate sputum specimens or who are smear negative for AFB (refer **Appendix 5**).

Properly performed sputum induction is the preferred method over bronchoscopy as the sensitivities are 96.3% and 51.9% respectively ($p < 0.005$). The positive yield is higher if the patient has respiratory symptoms ($p = 0.02$) and abnormal radiographs suggestive of active disease ($p = 0.003$).^{28, level III}

Three induced sputum samples have higher sensitivity for detecting TB compared to three gastric washings samples (39% vs 30%; $p = 0.03$).^{29, level III}

In patients who are smear negative for AFB or who have difficulty in producing sputum, bronchoscopy can establish a diagnosis microbiologically or histopathologically in 86.6%^{30, level III} and 83.3%^{31, level III} of cases. Immediate diagnosis can be established in 48.3% of patients.^{31, level III}

Refer to **Appendix 5** for **Sputum Induction Guidelines**.

Recommendation 6

- Sputum induction should be considered to establish the diagnosis in patients suspected to have pulmonary tuberculosis who are smear negative or unable to produce sputum, whenever appropriate. **(Grade C)**
- Gastric lavage or bronchoscopy may be considered in patient who is not suitable for sputum induction. **(Grade C)**

b. ExtraPTB (EPTB)

The diagnosis of EPTB is challenging as they have a lower bacterial load compared to PTB and sample collection is problematic. A relatively low proportion of cases have positive microscopy and culture for *Mycobacterium tuberculosis*, even with rapid culture methods. In clinically suspected cases of EPTB, some relevant procedures are required in order to support or confirm the diagnosis, such as lumbar puncture, thoracentesis, fine needle aspiration and biopsy, pleuroscopy, colonoscopy and cystoscopy.

Obtaining samples for *Mycobacterium tuberculosis* culture from the affected sites such as cerebrospinal fluid (CSF), pleural fluid, fine needle aspiration (FNA) and/or biopsy from lymph node, pleura, intestines, skin and any other infected sites are important as this confirms the diagnosis and provides the drug susceptibility profile of the organism.

Presence of caseating granulomas, or granulomas with Langerhan's giant cells on histology or cytology of the specimen is highly suggestive of tuberculosis but they are not specific.

- **Tuberculous lymphadenitis**

A definitive diagnosis of tuberculous lymphadenitis can be made by culture or PCR demonstration of *Mycobacterium tuberculosis* in the affected lymph node.

Although excisional biopsy is an invasive approach, it has traditionally been used to diagnose tuberculous lymphadenitis, FNA has emerged as a first-line diagnostic technique currently as it is safer, less invasive and more practical. Excisional biopsy could be reserved for cases where diagnosis by FNA cannot be made or for persistent lymph node diseases despite a full course of antiTB treatment.

In tuberculous lymphadenitis, fine needle aspiration cytology alone provides reliable diagnosis in 72% of patients.^{32, level III} Combining cytology with microbiology (smear and culture) increases diagnostic yield from 67% to 91% in clinically suspected tuberculous lymphadenitis.^{33, level III}

The efficacy of conventional transbronchial needle aspiration (TBNA) in suspected tuberculous mediastinal lymphadenitis had been studied. The sensitivity, specificity, positive and negative predictive values and accuracy of TBNA were 83%, 100%, 100%, 38% and 85% respectively.^{34, level III}

- **Pleural TB**

Pleural TB is a common EPTB. Thoracentesis or pleural tapping is often an initial diagnostic procedure in most patients suspected to have it. Presence of exudative type of pleural fluid with high proportion of lymphocytes may suggest the diagnosis but it is not specific.

Ziehl-neelsen staining of pleural fluid and biopsy specimens is not helpful as the sensitivity is only 0.0% and 3.8% respectively. The sensitivity of culture in both liquid medium and on Lowenstein Jensen medium is higher for pleural biopsy specimens than for pleural fluid specimens (92.3% vs 15.4%; $p < 0.05$).^{35, level III} The real time Polymerase Chain Reaction (PCR) for pleural fluid has a sensitivity of 42.8% (95% CI 38.4 to 44.8), specificity of 94.2% (95% CI 85.8 to 98.0), PPV of 93.3% (95% CI 83.6 to 97.7) and NPV of 48.5% (95% CI 44.2 to 50.4).^{36, level III} For pleural biopsy, the sensitivity of PCR is 90%, specificity 100%, PPV 100% and NPV 86.7%.

Although these rates are similar to those of pleural biopsy culture, the PCR is able to provide a much faster diagnosis.^{35, level III}

The measurement of Adenosine Deaminase (ADA) level in pleural effusion is a useful diagnostic test for tuberculous pleurisy. In a meta-analysis of ADA for the diagnosis of pleural TB by Liang QL et al., the sensitivity of the test was 0.92 (95% CI 0.90 to 0.93), specificity 0.90 (95% CI 0.89 to 0.91), positive LR 9.03 (95% CI 7.19 to 11.35), negative LR 0.10 (95% CI 0.07 to 0.14) and diagnostic OR 110.08 (95% CI 69.96 to 173.20).^{37, level III} In a study by Diacon AH et al., pleural fluid adenosine deaminase (ADA) of >50 U/L had a sensitivity of 95% and specificity of 89% for pleural TB.^{38, level III}

Medical thoracoscopy is a better diagnostic procedure compared to closed needle biopsy in diagnosing pleural TB. The sensitivities of histology, culture and combined histology and culture by medical thoracoscopy are 100%, 76% and 100% respectively compared to 69%, 48% and 79% by closed needle pleural biopsy. However, a combination of ADA, lymphocyte/neutrophil ratio 0.75 and closed needle biopsy reaches a sensitivity of 93% and specificity of 100% and thus might substitute thoracoscopy for the diagnosis of pleural TB.^{38, level III}

• Tuberculous Meningitis

Diagnosis of tuberculous meningitis requires high index of clinical suspicion especially in high-risk groups as their presentations are almost similar to other meningoencephalitis. Due to the urgency of the condition, treatment has to be commenced based on clinical judgement alone, often with only supportive but nonspecific laboratory indicators. Multiple diagnostic modalities including blood tests, CT scan or MRI brain are among the initial work up for tuberculous meningitis. Lumbar puncture or spinal tap is an important diagnostic procedure to obtain cerebrospinal fluid for further investigations in diagnosing tuberculous meningitis. High protein, low glucose and presence of inflammatory cells, predominantly lymphocyte, in CSF may suggest the diagnosis but other causes of meningitis can have similar features.

The role of ADA and PCR in diagnosing tuberculous meningitis was studied in a meta-analysis of ten studies. The sensitivity of ADA was 0.79 (95% CI 0.75 to 0.83), specificity 0.91 (95% CI 0.89 to 0.93), positive LR 6.85 (95% CI 4.11 to 11.41), negative LR 0.29 (95% CI 0.19 to 0.44) and diagnostic OR 26.93 (95% CI 12.73 to 56.97).^{39, level III} In another study, using a cut-off level of >10 U/L, CSF-ADA had a sensitivity of 92.5% and specificity of 97% for the diagnosis of tuberculous meningitis compared to PCR for *Mycobacterium tuberculosis* which had a sensitivity of 44.5% and specificity of 92.0%.^{40, level III}

Recommendation 7

- All attempts should be made to obtain specimen from patients suspected to have extrapulmonary tuberculosis (EPTB) including tissue or fluid from the affected sites for cytology/histopathological examination and *Mycobacterium tuberculosis* culture. **(Grade C)**
- *Mycobacterium tuberculosis* culture and sensitivity testing should be performed on specimen taken from patients suspected to have EPTB including biopsy specimen. **(Grade C)**
- Measurement of Adenosine Deaminase level in pleura or cerebrospinal fluid may be considered as an adjunct in diagnosing pleural TB and tuberculous meningitis respectively. **(Grade C)**

3.3 Imaging

The radiologic features of TB may mimic those of many other diseases, thus a high degree of clinical suspicion is required when interpreting the imaging manifestation. Culturing of *Mycobacterium tuberculosis* is the definitive diagnosis of TB, but imaging can suggest the possibility of the disease.

a. Imaging in PTB

TB commonly affects the respiratory system. However, imaging of the thorax should include an evaluation of the pleura, mediastinum, soft tissues and bones. Historically, PTB has been divided into primary and post-primary TB. Primary TB is the first infection occurring due to initial exposure to *Mycobacterium tuberculosis*, whilst post-primary TB is due to reactivation of a previous focus. Primary TB can occur in children as well as adults. The distinguishing chest radiographic features of both primary and post-primary are mentioned in **Appendix 4**. It may sometimes be difficult to make the differentiation between primary and post-primary as the features can overlap.

Imaging modalities include:-

- Chest radiography remains the primary imaging modality for PTB in children, adults and even pregnant women (with abdominal shield). Refer to Appendix 4 for **Chest X-ray (CXR) Features of TB**
 - ▶ Consolidation with cavitation is the hallmark of adult-type PTB but any abnormality in the CXR has to be considered suspicious when diagnosing PTB.^{41 - 42, level III}
 - ▶ A normal CXR may be seen in up to 15% of patients with proven primary TB.^{43, level III}
 - ▶ A severity grading of the CXR features based on the extent of involvement of the lungs is used in the primary health care facilities (refer to **Appendix 4**).^{44, level III}
 - ▶ CXR has a higher sensitivity and specificity for TB when read by trained readers compared to inexperienced readers. Detection of TB is improved by 1.23 fold (95% CI 1.02 to 1.48) in diagnostic OR per 10 years of experience.^{45, level III}
- Computerised tomography (CT) is more sensitive in demonstrating endobronchial spread, lymphadenopathy and pleural complication than chest radiography. It is useful in cases with high clinical suspicion of TB with normal CXR.
 - ▶ High Resolution CT (HRCT) has a sensitivity, specificity and positive predictive values of 84%, 97% and 98% respectively in distinguishing active PTB (AUC=0.951±0.021).^{46, level III}
- Magnetic Resonance Imaging (MRI) may be considered in special circumstances (children and pregnant women) as there is no ionising radiation. However, its high cost and limited accessibility does not favour this modality.
 - ▶ In comparison to chest radiography and CT, MRI has a better soft tissue characterisation and thus more useful in assessing pleural and lymph node complications.
 - ▶ MRI & HRCT have very good κ values (0.9 to 1.0) in detecting parenchymal changes. Although the κ value is only 0.54 for pleural abnormalities, MRI picks up more pleural changes and nodal involvement.^{47, level III}

b. Imaging in EPTB

Immunocompromised patients have a higher prevalence for EPTB involvement. A study had shown that 38% of immunocompromised patients with TB had pulmonary involvement only, 30% had extrapulmonary involvement only and 32% had both pulmonary and extrapulmonary involvement.^{43, level III} A limited immune response can give rise to a normal CXR. A normal CXR may be seen in up to 10 - 15% of HIV positive patients with proven TB. Thus in EPTB, an abnormal CXR or a positive tuberculin skin test (TST) supports the diagnosis but negative results do not exclude its possibility.

- Pleural TB
 - ▶ In clinical practice, ultrasonography (US) can be used to demonstrate pleural collection and guide diagnostic or therapeutic procedures such as pleuroscopy.
- Musculoskeletal TB

The imaging modalities used in diagnosis are plain radiography, CT and MRI.

 - ▶ CT and MRI imaging are of great value in demonstrating a small focus of bone infection and also the extent of the disease process.^{43, level III; 48, level III}
 - ▶ MRI is the preferred imaging modality in the assessment of tuberculous spondylitis because of its superior ability to demonstrate soft tissue abnormalities.^{43, level III; 48 - 49, level III}
- Central Nervous System TB

The modalities that are used to image the brain and spine are CT and MRI.

 - ▶ CT better demonstrates hydrocephalus which is a common complication of TB meningitis. It may also show abnormal meningeal enhancement and parenchymal changes.^{43, level III; 48, level III}
 - ▶ In addition to the above, MRI better demonstrates the involvement of the spinal cord and cranial nerves.^{43, level III; 48, level III}
- Abdominal TB

The imaging modalities mostly used in the investigation are US, CT and barium studies.

 - ▶ The diagnostic yields for the different modalities are 83% for barium meal follow through, 80% for CT and 77% for US.^{50, level III}
 - ▶ Features suggestive of abdominal TB are ascites (79%), enlarged LN (35%) omental thickening (29%) and bowel wall thickening (25%).^{50, level III}
- Genitourinary TB

Investigation include intravenous urography (IVU), US, CT and MRI.

 - ▶ IVU can demonstrate the 'moth-eaten' calyx which may be the earliest evidence of renal TB. It can also demonstrate ureteral abnormalities.^{51, level III}
 - ▶ US, CT or MRI can demonstrate the renal parenchyma and urinary bladder better than IVU.^{43, level III; 48, level III}
 - ▶ US and CT are used in genital TB to evaluate the uterus and adnexa in females and the prostate in males but the imaging features are non specific.^{43, level III; 48, level III}

- Head and Neck TB
CT and MRI can be used to evaluate head and neck TB.
 - ▶ Caseation and calcification of cervical lymphadenopathy may be highly suggestive but is not pathognomonic of TB.^{43, level III; 48, level III}

Recommendation 8

- Chest radiography should be used as the primary imaging modality to aid diagnosis and management of pulmonary and extrapulmonary tuberculosis. **(Grade C)**
- Computerised tomography maybe considered in cases of normal chest radiography but with high clinical suspicion or in the management of complication of pulmonary tuberculosis. **(Grade C)**

4. TREATMENT OF TB IN ADULTS

Aim of TB treatment should be both cure and reduce risk of transmission. TB is an airborne infectious disease. The risk of TB infection post-exposure is further determined by a few factors:-

- Infectiousness of the index case
- Nature and duration of the contact
- Immune status of the contact

In general, individuals with pulmonary and laryngeal TB are infectious, whereas those with EPTB are regarded as noninfectious. Amongst those with PTB, the infectiousness increases when the sputum smear is positive or multiple pulmonary cavities are shown in the chest radiograph.

The risk of infection is also related to the degree of shared ventilation, physical distance and duration of exposure between the index case and the contact. The risk increases if the contact has been in close proximity and if the contact has spent a longer time together with the index case. In addition, individuals who are immunocompromised are more susceptible to TB disease.

Health education must be given to the patient and family members/carers at the time of starting treatment. This should include:-

- a. nature of the disease
- b. necessity of strict adherence with the prolonged treatment
- c. risks of defaulting treatment
- d. side effects of medication
- e. risks of transmission and need for respiratory hygiene as well as cough/sneeze etiquette

4.1 PULMONARY TB (PTB) IN ADULTS

A standardised TB treatment regimen is of utmost importance in the control of PTB. Appropriate regimens, duration of treatment as well as adherence are required to achieve cure, prevent mortality and morbidity, reduce transmission of tuberculosis and prevent emergence of MDR-TB.

4.1.1 Treatment of New Cases

Presently, six-month regimen consisting of two months of daily EHRZ* (2EHRZ) followed by four months of daily HR* (4HR) is recommended for newly-diagnosed PTB^{1, level III} based on many years of well-designed randomised controlled trial (RCT).^{52, level III} Refer to **Table 1** for **Dosages of First-Line Antituberculosis (AntiTB) Drug**.

Table 1: Dosages of First-Line AntiTB Drugs

Drug*	Recommended dose			
	Daily		3 times per week	
	Dose (range) in mg/kg body weight	Maximum in mg	Dose (range) mg/kg body weight	Daily maximum in mg
Isoniazid (H)	5 (4 - 6)	300	10 (8 - 12)	900
Rifampicin (R)	10 (8 - 12)	600	10 (8 - 12)	600
Pyrazinamide (Z)	25 (20 - 30)	2000	35 (30 - 40)*	3000*
Ethambutol (E)	15 (15 - 20)	1600	30 (25 - 35)*	2400*
Streptomycin (S)	15 (12 - 18)	1000	15 (12 - 18)*	1500*

Pyridoxine 10 - 50 mg daily needs to be added if isoniazid is prescribed.

* Daily treatment is the preferred regimen.

Adopted from World Health Organization. Treatment of Tuberculosis Guidelines Fourth Edition. Geneva: WHO; 2010

In a SR, recurrence rate was low for both ethambutol-based regimen (3.1%,95% CI 0.9 to 7.9) and for streptomycin-based regimen (2.4%,95% CI 0.7 to 6.1).^{53, level I}

Whenever possible, rifampicin should be used for the whole duration of treatment. Unfavourable outcomes are significantly higher in regimens without rifampicin compared to those with rifampicin in the maintenance phase.^{54 - 55, level I}

There is no significant difference in effectiveness and safety between rifampicin and other antibiotics in the rifamycin group.^{56 - 57, level I}

Based on early bactericidal activity studies, rifampicin has a narrow therapeutic index. Thus whenever possible, its dosage should not be lower than recommended dosage (10 - 12 mg/kg).^{58 - 59, level III} Findings from a SR suggested that higher than standard rifampicin dosing improved culture conversion rates and more RCTs were needed to confirm efficacy and tolerability.^{60, level I}

Using pyrazinamide beyond two months during the intensive phase did not confer further advantage if the organism is fully susceptible.^{61, level I}

Recommendation 9

- New patients with pulmonary tuberculosis should receive daily 2EHRZ and followed by daily 4HR**. **(Grade A)**
 - Regimen should contain six months of rifampicin. **(Grade A)**
 - Rifampicin should be rounded to higher recommended dose if tolerated. **(Grade C)**
 - If ethambutol is contraindicated, streptomycin can be substituted. **(Grade A)**

**H=isoniazid, R=rifampicin, Z=pyrazinamide, E=ethambutol

4.1.2 Treatment of Previously Treated Cases

Previously treated TB patients include those patients treated as new cases who have taken treatment for more than one month and are currently smear or culture positive again (i.e. failure, relapse or return after default).^{1, level III}

There is no retrievable evidence on empirical regimens used for retreatment of PTB.

WHO recommends retreatment regimen containing first-line drugs 2HRZES/1HRZE/5HRE if country-specific data show low or medium levels of MDR-TB in these patients or if such data is not available. Drug sensitivity test (DST) must be done for the patients. When the results become available, the drug regimen should be adjusted appropriately.^{1, level III}

All efforts must be made to rule out drug resistance including usage of rapid DST at the point of diagnosis.^{1, level III}

When there is interruption in treatment, the treating doctor needs to ascertain reason and duration of the interruption and then decide whether to restart the entire course, to continue from the last dose or to stop the treatment. There is no retrievable evidence on treatment after interruption. In most cases, the decision needs to be individualised, taking into consideration the reason for the interruption, response to treatment up to the point of interruption and and total planned/expected doses of treatment. The following is recommended by the Development Group:-

- i. Interruption in the intensive phase:
 - a. If ≥ 14 days, to restart from the beginning i.e. Day 1
 - b. If < 14 days, to continue from the last dose

In either (a) or (b), the total number of planned doses for the intensive phase should be given.
- ii. Interruption in the maintenance phase:
 - a. If interruption occurs after patient receives 80% of the total planned doses, the treatment may be stopped If the sputum AFB smear was negative at the initial presentation. If the sputum AFB smear was positive, the treatment should be continued to achieve the total number of planned doses
 - b. If patient receives $< 80\%$ of total planned doses and interruption lapse is ≥ 2 months, restart treatment from the beginning
 - c. If patient receives $< 80\%$ of total planned doses and interruption lapse is < 2 months, continue treatment from date it stops to complete full course

Recommendation 10

- Physician with experience in tuberculosis (TB) management should be consulted for all patients requiring retreatment of TB. **(Grade C)**

4.1.3 Optimal Duration of Treatment

Current evidence suggests that the optimal duration of treatment for sputum positive PTB is at least six months.

Regimens with shorter duration of rifampicin are associated with higher risk of failure, relapse and acquired drug resistance.^{54, level I; 62, level I} Failure rates, relapse rates and acquired resistance rates for a one to two months regimen is 5.8 (95% CI 2.9 to 11.0), 3.6 (95% CI 2.5 to 5.3) and 4.6 (95% CI 2.0 to 0.4) respectively.^{54, level I}

Even in patients with non-cavitary disease and confirmed sputum culture, conversion at two months fares poorer with a 4-month regimen compared to 6-month regimen (HR=4.1, 95% CI 1.2 to 14.6).^{63, level I}

There is little or no difference in the rates of adverse reactions between the shorter and longer regimens.^{62, level I}

Recommendation 11

- Patients with sputum positive pulmonary tuberculosis should receive antituberculous drugs for a minimum duration of six months. **(Grade A)**

4.1.4 Regimen During the Maintenance Phase of Treatment

Intermittent drug regimen was designed for administration under Directly Observed Therapy (DOT). It has the potential to improve adherence to treatment. However, if this regimen is not administered under DOT, there are concerns it may lead to treatment failure, relapse and acquired drug resistance.

There is no difference in treatment failure, relapse and acquired drug resistance rates between daily and different intermittent dosing regimens in the maintenance phase:-

- IRR of failure rate for daily then thrice weekly and daily then twice weekly is 0.7 (95% CI 0.2 to 2.1) and 0.9 (95% CI 0.5 to 1.6) respectively.^{54, level I}
- RR for bacteriological cure rates between fully intermittent arm and daily arm is 0.99 (95% CI 0.90 to 1.10).^{64, level I}
- IRR of relapse rate for daily then thrice weekly and daily then twice weekly is 1.0 (95% CI 0.6 to 1.5) and 0.8 (95% CI 0.5 to 1.2) respectively.^{54, level I} However in another SR, a significant dose response relationship between dosing schedules and relapse was noted; the OR were 1.6 (95% CI 0.6 to 4.1) for daily then thrice weekly and 2.8 (95% CI 1.3 to 6.1) for daily then twice weekly.^{65, level I}
- RR for recurrence rate in fully intermittent arm compared to daily arm is 4.0 (95% CI 0.7 to 24.10).^{64, level I}
- IRR of acquired drug resistance rate for daily then thrice weekly and daily then twice weekly is 0.7 (95% CI 0.2 to 2.6) and 0.5 (95% CI 0.3 to 1.2) respectively.^{54, level I}

In new patients with PTB, WHO recommends daily dosing throughout the course of anti-TB treatment. However, a daily intensive phase followed by thrice weekly maintenance phase is an option provided that each dose is directly observed and patient has improved clinically. A maintenance phase with twice weekly dosing is not recommended since missing one dose means the patient receives only half the total dose for that week.^{1, level III}

Recommendation 12

- New patients with pulmonary tuberculosis should receive daily intensive regimen followed by daily maintenance regimen. **(Grade A)**
 - o Thrice weekly maintenance regimen can be considered under direct observation. **(Grade A)**

4.1.5 Fixed-Dose Combinations (FDCs)

There is considerable urgency to prevent the emergence of drug-resistant TB. Among the important steps to prevent this situation is to ensure patients adhere to their treatment. FDC drugs incorporate two or more drugs in single tablet and offer reduction in number of pills that need to be consumed. The following FDC preparations are registered in Malaysia:-

- Forecox-Trac Film Coated Tab: Isoniazid, Rifampicin, Ethambutol and Pyrazinamide
- Rimactazid 300 Sugar Coated Tab: Isoniazid and Rifampicin
- Rimcure 3-FDC Film Coated Tab: Isoniazid, Rifampicin and Pyrazinamide
- Akurit-Z Tab: Isoniazid, Rifampin (Rifampicin) and Pyrazinamide
- Akurit Tab: Isoniazid and Rifampin (Rifampicin)
- Akurit-Z Kid Dispersible Tab: Isoniazid, Rifampin (Rifampicin) and Pyrazinamide
- Akurit-4: Ethambutol, Isoniazid, Rifampin (Rifampicin) and Pyrazinamide

The two FDCs available in MoH Drug Formulary for adults are:-

- a. 4-Drug combination: Isoniazid 75 mg, Rifampicin 150 mg, Pyrazinamide 400 mg and Ethambutol 275 mg tablet
- b. 3-Drug combination: Isoniazid 75 mg, Rifampicin 150 mg and Pyrazinamide 400 mg tablet

The recommended dosages for the two FDCs are:-

- 30 - 37 kg body weight: 2 tablets daily
- 38 - 54 kg body weight: 3 tablets daily
- 55 - 70 kg body weight: 4 tablets daily
- More than 70 kg body weight: 5 tablets daily

FDCs compared to separate-drug regimens reduce the risk of non-compliance by 17% (pooled RR=0.83, 95% CI 0.64 to 1.07) and consequently improve effectiveness of therapy.^{66, level I} Smaller number of tablets to be ingested may also encourage patient adherence.^{1, level III}

RCTs showed that FDCs are as effective as separate-drug regimens for the treatment of tuberculosis:-

- Negative culture result at 18 months for FDCs and separate-drugs group was 93.9% and 94.6% respectively (RD= -0.7%, 95% CI -3.0% to 1.5%).^{67, level I}
- Smear conversion rate for FDCs and separate-drugs group was 98.1% and 98.6% respectively (RD= -0.51, 95% CI -2.27 to 1.23).^{68, level I}
- Adverse events were similar in both groups.^{67, level I}

Prescription errors are likely to be less frequent for FDCs due to easy adjustment of dosage according to patient weight.^{1, level III}

In term of bioavailability, FDCs are proven to be bioequivalent to separate-drugs formulations at the same dose levels (bioequivalence assessment within acceptable limits of 0.80 - 1.25).^{69, level I} This is important to maintain the effectiveness of therapy.

However, using FDCs does not obviate the need for separate drugs regimen for patients who develop drug toxicity, intolerance or contraindications to specific component drugs.^{1, level III; 67, level I}

Recommendation 13

- Fixed-Dose Combinations (FDCs) are preferred to separate-drugs combination for the treatment of tuberculosis. **(Grade A)**
 - In patients who develop toxicity, intolerance or contraindication to specific component drugs, FDCs can be substituted with separate-drug regimens. **(Grade A)**

4.1.6 Directly Observed Therapy (DOT)

Despite improvement of antiTB treatment since the 1950s, TB has not yet been eradicated. WHO launched Direct Observed Therapy, Short Course (DOTS) in 1995. This strategy combines drug treatment with political commitment, sputum smear microscopy for diagnosis and directly observed therapy (DOT) to ensure adherence and good management practice.

A SR comparing directly observing patient taking their medication (DOT) vs self-administered therapy (SAT) failed to demonstrate improvement in cure rate or completion of treatment rate (RR=1.06, 95% CI 100 to 1.13).^{70, level I} This was regardless of whether it was home-based or clinic-based DOT. However, a recent cohort study showed that DOT increased the completion rate compared to those on SAT (OR=3.3, 95% CI 2.4 to 4.5).^{71, level II-2}

The practice of DOT in Malaysia was reported to be 97% (ranging from 93% to 100%).^{2, level III} However a study in Thailand in 2002 showed that despite assignment of observers, only 65% to 89% of those assigned actually watched the patients taking the drugs.^{72, level II-2}

Direct observation of drug ingestion of the DOTS component should not be the sole emphasis in TB control programmes. It should not be a blanket approach; instead it should be a process of negotiation and support, incorporating patients' characteristics and choices. A controlled trial in Tanzania comparing patient-centred approach where patient was given the choice to receive treatment at home observed by a supporter of their own choice vs daily treatment at health facilities observed by healthcare worker showed a better treatment success rate in the patient-centred approach (RR=1.10, 95% CI 1.05 to 1.15).^{73, level II-1}

Besides DOT, other proven good management practices include defaulter tracing and contact tracing. Late tracer system or defaulter action, including reminder letters (RR=0.4, 95% CI 0.2 to 0.8)^{74, level I} or home visits by healthcare worker (RR=0.2, 95% CI 0.1 to 0.4)^{75, level I} have been shown to reduce the number of patients who fail to complete treatment. Success rate is also improved if a daily mobile phone call is used to remind MDR-TB patients to take medication and continue follow-up ($p=0.047$).^{76, level II-1}

Reminder system using automated telephone message has been shown to reduce non-attendance at clinic appointment (RR=0.7, 95% CI 0.6 to 0.9).^{74, level I}

In areas where DOT clinic is not possible, daily home visit and support by trained non-healthcare worker can improve cure rate ($p=0.02$) and reduce treatment failure rate ($p=0.0009$).^{77, level I}

Enhanced DOTS involving intensive contact tracing and treating the contacts with tuberculosis can reduce incidence of TB within a community ($p=0.04$).^{78, level I}

Staff and patient education is also important in improving compliance and success of anti-TB treatment. Instructions regarding compliance involving individuals with a prior history of TB and providing advice to patients currently under treatment (peer training) can reduce TB treatment default (OR=0.67, 95% 0.33 to 0.99).^{79, level II-2}

Recommendation 14

- When possible, directly observed therapy (DOT), either by healthcare worker or family member, should be adopted to improve compliance in tuberculosis (TB) management. **(Grade C)**
 - DOT should be patient-centred, incorporating negotiations, and patient's characteristics and preferences. **(Grade A)**
- Reminder system for clinic appointments should be encouraged. **(Grade A)**
- Prompt reminders should be sent to TB patients who default treatment. Failing that, home visit by healthcare workers should be carried out. **(Grade B)**
- Contact tracing should be done intensively, including home visits to retrieve contacts who do not come for screening. **(Grade C)**
- Trained non-governmental organisation staff, community members and peers should be used to reinforce compliance to treatment and provide support to patient suffering from tuberculosis. **(Grade C)**

4.2 EXTRAPULMONARY TB (EPTB) in ADULTS

EPTB is common but difficult to diagnose. With the current HIV epidemic, the prevalence of the condition is increasing. The treatment of EPTB has mainly been extrapolated from PTB treatment.

4.2.1 Optimal Duration of Treatment

Duration of EPTB treatment cannot be precisely determined due to lack of evidence. However, the basic treatment principles for PTB are applied when treating EPTB.

In three SRs of at least 12 months follow-up, 6-month chemotherapy was comparable with longer duration chemotherapy in preventing relapse of EPTB:-

- Relapse rate in cervical TB lymphadenitis was 3.3% (95% CI 1.7±5.5) in 6-month regimen as compared to 2.7% (95% CI 0.6±7.8) in 9-month regimen. Mean follow-up was 31 months for 6-month regimen and 20 months for 9-month regimen.^{80, level I}
- Relapse rate in spinal TB was 0% (95% CI 0.0 to 6.4) in 6-month regimen as compared to 2.0% (95% CI 0.6 to 5.0) in more than 6-month regimen.^{81, level II-2}
- Relapse rate in TB meningitis was 1.5% in 6-month regimen as compared to 0% in more than 6-month regimen.^{82, level II-2}

Two RCTs showed that 6-month regimen was also comparable with longer duration regimen in treating peritoneal TB:-

- 6-month regimen was as effective as 9-month regimen in preventing relapse in 12 months follow-up.^{83, level I}
- 4% of patients in 6-month and 6% in 12-month regimens required retreatment during 60 months follow-up.^{84, level I}

NICE recommends duration of EPTB treatment as follows:-⁸⁵

- meningeal TB – 2 months S/EHRZ+10HR*
- peripheral lymph node TB – should normally be stopped after 6 months
- bone and joint TB – 6 months
- pericardial TB – 6 months

Recommendation on duration of EPTB treatment by WHO are:-^{1, level III}

- regimen should contain 6 months of rifampicin: 2HRZE/4HR*
- duration of treatment for TB meningitis is 9 - 12 months and bone and joint TB is 9 months

There is no retrievable evidence on optimal duration of treatment for disseminated TB and miliary TB. There should be low threshold to suspect TB meningitis in these groups of patients and treatment duration should be prolonged between nine to twelve months.

*S=streptomycin, E=ethambutol, H=isoniazid, R=rifampicin, Z=pyrazinamide

Recommendation 15

- All extrapulmonary tuberculosis should be treated with antituberculosis treatment for a minimum of six months except for bone (including spine) and joint tuberculosis for 6 - 9 months and tuberculous meningitis for 9 - 12 months. **(Grade C)**
- Streptomycin should be used instead of ethambutol in adult TB meningitis. **(Grade C)**

4.2.2 Corticosteroids

Corticosteroid therapy may benefit patients with some forms of EPTB. However literature on corticosteroids in various form of EPTB is scant.

In two Cochrane SR, corticosteroids had been associated with improvement in survival and TB symptoms in HIV negative patients:-

- tuberculous meningitis (in all stages of severity)^{86, level I}
 - RR on mortality=0.8 (95% CI 0.7 to 0.9) and NNT=10
 - RR on death or disabling residual neurological deficit at 3 – 9 months follow-up =0.82 (95% CI 0.70 to 0.97) and NNT=10
 - the dose of dexamethasone was 12 - 16 mg daily and the duration of treatment was 6 weeks in tapering doses
- tuberculous pericarditis^{87, level I}
 - RR on mortality=0.43 (95% CI 0.18 to 0.99) and NNT=16
 - RR on death or persisting disease at two years follow-up=0.69 (95% CI 0.48 to 0.98) and NNT=10
 - the dose of oral prednisolone was 1 mg/kg (maximum 60 mg) daily for four weeks and tapering dose in next 12 weeks

A small cohort study on peritoneal TB with a mean follow-up of 23 months showed that only 11% of patients treated with corticosteroids complained of repeated abdominal pain compared to 73% in control group ($p=0.0019$). The dose of oral prednisolone was 0.5 - 1 mg/kg, tapered every 2 weeks in 4 to 9 weeks of treatment.^{88, level II-2}

In another Cochrane SR, corticosteroids reduced pleural thickening in HIV-negative patients with tuberculous pleurisy (RR=0.7, 95% CI 0.5 to 0.9). There is no pooled data on specific mortality. The dose of oral prednisolone was 1 mg/kg (maximum 60 mg) and duration of treatment was 12 weeks. The follow-up of the studies ranged between 24 and 46 weeks and no complete drainage was done except in one study.^{89, level I}

There is no good evidence for recommending corticosteroids in endobronchial TB. WHO states that unless drug resistance is suspected, adjuvant corticosteroid treatment is recommended for TB meningitis and pericarditis. **A Suggested Steroid Regimen for TB Meningitis and TB Pericarditis** are shown in **Appendix 6**.

Recommendation 16

- Corticosteroids should be used in tuberculous meningitis or pericarditis. **(Grade A)**

4.3 ROLE OF SURGERY IN PTB TREATMENT

Surgery can be a useful adjunct in the following situations:-

1. Diagnosis and obtaining tissue for culture and drug sensitivity
 - Surgical biopsy of lung parenchyma lesions, pleural lesions and mediastinal lymphadenopathies using video-assisted thoracoscopy surgery (VATS)/ thoracotomy and mediastinoscopy
2. Management of TB complications
 - This may includes selected cases of localised disease such as a focally destroyed lung or cavitory lesion that has developed complications (such as haemoptysis or abscess formation), empyema thoracis that has failed drainage and lung entrapment
3. Treatment of the disease itself where drug therapy alone may be deemed insufficient to achieve cure
 - This includes the treatment of MDR-TB, persistent smear and/or culture-positive TB despite adequate drug therapy. Factors predictive of poor outcome in surgical resection for MDR-TB include poor lung function, pre-operative haemoptysis, low body mass index, primary resistance, resistance to ofloxacin and cavitory lesions that are not amenable to complete resection.^{90, level III}

While the advancement in surgical techniques including VATS/thoracotomy has reduced the surgical mortality and morbidity, surgery for PTB is still associated with significant complications due to the presence of adhesions and scarring. The risks and benefits of surgery for each potential candidate as well as the timing of surgery should therefore always be carefully assessed on a case-by-case basis by a multidisciplinary panel involving experienced respiratory physicians, microbiologists, internists, anaesthesiologists, radiologists, physiotherapists, social workers and dietitians as well as thoracic surgeons.^{90, level III}

5. LATENT TB INFECTION (LTBI) IN ADULTS

5.1 Introduction

Many people living in high TB prevalence areas, like Malaysia, have been exposed to infectious TB either by a direct contact with a known index case or inadvertently exposed to an unsuspected active TB patient.

Some of these exposed individuals will acquire the infection. Notwithstanding, many infected individuals will ultimately develop adequate immunity to keep the infection at bay. Hence, only a small number will eventually develop active disease. Patients who have been infected but do not show any clinical manifestation of disease activity is said to have LTBI. Studies have shown that the lifetime risk of developing TB reactivation among those with LTBI is about 5 - 10%.^{91, level III} This reactivation tends to occur within the first two years after exposure. However, the risk of reactivation is much higher in immunocompromised individuals.

In countries with a low incidence of TB, most active cases have occurred among persons who were once infected, contained and then later develop active disease. The identification and treatment of individuals with LTBI who are at high risk for developing active disease have been shown to benefit both the infected individuals and the susceptible people in their communities. In the United States, this strategy and other TB control programmes had helped to prevent 44% of active TB cases from 1993 to 2004.^{92, level III}

Latent TB is defined as infection with *Mycobacterium tuberculosis* complex, where the bacteria may be alive but in the state of dormancy and not currently causing any active disease/symptoms.

5.2 Diagnosis

Traditionally, LTBI is diagnosed based on the following criteria:-

- No symptoms to suggest active disease
- Normal CXR/static CXR findings.
 - If abnormal findings are found on CXR, there should be no changes seen on repeat CXR over a period of at least six months. Most patients with LTBI have a normal CXR.^{93, level III}
 - Repeat sputum induction or bronchoalveolar lavage for AFB smear and culture should be considered in patients with abnormal CXR, even though there are no changes seen on repeat CXR.
 - Healed lesions are often characterised by nodules and fibrotic lesions that are well-demarcated.
 - Calcified nodular lesions (calcified granulomas) and apical or basal pleural thickening pose a lower risk for future progression to active TB.
- Smear/culture negative on sputum or bronchoalveolar lavage for *Mycobacterium tuberculosis* (if collected).
 - Induced sputum or bronchoalveolar lavage should be considered before initiating LTBI treatment in those with abnormal CXR findings.

- Positive TST (Mantoux Test). Refer to **Appendix 5** on the conduct of the test.
Note: Positive TST is interpreted on a graded-system based on PPVs which are largely dependent on the risk of acquiring the disease and risk of latent TB reactivation.^{94, level III}
Refer to **Table 2** on Individuals with moderate/high risk of developing TB reactivation.
 - IGRA may be used as an alternative test for TST in all situations for adults

The diagnosis of LTBI is often challenged by the lack of a gold standard diagnostic test and the absence of clinical symptoms. Until recently, TST was the only diagnostic test available to confirm the diagnosis. However, the interpretation of the result is compounded by the fact that the reagent (tuberculin) used in the test cross-reacts with BCG and NTM. This gives rise to false positive results in some individuals.

At the moment, there are two commercial tests, i.e. the T-SPOT.TB (Oxford, Immunotec) and the QFT-GIT Test (Cellestis) available to diagnose LTBI. Both are known collectively as the Interferon- γ Release Assays (IGRAs). They employ certain antigens like the ESAT-6 and CFP-10 (for T-SPOT and QFT-GIT), as well as TB7.7 (only for QFT-GIT) to stimulate the production of Interferon- γ from the T-cell lymphocytes. These antigens are theoretically more specific as they do not cross-react with the BCG and most NTM.

In a recent published meta-analysis comparing IGRAs and TST in low TB prevalence countries, IGRAs have been shown to have higher specificity and better PPV and NPV than TST in adult population.^{95, level III}

However, the same conclusion may not be applicable to countries with high incidence of TB (usually from low- and middle-income countries).^{96, level III}

- An expert group commissioned by WHO to examine the evidence of IGRAs in low- and middle-income countries concluded that the quality of evidence on the use of IGRAs in LTBI screening for healthcare workers, contacts and outbreak investigations in these countries is very low. Due to heterogeneity in study designs and outcomes, the data could not be pooled. The majority of studies showed comparable LTBI prevalence by TST or IGRA in contacts and four studies reported a statistically significant difference between positivity rates estimated by TST, T-SPOT or QFT. Both IGRAs and the TST seemed to show positive associations but the strength of the association (after adjustment) varied across studies, irrespective of BCG vaccination. Results indicated that concordance between TST and IGRAs ranged widely.
- Three studies included the analysis of IRR stratified by IGRAs and TST. The association with subsequent incidence of TB in test-positive individuals compared to test-negatives appeared higher for IGRAs than for TST; however, this was not statistically significant [IRR for IGRA=3.2 (95% CI 0.6 to 5.9) and TST=2.3 (95% CI 0.8 to 3.7)].
- In addition, there was no statistically significant increase in incidence rates of TB in IGRA-positives compared to IGRA-negatives in vast majority of individuals (>95%) during follow-up. Both IGRAs and the TST appeared to have only modest predictive value and did not help identify those who are at highest risk of progression to disease.
- The Development Group suggests that the situations where IGRAs may be used are as the following:
 - i. As an alternative to TST for
 - Patients who are not expected to/could not come back for a reading of skin induration after 48 - 72 hours
 - Patients who had recent BCG vaccination or past NTM infection

- ii. Where a 2-step test is considered (TST followed by IGRA)
 - Close-contacts whose TST is in the range of 5 - 9 mm
 - Patients who are offered LTBI treatment but are not convinced that they have LTBI
 - Individuals who require annual screening of LTBI such as healthcare providers working in high risk areas)

5.3 Treatment

There is no good evidence to support the various cut-off measurements of TST in diagnosing LTBI for individuals living in high prevalence countries with moderate/high risk of developing TB reactivation. Thus, the Development Group suggests that a TST of ≥ 10 mm should be considered as a positive test for LTBI for most individuals investigated in this country except for categories listed in the table below:-

Table 2: Positive TST for LTBI

Positive TST Reaction (Measurement)	Type of Individual
≥ 5 mm	<ul style="list-style-type: none"> • HIV-infected persons • Organ transplant recipients • Persons who are immunosuppressed for other reasons (such as those taking the equivalent of >15 mg/day prednisolone for ≥ 1 month or taking TNF-α antagonists)
≥ 15 mm	<ul style="list-style-type: none"> • Individuals from countries with low incidence of TB
≥ 10 mm	<ul style="list-style-type: none"> • All other high risk individuals

It is further suggested that only individuals who are at high risk of acquiring LTBI or developing TB reactivation should be investigated. These include:-

- HIV-infected persons
- Organ transplant recipients
- Persons who are receiving immunosuppressant drugs
- Recent close contacts (<2 years)
- Recent immigrants (<2 years) from high prevalence countries
- Injecting drug users
- Residents and employees of high risk congregate settings (such as correctional facilities, nursing homes, homeless shelters, hospitals and other health care facilities)
- Persons with fibrotic changes on CXR consistent with old TB (patients with calcified lesions should be excluded)

Patients with LTBI should be treated with one of the following regimens as shown in **Table 3**:-

Table 3: AntiTB Regimens for LTBI in Adults

Drugs	Duration	Interval	Completion criteria
Isoniazid	6 - 9 months	Daily	<ul style="list-style-type: none"> • 180 doses in 9 months (6-month regimen) • 270 doses in 12 months (9-month regimen)
Isoniazid + rifampicin	4 months	Daily	<ul style="list-style-type: none"> • 120 doses within 6 months
Rifampicin	4 months	Daily	<ul style="list-style-type: none"> • 120 doses within 6 months
Isoniazid and rifapentine*	3 months	Once weekly	<ul style="list-style-type: none"> • 12 doses

*Rifapentine is not currently registered in Malaysia. Its use should be restricted to those on DOT (Directly observed therapy).

(Adapted from Centers for Disease Control and Prevention. Treatment Options for Latent Tuberculosis Infection. Available at <http://www.cdc.gov/tb/publications/factsheets/treatment/LTBITreatmentOptions.htm>)

Notes:

- Isoniazid
 - This regimen has a long established track record for efficacy in preventing TB reactivation.
 - The recommended treatment regimen for LTBI is nine months of daily isoniazid. The shorter course of six month is an acceptable alternative.
 - This regimen is also very effective and preferred for HIV-infected people taking antiretroviral treatment and children aged 2 - 11 years of age.
- Rifampicin and pyrazinamide (for 2 months)^{97, level III; 98, level II-1}
 - This regimen should no longer be used due to concerns on severe liver injury and deaths.
- Isoniazid and rifapentine^{99, level I}
 - This is the latest addition to the LTBI treatment regimens.
 - The 12-dose regimen does not replace other recommended LTBI treatment regimens; it is another effective regimen option for otherwise healthy patients aged ≥12 years who have increased risk of developing TB.
 - This regimen is not recommended for:-
 - Children younger than 2 years old
 - People with HIV/AIDS who are taking antiretroviral treatment
 - People presumed to be infected with isoniazid- or rifampicin-resistant *Mycobacterium tuberculosis*
 - Pregnant women or women expecting to become pregnant within the 12-week regimen

For treatment of contacts with index case of MDR-TB:-

- There is no RCT addressing the effectiveness of preventive therapy in close contacts of MDR-TB cases.^{100, level I}
- The Centers for Disease Control and Prevention (CDC) USA, American Thoracic Society and IDSA recommend that immunocompetent people exposed to MDR-TB be followed up for six months, whether they are treated or not.^{101, level III}

- If treatment is administered (should only be considered for individuals with high risk of TB reactivation), the following 6 - 12 month two-drug regimens are recommended (if the organisms from the index case patient are known to be susceptible to these agents): pyrazinamide and ethambutol or pyrazinamide and a quinolone (levofloxacin or ofloxacin).^{101, level III}

Recommendation 17

- Latent tuberculosis infection (LTBI) should be diagnosed based on the absence of symptoms, normal/static chest x-ray findings and positive tuberculin skin test (TST) / interferon-gamma release assays (IGRA). **(Grade C)**
- LTBI screening should only be performed on high risk individuals*. **(Grade C)**
- TST should be used as the preferred test in diagnosing LTBI. **(Grade C)**
- IGRA could be used as an alternative test to TST for LTBI especially in certain situations**. **(Grade C)**
- If LTBI testing is inconclusive, the patient should be referred to a specialist with experience in tuberculosis management. **(Grade C)**
- Patients with LTBI may be offered treatment. **(Grade C)**

*Refer to 5.3 above.

**Refer to 5.2 above.

The effectiveness of LTBI treatment in this country with relatively high TB incidence has not been well-established. A long-term local longitudinal study will need to be conducted before firm recommendation could be given

6. TB IN CHILDREN

There is an increasing trend of TB cases among children in Malaysia.^{2, level III} PTB and lymph node TB are the commonest presentations. Most children with PTB are sputum negative, hence high index of clinical suspicion is required for the diagnosis. Contact with an active TB person is a strong factor to suspect TB in a symptomatic child. Common clinical features suggestive of TB in children are prolonged fever, failure to thrive, unresolved pneumonia, loss of weight and persistent lymphadenopathy. The symptoms are non-specific therefore other chronic diseases must also be ruled out especially if there is no history of contact.

6.1 Diagnostic Tests for Active TB

Diagnosing PTB in children remains a challenge, especially in younger children who cannot produce sputum. CXR (both antero-posterior and lateral views) remain the most appropriate initial test if TB is suspected in a child.

Gastric lavage/aspiration is performed in infants and young children who are unable to expectorate sputum. For better diagnostic yield of gastric lavage or aspiration, standard protocols need to be followed during the procedure (refer to **Appendix 5**).

Studies showed that with specific definitions in performing gastric lavage i.e. clinical indications or radiological suspicion, the bacteriologic yield for microscopy and culture were 4 - 21% and 17 - 50% respectively.^{102, level III}

Gastric aspirate has a twice the yield in case detection by culture as compared to nasopharyngeal aspirate (NPA).^{103, level II-2}

Both positive T-SPOT.TB (IGRA) and TST responses are strongly associated with increasing likelihood of TB ($p < 0.05$) and increases with exposure ($p < 0.05$). However, children ≤ 12 months of age are more likely to have positive TST results (40% [95% CI 25 to 58]) rather than positive T-SPOT.TB results (3% [95% CI < 0.0001 to 18]).^{104, level III}

In newborn, TST is often negative at presentation and should be repeated after 3 months by which time it is frequently reactive.^{105; 106-108, level III}

The investigations for EPTB in children are similar as in adults.

Recommendation 18

- Children suspected of pulmonary tuberculosis should have sputum examination, chest x-ray and tuberculin skin test performed. **(Grade C)**
 - Gastric lavage/aspiration should be performed in infants and children who are unable to expectorate sputum. **(Grade C)**

6.2 Treatment of Active TB

Anti-TB drug and management of children with TB should be in line with the WHO Stop TB Strategy, taking into consideration the epidemiology and clinical presentation of TB in children.

Obtaining good treatment outcome depends on the application of standardised treatment regimens according to the relevant diagnostic category (refer to **Table 4**), with support for the child and caregivers that maximises adherence to treatment.

Table 4: Recommended Treatment Regimens for Children in Different TB Diagnostic Categories

TB cases	Regimen*		Remarks
	Intensive phase	Continuation phase	
New smear positive PTB New smear negative PTB Less severe EPTB	2HRZ	4HR	Ethambutol can be added in the intensive phase of suspected isoniazid-resistance or extensive pulmonary disease cases.
Severe concomitant HIV disease	2HRZE	4HR	
Severe form of EPTB TB meningitis/ spine/bone	2HRZE	10HR	
Previously treated smear positive PTB including relapse and treatment after interruption	3HRZE	5HRE	All attempt should be made to obtain culture and sensitivity result. In those highly suspicious of MDR-TB, refer to paediatrician with experience in TB management.
Treatment failure TB			Refer to paediatrician with experience in TB management.
MDR-TB	Individualised regimen		Refer to paediatrician with experience in TB management.
*Direct observation of drug ingestion is recommended especially during the initial phase of treatment and whenever possible during the continuation phase.			

H=isoniazid, R=rifampicin, Z=pyrazinamide, E=ethambutol

Modified from:

1. World Health Organization. Rapid advice - treatment of tuberculosis in children. Geneva: WHO; 2010
2. World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. Geneva: WHO; 2006

A SR showed that ethambutol can be used safely in children, especially in situations where it is possible to monitor the complications (particularly optic neuritis) regularly. For a given dose of ethambutol, its serum concentration is lower in children compared to adults.^{58, level III} Therefore the doses of ethambutol recommended in children are higher than in adults.

AntiTB drug doses for children are usually extrapolated from adult pharmacokinetic studies. Recent data showed inadequacy of currently recommended doses of isoniazid and rifampicin in children in achieving the desired serum level. Refer to **Table 5** on recommended doses of antiTB drugs

Serum concentration of isoniazid in children taking adult dose of the drug is below the recommended level in 70% of children. Median peak concentration of isoniazid in children is lower in those prescribed 4 - 6 mg/kg compared to those prescribed 8 - 10 mg/kg. The risk of hepatitis is not significantly raised when comparing the 4 - 6 mg/kg dose and 8 - 10 mg/kg dose.^{109, level III-2} Children eliminate isoniazid faster and require a higher body weight dose (mg/kg) to achieve serum concentrations comparable to those in adults. Supplemental pyridoxine (5 - 10 mg/day) is recommended in malnourished children, HIV-infected children, breastfeeding infants and pregnant adolescents.^{110, level III}

Low serum rifampicin concentrations have been documented in children receiving the standard dose of 8 - 12 mg/kg. While this may be of no consequence in the management of less serious forms of childhood TB, it might well be very relevant in more severe forms of TB.

Table 5: Recommended Doses of AntiTB Drugs in Children

Drug	Dose (range) in mg/kg	Maximum dose
Isoniazid	10 (10 - 15)	300 mg
Rifampicin	15 (10 - 20)	600 mg
Pyrazinamide	35 (30 - 40)	2 g
Ethambutol	20 (15 - 25)	1 g

Pyridoxine 5 - 10 mg daily needs to be added if isoniazid is prescribed.

Recommendation 19

- All children with tuberculosis should be given standardised treatment regimens and dosages according to the relevant diagnostic categories. **(Grade C)**

6.3 Diagnostic Tests for LTBI

Young children living in close contact with a case of smear-positive PTB are at risk of TB infection and disease. The risk of developing disease after infection is much greater for infants and young children under five years. Active TB usually develops within two years of infection but the time-lag can be as short as a few weeks in infants.^{110, level III}

The cornerstone of LTBI diagnosis for the past 100 years has been the TST (refer **Appendix 5**). The lack of a gold standard for LTBI is a recognised inherent limitation of all studies that investigate the use of IGRAs for the detection of LTBI. Therefore estimating the sensitivity of any new test for LTBI problematic.^{111, level III}

Studies showed wide range of agreement (poor to good with κ ranging from 0.17 to 0.55) between TST and IGRAs.^{111 - 114, level III} However the χ values increased when more-stringent TST cut-off criteria were used:^{113, level III}

- $\chi=0.19$ for >10-mm induration in TST (poor agreement)
- $\chi=0.31$ for >15-mm induration in TST (moderate agreement)
- $\chi=0.30$ for >20-mm induration in TST (moderate agreement)

The proportion of contacts positive by TST, T-SPOT and QFT-GIT increases with increasing exposure to the index case. The increase is most evident for TST ($p<0.0001$). Positive results from TST and two commercially available IGRAs (T-SPOT and QFT-GIT) are not confounded by the presence or absence of a BCG scar.^{112, level III}

QFT-GIT test is less likely to be positive when the infection occurs in children less than two years of age. The amount of Interferon Gamma (IFN- γ) released is correlated directly with age ($p<0.0001$).^{113, level III} WHO states that the sensitivity of both IGRAs and TST are reduced in young and HIV-positive children.^{96, level III}

Recommendation 20

- Tuberculin skin test (TST) should be used as a standard test to diagnose latent tuberculosis infection (LTBI) in children. **(Grade C)**
- Interferon Gamma Release Assay should not be used as a replacement for TST in diagnosing LTBI in children. **(Grade C)**

6.4 Treatment of LTBI

TB infected children are important reservoir in sustaining the disease over future decades.

Risk of progression to disease is increased when primary infection occurs before adolescence, particularly in the very young (0 - 4 years old) and in immunocompromised children.^{115, level III}

Children younger than 5 years of age with LTBI have a 10 - 20% risk of developing TB disease.^{116, level III}

a. Treatment of LTBI in non-HIV infected children

Active TB must be ruled out before starting LTBI regimen.

In a cross-sectional study on LTBI in children, 3-month isoniazid plus rifampin (3HR) regimen had a failure rate of 0.87%, 95% CI 0.3 to 2.5.^{117, level III}

A large biphasic RCT of 9-month isoniazid (9H) vs 4-month isoniazid plus rifampin (4HR) [phase 1] and 3HR vs 4HR [phase 2] showed that the 4HR regimen was more effective compared to 9H regimen for children having LTBI with treatment failure rates of 11.8% & 24% respectively ($p=0.001$). Subsequent second phase of the study noted that 3HR was as equally effective as 4HR ($p=0.418$).^{118, level III}

There was no significant difference in adherence rates between the 3HR and 4HR ($p=0.533$), but 9H had lower adherence rate compared to 4HR ($p=0.029$). Short course 3HR and 4HR had equal minor side effects as 9H which did not warrant discontinuation or modification of treatment.^{118, level III}

Alternatively, 6-month of isoniazid for children with LTBI is recommended by WHO.^{110, level III} Studies on LTBI in adults showed that 12-month of preventive isoniazid was better than 6-month treatment in reducing the number of TB cases i.e. 75% and 65% respectively. However, the 6-month isoniazid is recommended considering the problems of adherence and hepatotoxic effects of longer duration of isoniazid.^{119, level I}

NICE guidelines recommend a regimen of either three months of rifampicin plus isoniazid or six months of isoniazid for children with LTBI.⁸⁵

In US, nine months of daily isoniazid is the recommended regimen for children and adolescents with LTBI. Statistical analysis revealed no additional benefit between 9-month and 12-month of isoniazid.^{120, level III}

There was no retrievable evidence comparing 6-month isoniazid regimen with other shorter duration regimens.

Table 6: AntiTB Regimens for LTBI in Children

Drugs	Duration	Interval
Isoniazid	6 months	Daily
Isoniazid + rifampicin	3 months	Daily

b. Treatment of LTBI in HIV-infected children

There is no retrievable evidence of treatment for LTBI in HIV-infected children. However, WHO recommends 6-months isoniazid therapy.^{121, level I}

Recommendation 21

- Non-HIV infected children with latent tuberculosis infection should be treated with 6-month of isoniazid or 3-month of isoniazid plus rifampicin. **(Grade C)**

6.5 MDR-TB Contacts

WHO does not recommend second-line drugs for chemoprophylaxis of MDR-TB contacts. Children who are close contacts of MDR-TB patients must be followed-up for at least two years. They are treated promptly if active disease develops with the regimen recommended for MDR-TB.^{110, level III}

6.6 BCG Lymphadenitis

BCG lymphadenitis tends to occur 2 - 4 months after vaccination and suppuration can occur in 30 - 80% of lymphadenitis. Although it is normally self-limiting, management is advised if the node is more than 3 cm in diameter, fluctuant and the overlying skin is inflamed.

For children who need further management, needle aspiration has a role in BCG lymphadenitis. The rate of regression was higher with a difference of 0.3 (95% CI 0.2 to 0.4) and the rate of spontaneous drainage was lower with a difference of 0.4 (95% CI 0.2 to 0.6) in the needle aspiration compared to control group at six months.^{122, level III}

Complete surgical excision is curative and reduces healing time when aspiration fails or if multiple nodes are involved. Addition of antiTB drugs after excision is of no extra benefit. Surgical incision and drainage is not recommended.^{123, level III}

Medical therapy such as erythromycin, isoniazid and rifampicin have been used, but no proper trials have shown that it can reduce suppuration or shorten duration of healing.^{123, level III}

Recommendation 22

- Medical therapy should not be offered routinely in BCG lymphadenitis. **(Grade C)**

6.7 Congenital & Perinatal TB

Timely and properly administered antiTB treatment for the mothers with TB is the best way to prevent infections in their infants. These mothers should continue breastfeeding (refer to **Chapter 8 on TB in Pregnancy, Lactation and Oral Contraceptive Use**).^{1, level III; 124, level III}

Congenital TB is defined as a direct spread through the umbilical cord, by aspiration or swallowing of infected amniotic fluid, or by direct contact with maternal genital lesions during delivery. Perinatal TB includes early postnatal transmission of the disease and is a more inclusive term.^{107 - 108, level III}

The distinction between congenital TB and postnatally acquired disease in neonates has little practical significance since the clinical manifestations, treatment and prognosis are the same. The clinical features are respiratory distress, hepatosplenomegaly, fever, lymphadenopathy and poor feeding.^{106, level III; 108, level III}

Perinatal TB infection should be considered in all infants with sepsis, pneumonia unresponsive to standard treatment and congenital viral infections.^{105; 106, level III} For investigations, refer to **Section 6.1** above. When a woman is suspected of having TB, the placenta and vaginal or endometrial samples/biopsy should be obtained for culture and histopathological examination. However, this is frequently difficult given the later presentations.^{106 - 107, level III}

After active TB is ruled out, babies at risk of infection from their mothers should be given six months of isoniazid preventive therapy, followed by BCG vaccination (refer to **Table 7**).^{1, level III; 107, level III; 124 - 125, level III}

Alternatively, if three months of isoniazid is given, TST should be done on completion of treatment.^{105; 107, level III}

- If TST is negative (<5 mm), BCG vaccine should be administered and treatment stopped
- If TST is positive (≥5 mm), treatment should continue for six months, followed by the BCG at the end of treatment.

Table 7: Prophylaxis for Infants with Maternal TB

Active PTB diagnosed before delivery		Active PTB diagnosed after delivery	
>2 months before		<2 months before	>2 months after
Smear negative just before delivery	Smear positive just before delivery	-	-
No prophylaxis for infant	Give prophylaxis: Isoniazid for six months OR isoniazid for three months followed by TST	Give prophylaxis: Isoniazid for six months OR isoniazid + rifampicin for three months	
BCG at birth	Defer BCG at birth, give after stopping isoniazid	Reimmunise with BCG after stopping isoniazid	If BCG given at birth, no need to reimmunise

Modified: World Health Organization. Breastfeeding and Maternal Tuberculosis, Geneva: WHO; 1998

Recommendation 23

- BCG should not be given to babies on prophylactic tuberculosis (TB) treatment. **(Grade C)**
- Prophylactic TB treatment should be given to babies born to mothers with active pulmonary TB except those diagnosed more than two months before delivery who have documented smear negative before delivery. **(Grade C)**

7. TB IN PREGNANCY, LACTATION & USE OF ORAL CONTRACEPTIVE PILLS

Maternal TB has been associated with increased risk of maternal mortality and perinatal morbidity, namely premature delivery, small-for-gestation age and low birth weight.^{126 - 127, level III} A pregnant or lactating woman should be advised that successful treatment of TB with the standard regimen is important to ensure best outcome to the mother and her baby.

7.1 Pregnancy

Women of child bearing age should be asked about current or planned pregnancy prior to starting antiTB drugs.^{1, level III}

Isoniazid, rifampicin, ethambutol and pyrazinamide are safe to be used in pregnancy.^{1, level III; 105: 125, level III}

There was no increased risk of congenital abnormalities in babies after their mothers receive treatment with isoniazid and other antiTB drugs. However, this study involved small number of mothers on antiTB drugs in first trimester.^{128, level II-2}

Streptomycin should be avoided in pregnancy due to foetal ototoxicity. Pyridoxine (25 mg daily) should be given to all pregnant women on isoniazid to prevent foetal neurotoxicity.^{1, level III; 105: 125, level III}

The usage of second-line antiTB drugs in pregnancy should be instituted after consultation with TB specialist as little is known of their safety.¹⁰⁵

7.2 Lactation

Breastfeeding mothers with TB should receive a full course of antiTB drugs. Timely and proper administration of such drugs is the best way to prevent TB transmission to the baby.^{1, level III; 105}

First-line antiTB drugs are safe in breast feeding.^{125, level III; 129, level II-3}

Mother and baby should stay together for continuation of breastfeeding. Once active TB in the baby is ruled out, the baby should be given six months isoniazid prophylaxis, followed by BCG vaccination (refer to **Chapter 6 on TB in Children**).^{1, level III; 124, level III} Surgical mask should be used if the mother is deemed infectious.

Separation of the infant from the mother should be considered if the mother has MDR-TB or is non-compliant to treatment.^{125, level III}

Pyridoxine supplementation is recommended for all pregnant or breastfeeding women taking isoniazid.^{1, level III}

7.3 Use of Oral Contraceptive Pills

Rifamycin drugs such as rifampicin and rifabutin reduce the contraceptive efficacy of both combined oral contraceptives and progesterone-only pills. Alternative contraceptive methods should be used during rifamycin therapy and for one month after stopping the therapy even if it has been administered for less than a week.¹⁰⁵

Recommendation 24

- All women of child bearing age suspected of tuberculosis (TB) should be asked about current or planned pregnancy. **(Grade C)**
- First-line antiTB drugs except streptomycin can safely be used in pregnancy. **(Grade C)**
- First-line antiTB drugs can safely be used in breastfeeding. **(Grade C)**
- Pyridoxine supplementation should be given to all pregnant and breastfeeding women taking isoniazid. **(Grade C)**
- Patient on rifampicin should use alternative contraception methods other than oral contraceptives and progesterone-only pills. **(Grade C)**

8. LIVER & RENAL IMPAIRMENT

Patients with liver and renal impairment may need frequent monitoring while on antiTB treatment. They may develop side effects due to treatment or may end up receiving inadequate therapy. Expert consultation is advisable when treating these patients.

8.1 Liver Impairment

In patients with unstable or advanced liver disease, baseline liver function tests should be done at the beginning of treatment.^{1, level III} Regular monitoring at weekly/biweekly intervals for the initial two months should be done and followed by more widely spaced assessments all through the rest of treatment.^{130, level III}

If baseline liver enzyme, alanine aminotransferase (ALT), is more than three times upper limit of normal before the initiation of treatment, one of the following antiTB regimens should be considered. The more unstable or severe the liver disease, the fewer hepatotoxic drugs should be used:^{-1, level III}

- Two hepatotoxic drugs (rather than three in the standard regimen)
 - 9 months of isoniazid and rifampicin, plus ethambutol (until or unless isoniazid susceptibility is documented)
 - 2 months of isoniazid, rifampicin, streptomycin and ethambutol, followed by 6 months of isoniazid and rifampicin;
 - 6 - 9 months of rifampicin, pyrazinamide and ethambutol.
- One hepatotoxic drug
 - 2 months of isoniazid, ethambutol and streptomycin, followed by 10 months of isoniazid and ethambutol.
- No hepatotoxic drugs
 - 18 - 24 months of streptomycin, ethambutol and fluoroquinolones*.

*Newer fluoroquinolones such as levofloxacin and moxifloxacin are preferred over the older generations.^{131, level I}

Recommendation 25

- Regular monitoring of liver enzymes should be performed in patients on antituberculosis treatment with pre-existing liver disease or at risk of drug-induced hepatitis. **(Grade C)**
- Expert consultation is advisable in treating tuberculosis patients with advanced or unstable liver disease. **(Grade C)**

8.2 Renal Impairment

The recommended initial TB treatment regimen for patients with renal failure or severe renal insufficiency is two months of isoniazid, rifampicin, pyrazinamide and ethambutol, followed by four months of isoniazid and rifampicin.^{1, level III}

There is significant renal excretion of ethambutol and metabolites of pyrazinamide, and doses should therefore be adjusted. Three times per week administration of these two drugs at the following doses is recommended: pyrazinamide (25 - 30 mg/kg), and ethambutol (15 - 25 mg/kg).^{1, level III; 132, level III} This should provide adequate maximum plasma concentration of the drug (C_{max}), avoid accumulation of pyrazinamide metabolites and ethambutol.^{132, level III}

Pyrazinamide should be administered after hemodialysis to avoid premature drug removal. All four antiTB drugs may be administered after hemodialysis to facilitate directly observed therapy.^{132, level III}

Because of an increased risk of nephrotoxicity and ototoxicity, streptomycin should be avoided in patients with renal failure. If streptomycin need to be used, the dosage is 15 mg/kg, 2 or 3 times per week, to a maximum of 1 gram per dose, and serum levels of the drug should be monitored.^{1, level III}

Refer **Appendix 6** for **Suggested AntiTB Dosing for Adult Patients with Reduced Renal Function**

Recommendation 26

- Frequency of pyrazinamide and ethambutol should be adjusted in patients with tuberculosis (TB) and renal failure. **(Grade C)**
- Streptomycin should be avoided if possible in patients with TB and renal failure. **(Grade C)**
- Physician with experience in TB management should be consulted for all TB patients with renal impairment. **(Grade C)**

9. HIV INFECTION

TB is one of the leading causes of death among people infected with HIV. The management of HIV-related TB is complex.

9.1 Prevalence of TB-HIV Co-Infection

TB and HIV Infection have a bidirectional interaction, resulting in an accelerated development of both diseases. HIV infection accelerates the development of TB from infection to advanced disease. In turn, TB depletes the CD4 T-lymphocytes count and intensifying the immunodepressant effect of HIV.^{133, level III}

At least one-third of HIV-positive persons worldwide are infected with *Mycobacterium tuberculosis* and 8 - 10% of them develop clinical disease every year.^{134, level III} For the past three years, local registry showed that HIV-TB coinfection in Malaysia has stabilised.^{2, level III}

PTB is still the major type of presenting disease in HIV-TB co-infection. However, many EPTB lesions are also found: pulmonary (44.0 - 79.5%), extrapulmonary (14.0 - 18.8%), both pulmonary and extrapulmonary TB (2.7 - 3.0%).^{135, level II-2; 136, level III} In a retrospective study, Leeds found that the most common sites of EPTB were:^{137, level III}

- lymphatic (28%)
- disseminated TB (28%)
- meningeal (22%)

In those with HIV and EPTB, 40% of cases have concomitant PTB and these patients are more likely to have disseminated TB (OR=1.9, 95% CI 1.3 to 2.8). HIV patients with EPTB and CD4 <100 cells/μl are more likely (OR=1.6, 95% CI 1.0 to 2.4) to have severe form of EPTB (central nervous system (CNS)/meningeal or disseminated) compared to lymphatic EPTB.^{137, level III}

TB rates are higher in individuals who are Highly Active Antiretroviral Therapy (HAART)-naïve (1.6/100 person-years, 95% CI 1.4 to 1.8) compared to those who are on HAART (0.5/100 person-years, 95% CI 0.3 to 0.8).^{138, level II-2}

In treatment-naïve TB patients, pooled prevalence of MDR-TB among HIV patients was noted to be 2.7 (95% CI 2.0 to 3.7)^{139, level III} In a SR, HIV infection had been identified as an independent risk factor for primary MDR-TB with OR=2.5 (95% CI 1.2 to 5.2).^{140, level III}

Risk of mortality is 2.6 times higher (95% CI 1.6 to 4.1) in HIV-positive patients who develop TB compared to those who do not.^{141, level II-2}

Recommendation 27

- Active tuberculosis should be ruled out in all HIV-positive patients. **(Grade C)**

9.2 Diagnostic Tests

TB-HIV co-infected patients require the diagnostic tests as in HIV-negative individuals. Nevertheless, the work up remains a diagnostic challenge in advanced HIV-positive TB patients due to various issues:-

- Many patients have no cough (45%) and negative sputum AFB smears (49%).^{136, level III}
- HIV infection is associated with lower AFB concentration in sputum among patients with active PTB.
 - o AFB density in sputum decreases with decreasing CD4 count ($p=0.001$).^{142, level III}
 - o Sensitivity of microscopic examination of two sputum AFB is only 38%.^{143, level III}
- The rate of normal CXR among patients with culture-confirmed PTB is high (22% in HIV-positive vs 6% HIV-negative patients with $p<0.001$).^{144, level II-2}
- HIV-positive cohort has less cavitary disease on initial CXR as compared to HIV-negative cohort ($p<0.001$).^{145, level II-2}

Hence, respiratory specimen cultures should be obtained in all TB suspects with a normal CXR, particularly HIV-positive persons.^{144, level II-2} TB cultures are also required for biopsy specimen from extrapulmonary sites as in HIV-negative TB patients.

The pooled sensitivity (61 - 77%) and specificity (63 - 76%) of IGRA in HIV-positive patients are suboptimal for being used alone to rule in or rule out active TB.^{146 - 147, level III}

Recommendation 28

- In all HIV-positive patients suspected of pulmonary tuberculosis, sputum tuberculosis (TB) culture should be done regardless of smear acid fast bacilli status. **(Grade C)**
- TB culture and biopsy specimen should be obtained to diagnose extrapulmonary TB in HIV-positive patients. **(Grade C)**
- Interferon-Gamma Release Assays should not be used alone in diagnosing active TB in HIV-positive patients. **(Grade C)**

9.3 Treatment Regimen for TB-HIV Co-Infection

Active pulmonary or extrapulmonary TB in HIV-infected patients require prompt initiation of TB treatment.^{148, level III} The treatment of TB among HIV-infected patients is complicated by higher rate of TB relapse ($p<0.001$)^{145, level II-2} and increased mortality rate during treatment (overall rate=30.0%, 95% CI 17.9 to 44.6%).^{149, level II-2}

Recommendations for the treatment of TB in HIV-infected adults are identical to those for HIV-uninfected adults which is six month regimen consisting of:-^{150 - 151 level III}

- an initial phase of isoniazid, rifampicin, pyrazinamide and ethambutol for two months followed by
- isoniazid and rifampicin for four months

when the disease is caused by organisms that are known or presumed to be susceptible to the first-line drugs.

Six months should be considered as the minimum duration of TB treatment. If there is evidence of a slow or suboptimal response such as cultures are still positive after two months of therapy, prolongation of the continuation phase to seven months (a total of nine months treatment) should be strongly considered.^{151, level III} All HIV-positive patients should receive daily treatment in maintenance phase.^{1, level III}

For patients with EPTB, a 6- to 9-month regimen (2 months of isoniazid, rifampicin, pyrazinamide and ethambutol followed by 4 - 7 months of isoniazid and rifampicin) is recommended. Many experts recommend 9 - 12 months of antiTB for CNS disease (tuberculoma or meningitis) and bone or joint TB.^{150, level III}

In those with HIV-TB co-infection, higher rate of TB relapse is associated with:-^{145, level II-2}

- 6-month of a rifamycin-based TB regimen vs >6-month regimen (HR=4.3, 95% CI 1.3 to 14.8)
- intermittent dosing vs daily dosing (HR=4.1, 95% CI 1.1 to 15.6)
(none of the HIV-infected adults received HAART during the study period)

Recommendation 29

- Antituberculosis (antiTB) regimen offered to HIV-positive adults should be the same as for HIV-negative adults. **(Grade C)**
 - o Daily treatment should be offered in the maintenance phase. **(Grade C)**
- Minimum duration of antiTB treatment to be considered in HIV-infected adults is:-
 - o six months for pulmonary tuberculosis. **(Grade C)**
 - o six to twelve months for extrapulmonary tuberculosis. **(Grade C)**

• Rifabutin in TB-HIV patients

Rifamycins (rifampin or rifabutin) are crucial component in drug-sensitive TB treatment. Rifampin is also known as rifampicin.

AntiTB regimens in which rifampin is only used for the first two months result in higher rates of treatment failure and relapse.^{55, level I} Therefore, regimen for patients with HIV-TB co-infection should consist of a rifamycin for the full course, unless the Mycobacterium is resistant to rifamycin or the patient has a severe side effect that is clearly due to the rifamycin.

Among the rifamycin, rifampicin is the most potent inducer of CYP450 system and is associated with significant interactions with most antiretroviral (ARV) drugs including all protease inhibitors (PIs). The administration of rifampicin with a combination of indinavir (800 mg) and zidovudine (100 mg) twice daily could lead to subtherapeutic concentrations of indinavir.^{152, level II-3} Hence, rifampicin is not recommended in combination with all PIs.^{148, level III}

Rifabutin, being a weaker enzyme inducer, has much less effect on drugs metabolism through the CYP3A system. It is also as effective as rifampicin.^{148, level III} The combination of rifabutin with PI-based ARV therapy is the preferred form of therapy for patients who are unable to take NNRTI-based ARV therapy.^{148, level III; 153, level III} Concomitant use of rifabutin and PIs is successful in the treatment of HIV-infected patients with TB.^{154, level II-2}

Recommendation 30

- Co-administration of rifampicin and protease inhibitors (PI) should not be used in HIV-TB co-infection. **(Grade C)**
- Rifabutin* should be used with PI-based Highly Active Antiretroviral Therapy for HIV-TB co-infected adults. **(Grade C)**

*Not registered in Malaysia

9.4 Isoniazid Prophylaxis Therapy (IPT)

HIV infection significantly increases the risk of progression from latent to active TB. On the other hand, active TB causes higher HIV viral loads and more rapid progression of HIV disease. Annual risk of TB reactivation is 5 - 10% among HIV-infected patients.^{155, level III}

IPT reduces the risk of developing TB by 33% regardless of mantoux status (RR=0.7, 95% CI 0.5 to 0.9).^{156, level I}

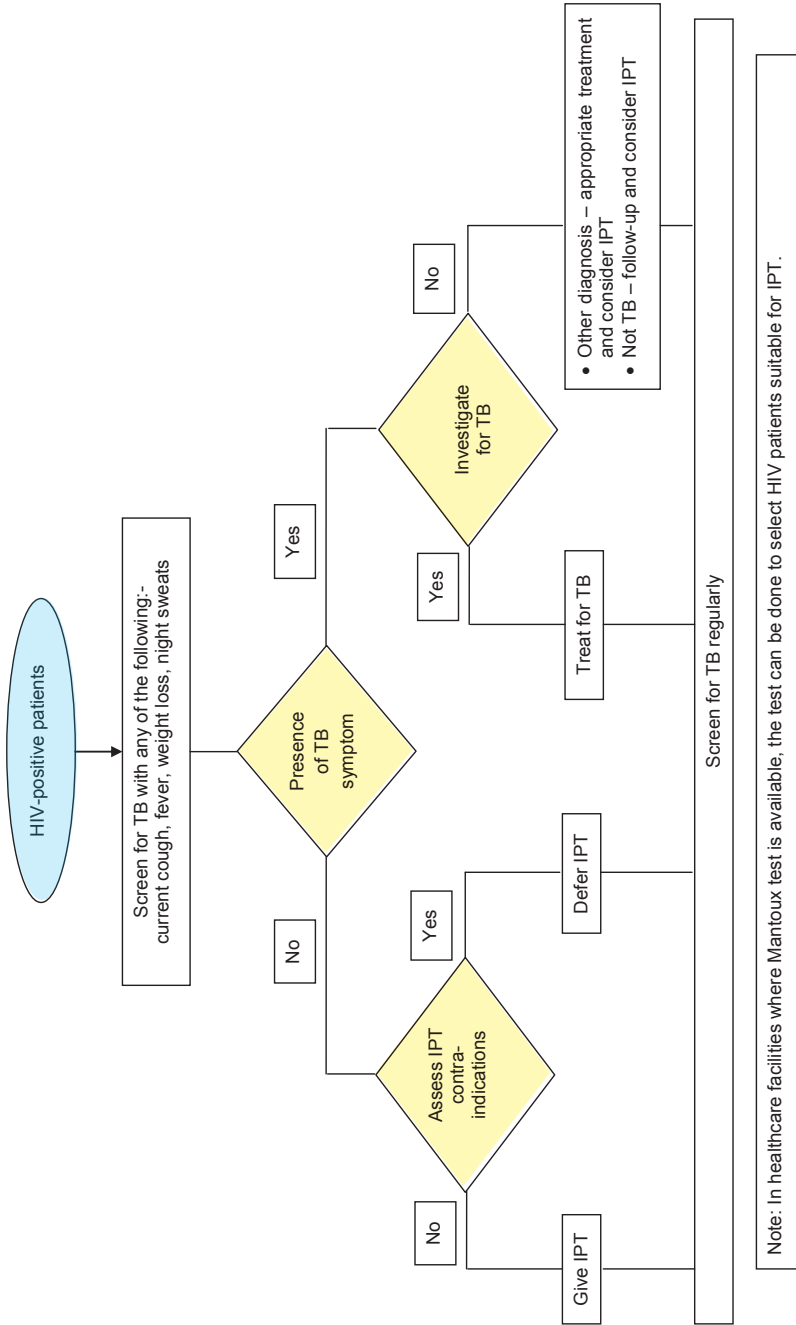
In a meta-analysis on sensitive TB screening rule, HIV-infected patients with absent current cough, fever, weight loss or night sweats had low probability of having active TB. The negative predictive value of this rule was 97.7% (95% CI 97.4 to 98.0) and 90.0% (95% CI 88.6 to 91.3) at 5% and 20% prevalence of TB among people living with HIV respectively.^{157, level II-2}

Another meta-analysis showed no difference in the development of active TB between six-month and 12-month IPT (RR=0.6, 95% CI 0.3 to 1.1).^{121, level I} Thus, the MoH circular recommends daily IPT to be given for at least six months.^{158, level III}

In the same meta-analysis above, IPT did not demonstrate an increased risk of isoniazid resistant TB (RR=6.88, 95% CI 0.01 to 3882.85).^{121, level I}

Refer to **Algorithm 3** below on TB Screening and IPT Prophylaxis. In a recent RCT on IPT among adults with HIV infection, negative TST did not benefit significantly from IPT ($p=0.40$).^{159, level I}

Algorithm 3: TB Screening and IPT in HIV-Positive Patients



Note: In healthcare facilities where Mantoux test is available, the test can be done to select HIV patients suitable for IPT.

Source: Ministry of Health (2011). Surat Pekeliling Ketua Pengarah Kesihatan Malaysia Bil. 5/2011. Pemberian Terapi Profilaksis Isoniazid (Isoniazid Prophylaxis Therapy, IPT) Di Kalangan HIV Positif Bagi Mencegah Jangkitan Tuberkulosis

Recommendation 31

- Isoniazid prophylaxis therapy for six months should be offered to all HIV patients with latent tuberculosis infection after ruling out active tuberculosis. **(Grade A)**

9.5 Timing to Initiate Highly Active Antiretroviral Therapy (HAART)

Risk of HIV progression if HAART is delayed must be balanced with the risk of having to stop therapies because of adverse effects, Immune Reconstitution Inflammatory Syndrome (IRIS) and drug interaction.

Survival benefits of earlier-HAART (after two weeks of antiTB intensive phase) are seen in TB patients with CD4 <200 cells/ μ l compared to later-HAART group ($p=0.002$).^{160, level I}

Initiation of earlier-HAART in patients with CD4 <50/cubic ml improves survival ($p=0.06$). Among those with CD4 \geq 50 cells/ μ l, deferral of HAART initiation to the first 4 weeks of maintenance phase reduces the risks of IRIS ($p=0.02$) and other adverse events related to HAART ($p=0.04$) without increasing the risk of Acquired Immune Deficiency Syndrome or death.^{161, level I}

Immediate HAART is associated with an increase in the frequency of grade 4 adverse events, suggesting that it may be safer to defer initiation of HAART in patients presenting with HIV-associated TB meningitis ($p=0.04$).^{162, level I}

Recommendation 32

- In patient with tuberculosis (TB) and HIV:-
 - o if CD4 <50 cells/ μ l, initiate Highly Active Antiretroviral Therapy (HAART) two weeks after starting intensive phase of antiTB treatment. **(Grade A)**
 - o if CD4 >50 cells/ μ l, defer initiating HAART until completion of intensive phase of antiTB treatment. **(Grade A)**
 - o if CD4 >350 cells/ μ l, complete antiTB treatment and consider HAART if CD4 drops below 350 cells/ μ l. **(Grade C)**

9.6 HAART in HIV-TB Co-Infection

HAART improves survival. However, it is important to stress on timing of HAART as potential drug interactions can occur between HAART and antiTB. The development of Immune Reconstitution Inflammatory Syndrome (IRIS) with TB after HAART initiation should be anticipated.

HAART during TB treatment is protective against mortality (RR=0.36, 95% CI 0.14 to 0.91) and result in earlier conversion of sputum [mean of 3.5 vs 5.9 week ($p=0.01$)] and cultures [mean of 5.1 vs 8.7 week ($p=0.003$)] to negative.^{145, level II-2}

i. Nucleoside Reverse Transcriptase Inhibitors (NRTIs) Option

There are no clinically significant interactions between nucleoside analog of NRTIs and rifampicin. Zidovudine is preferred because both stavudine and didanosine can cause peripheral neuropathy. This adverse effect can also be caused by isoniazid.

However, if zidovudine is not tolerated by patients, stavudine-or tenofovir-based regimen can be used.

ii. Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) Option

Efavirenz is the drug of choice because studies had shown that the virological outcomes of nevirapine-based antiretroviral therapy (ART) were inferior to efavirenz-based therapy. In the time-to- event analysis of confirmed virological failure, HIV-positive patients with concurrent TB who were started on nevirapine developed virological failure sooner compared to those on efavirenz (HR= 2.2, 95% CI 1.3 to 3.7).^{163, level II-2}

However, if the patient is already on a nevirapine-based ART when diagnosed with TB, the therapy can be continued with close monitoring of liver function test (LFT). In the same study, there was no difference in time to virological rebound in patients developing TB during follow-up while taking nevirapine (HR=1.0, 95% CI 0.5 to 2.0) or efavirenz (HR=0.8 95% CI 0.4 to 1.7).^{163, level II-2}

If efavirenz is intolerable due to adverse effects, nevirapine can still be used after discussion with the Infectious Disease Physician. No dosage adjustment for nevirapine is needed. The lead in dose of 200 mg daily for two weeks when nevirapine is commenced is not required if rifampicin has been given for more than one week. Nevirapine initiation at the maintenance dose of 200 mg twice daily is preferred.^{164, level III}

Recommendation 33

- Efavirenz is the preferred Non-Nucleoside Reverse Transcriptase Inhibitor in combination with antituberculosis treatment. **(Grade C)**

iii. Protease Inhibitors

Co-administration of rifampicin and protease inhibitor-based therapy is not recommended. In patients already on PI-based regimen, referral to an Infectious Disease Physician must be done for further evaluation of appropriate HAART regimen. Refer to Subchapter on Treatment Regimen of TB-HIV Co-Infection above.

iv. Drug interactions between HAART and antiTB regimen

It is recommended to use fixed-dose combination antiTB drugs if possible to reduce pill burden. Overlapping drug toxicities can be difficult to differentiate such as skin rash, hepatotoxicity and peripheral neuropathy (refer to **Table 8**).

Table 8: Overlapping or Additive Toxicities due to ARV Drugs and First-Line AntiTB Drugs

Toxicity	ARV Drugs	AntiTB Drugs
Peripheral neuropathy	Stavudine & didanosine	Isoniazid & ethambutol
Gastrointestinal intolerance	All	All
Hepatotoxicity	Nevirapine, efavirenz, all NRTIs & Pis	Isoniazid, rifampicin, rifabutin & pyrazinamide
Central nervous system toxicity	Efavirenz	Isoniazid
Bone marrow suppression	Zidovudine	Rifabutin, rifampicin
Skin rash	Abacavir, nevirapine & efavirenz	Isoniazid, rifampicin & pyrazinamide
Ocular effects	Didanosine	Ethambutol & rifabutin

Source: Kwara A, Flanigan TP, Carter EJ. Highly active antiretroviral therapy (HAART) in adults with tuberculosis: current status. *Int J Tuberc Lung Dis.* 2005 Mar;9(3):248-57

9.7 Immune Reconstitution Inflammatory Syndrome (IRIS)

IRIS is an augmented inflammatory response that occurs in patients commenced on HAART and antiTB. It may cause clinical deterioration but does not primarily contribute to mortality.

IRIS usually occurs within three months of TB treatment, typically within two to twelve weeks after the initiation of HAART. The major manifestations of IRIS are fever (40%), followed by lymphadenitis (38%).^{165, level III}

EPTB is the most significant risk factor associated with IRIS (83.33%) than those without IRIS (44.87%) ($p=0.0032$). For example, tubercular lymphadenitis ($p=0.0364$) and disseminated TB ($p=0.0217$) are significantly associated with IRIS.^{165, level III}

Baseline haemoglobin <100 g/l (OR=2.2, 95% CI 1.1 to 4.6) and baseline CD4 <50 cells/ μ l (OR=4.1, 95% CI 1.8 to 9.5) are predictors of IRIS.^{166, level II-2}

Severity of IRIS can range from mild to life threatening. A 4-week course of prednisolone i.e. 1.5 mg/kg/day for two weeks, followed by 0.75 mg/kg/day for two weeks improve symptoms and chest radiography findings as early as two weeks ($p<0.05$).^{167, level I}

HAART and antiTB treatment should not be stopped while managing IRIS

Recommendation 34

- Immune Reconstitution Inflammatory Syndrome should be suspected if there is paradoxical worsening of symptoms especially in patients with CD4 <50 cells/ μ l, anaemia or extrapulmonary tuberculosis. **(Grade C)**

9.8 Co-trimoxazole (CTX) Prophylaxis in TB-HIV Co-Infection

A RCT showed that CTX prophylaxis in TB-HIV co-infected adults was associated with a 21% reduction in all cause mortality (HR=0.79, 95% CI 0.63 to 0.99).^{168, level I}

CTX is generally safe and well tolerated.^{168 - 169, level I} There is no significant differences in mortality (HR=1.1, 95% CI 0.7 to 1.7) and occurrence of clinical events ($p>0.05$) between 480 mg and 960 mg doses of CTX.^{169, level I}

Co-trimoxazole preventive therapy should be initiated as soon as possible and given throughout TB treatment. Continuation after TB treatment is completed should be considered in accordance with national guidelines.^{1, level III}

Recommendation 35

- Co-trimoxazole prophylaxis should be given to patients with tuberculosis-HIV co-infection. **(Grade A)**

10. FOLLOW-UP & ADVERSE DRUG EVENTS

10.1 Follow-Up During & After Treatment

All patients on antiTB treatment should be monitored to assess their response to treatment and to identify problems associated with it. All patients should be aware of symptoms indicative of PTB and adverse drug reactions (refer **Appendix 6**). At each clinic visit, patients taking ethambutol should be questioned regarding possible visual disturbances.

There is no current retrievable evidence on follow-up during and after treatment.

In new patients with PTB, WHO recommends daily dosing throughout the course of antiTB treatment. However, a daily intensive phase followed by thrice weekly maintenance phase is an option provided that the sputum smear at the end of intensive phase is negative and each dose is directly observed. A maintenance phase with twice weekly dosing is not recommended since missing one dose means the patient receives only half the total dose for that week.^{1, level III}

NICE guidelines recommend follow-up clinic visits should not be conducted routinely after treatment completion. Patients should be told to watch for symptoms of relapse and how to contact the TB service rapidly through primary care or a TB clinic.⁸⁵

In the previous Malaysian CPG TB 2002, follow-up was recommended at two, four and six months during treatment. Sputum smear and chest radiograph were recommended to be done during each follow-up clinic visit.^{44, level III} In order to detect early adverse drug reactions and to enhance compliance, follow-up within one month of starting treatment is advisable.

The following flow chart provides recommendations on investigations during PTB treatment.

Flow Chart for the Recommended 6-months Treatment of PTB

Visit	Duration	Regimen	Investigations
1.	0 M	EHRZ/SHRZ	FBC, RBS, RP, LFT, HIV Sputum AFB direct smear Sputum MTB C&S CXR
2.	2 - 4 weeks	EHRZ/SHRZ	LFT
3.	2 M	HR H ³ R ³	LFT if necessary, CXR Sputum AFB direct smear* Sputum MTB C&S if smear remains positive
4.	4 M	HR H ³ R ³	Sputum AFB direct smear and CXR only if there is no clinical improvement
5.	6 M	Completion of 6 months treatment	Sputum AFB direct smear CXR

Patients with initial sputum smear negative should have repeat sputum smear at two months of antiTB treatment. If still negative, no further sputum sample is required.

*If smear AFB remains positive at two months, refer to specialists with experience in TB management and repeat sputum AFB and sputum MTB C&S at three months.

H³R³=thrice weekly of isoniazid and rifampicin

E - Ethambutol	FBC - Full blood count	RBS - Random blood sugar
H - Isoniazid	RP - Renal profile	
R - Rifampicin	LFT - Liver function Test	
Z - Pyrazinamide	HIV - HIV screening test	
	MTB C&S - Mycobacterium tuberculosis culture & sensitivity	
M - Month	CXR - Chest x-ray	

Recommendation 36

- Patients with initial sputum smear positive should have repeat sputum smear at two and six months of antituberculous (antiTB) treatment. **(Grade C)**
- Patients with initial sputum smear negative should have repeat sputum smear at two months of antiTB treatment. If still negative, no further sputum sample is required. **(Grade C)**
- Patients who remains sputum positive at two months should be referred to specialist with experience in tuberculosis (TB) management. **(Grade C)**
- Sputum *Mycobacterium tuberculosis* culture and sensitivity testing should be obtained at the start of antiTB treatment. **(Grade C)**
- Chest x-ray should be performed at two and six months of antiTB treatment. **(Grade C)**
- Follow-up within one month of starting antiTB treatment is advisable. **(Grade C)**
- Follow-up may not be conducted routinely after completion of antiTB treatment. Patients should be well-informed on symptoms of TB recurrence. **(Grade C)**
- Patients should be monitored for complications of antiTB drugs. **(Grade C)**

10.2 Adverse Drug Reactions & Their Management

An adverse drug reaction (ADR) is an expression that describes harm associated with the use of given medication at a normal dosage during normal use. The ADR of antiTB drugs can be classified into two categories:

1. ADRs which are troublesome but not serious such as nausea, tiredness, pruritus and minor rashes. These can be treated symptomatically without necessarily having to interrupt treatment. Most of these will resolve spontaneously even when treatment is continued.
2. ADRs which need immediate discontinuation of treatment such as severe skin reactions [such as Steven-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN) and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)] and hepatitis.

For antiTB treatment, most of ADRs occur within early stage of the treatment compared to the later stage (52.5% experience ADRs within 20 days, 7.5% in 21 - 40 days, 22.5% within 41 - 60 days and 17.5% in >60 days after starting treatment).^{170, level III}

Hepatobiliary is the system most affected with antiTB (57.1%) compared to others namely gastrointestinal tract (14.3%), skeletal system (9.5%), skin (7.1%) and renal (4.8%).^{170, level III} Shang P et al. found out that 2.6% (95% CI 2.0 to 3.16) of patients treated with antiTB treatment developed liver injury.^{171, level III} In a study in Singapore, the rate of hepatotoxicity requiring treatment cessation or regimen adjustment was 5%.^{172, level III}

Risk factors of ADRs of antiTB drug include:-

- Age >40 years (OR=3.9, 95% CI 1.75 to 9.4^{173, level III}; HR=2.9 95% CI 1.3 to 6.3^{174, level II-2})
- Overweight/obesity (OR=2.1, 95% CI 1.27 to 3.9)^{173, level III}
- Smoking (OR=2.00, 95% CI 1.03 to 3.87)^{173, level III}
- Alcoholism (RR=3.0, 95% CI 1.1 to 7.9)^{175, level III}
- Anaemia (OR=2.1, 95% CI 1.1 to 3.9)^{173, level III}
- Baseline ALT more than twice upper limit of normal (OR=5.9, 95% CI 1.2 to 10.1)^{176, level II-2}
- Baseline aspartate aminotransferase more than twice upper limit of normal (OR=4.3, 95% CI 1.7 to 8.6)^{176, level II-2}
- EPTB ($p=0.017$)^{177, level III}
- MDR-TB medication (OR=11.1, 95% CI 6.3 to 19.6)^{173, level III}
- HIV infection (HR=3.8, 95% CI 1.05 to 13.4^{174, level II-2}; $p=0.018$)^{177, level III}
- CD4 count <350 cells/mm³ (RR=2.6, 95% CI 1.4 to 5.0)^{175, level III}
- Hepatitis B virus infection ($p=0.0018$)^{178, level II-2}
- Hepatitis C virus infection (OR=2.9, 95% CI 1.1 to 8.0)^{176, level II-2}
- Concomitant use of other hepatotoxic drug (OR=1.3, 95% CI 1.1 to 2.4)^{176, level II-2}

Among antiTB drugs, pyrazinamide is the commonest drug associated with ADR. In a study conducted by Yee D et al., the incidence of pyrazinamide-induced hepatotoxicity and rash was substantially higher than other first-line antiTB drugs.^{174, level II-2} This is supported by a local study in which pyrazinamide was the commonest offending drug for Cutaneous ADRs with an incidence rate of 2.38%. Types of Cutaneous Adverse Drug Reaction related to antiTB treatment include morbiliform rash (72.3%), erythema multiforme syndrome (8.5%), urticaria (8.5%) and others (exfoliative dermatitis and lichenoid eruption).^{179, level III}

Between March 2000 and May 2012, the National Centre for Adverse Drug Monitoring, National Pharmaceutical Control Bureau (NPCB) received 26 reports related to serious cutaneous ADRs such as SJS, DRESS and TEN.^{180, level III}

a. Management of ADR

More than half of the patients (55%) do not need treatment for antiTB-induced ADR, while 25% need symptomatic treatment and another 17.5% need specific treatment. All cases of hepatitis can be managed with treatment cessation or sometimes with adjustment of the regimen. Biweekly LFT will help in monitoring the progress of the hepatitis.^{170, level III} Once the LFT returns to normal, drug challenge can be commenced until an acceptable treatment combination is reached. Most patients, however, could be safely restarted on previous regimen consisting of the primary drugs.^{177, level III}

• Drug-Induced Rashes

When severe cutaneous ADRs occur, antiTB drugs need to be discontinued until the rashes subside. Thereafter, individual drug is reintroduced sequentially to identify the offending drug. A suitable regimen can be provided when an offending drug is identified and if possible the regimen should include isoniazid and rifampicin (the two most potent drugs). If the offending drugs are both isoniazid and rifampicin, desensitisation may be required. Desensitisation is done by careful administration of increasing doses of the drug under close supervision. Desensitisation is only done if one is unable to devise a suitable regimen without the offending drugs. If a suitable drug combination is available, it is not necessary to perform desensitisation. Given that the management of significant cutaneous ADRs can be complex, consultation with specialists with experience in this field is recommended.

In patients who developed skin reactions due to antiTB drugs, no significance difference was found between patient group with successful desensitisation treatment and that with failure of desensitisation ($p > 0.05$). However, the interval between initiation of desensitisation treatment and the disappearance of adverse reactions was significantly shorter in the group showing failure of desensitisation (15.6 ± 1.2 , $p = 0.012$) than that in the successful group (27.2 ± 1.8 , $p = 0.012$).^{181, level III}

• Drug-Induced Hepatitis (DIH)

Risk factors for DIH include slow acetylators, old age, extensive TB disease, malnutrition, alcoholism, chronic viral hepatitis B and C infections, pregnancy until 90 days postpartum, HIV and organ transplant recipients. Hence it is important to assess for risk factors in the patient's history.^{130, level III; 151, level III}

DIH is usually caused by pyrazinamide, isoniazid and rifampicin; pyrazinamide being the most hepatotoxic and rifampicin the least. In patients with risk factors for developing drug-induced hepatitis (DIH), similar monitoring is recommended. In fact, monitoring at least for the first 2 - 4 weeks is recommended among all the remaining patients who require antiTB treatment as DIH usually occurs within the initial two months of treatment.^{130, level III}

It has been recommended to stop antiTB drugs when the serum transaminase level reaches three times the upper limit of normal for patients with symptoms suggestive of hepatitis or five times upper limit for those without symptoms.^{1, level III; 151, level III}

Subsequently, if the TB disease is of low severity in terms of radiographic extent, bacillary load and infectiousness, antiTB treatment can be withheld until liver chemistry recovers and patients symptoms resolve. Timing of restarting treatment also depends on whether hepatotoxicity sets in during the initial or the continuation phase of treatment, and the amount of treatment received prior to the onset of such toxicity. The patient can then be retreated with a regimen containing fewer potentially hepatotoxic drugs.^{130, level III}

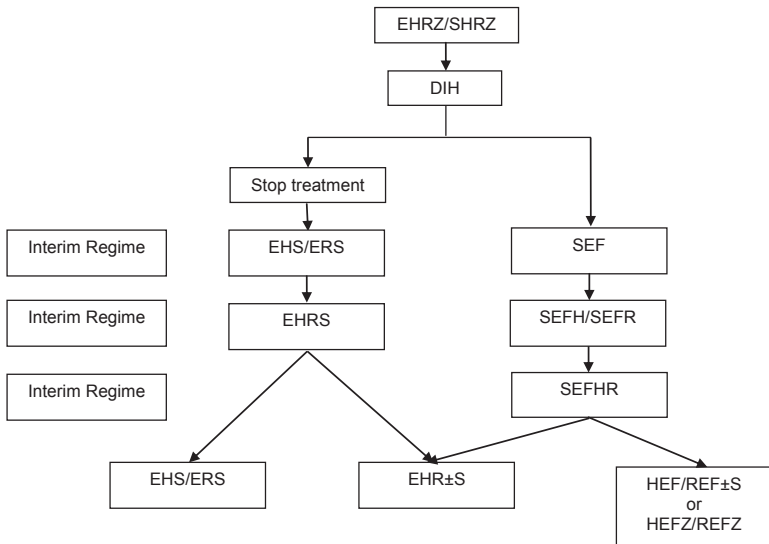
Retreatment regimen can contain fewer potentially hepatotoxic drugs such as streptomycin, ethambutol and isoniazid. Fluoroquinolones have low hepatotoxicity, hence can be used as part of 'non-hepatotoxic' drug regimens during the interim or even the definitive phase of treatment in the presence of DIH especially if interruption occurs during initial phase or for more than two weeks. Fluoroquinolones should be included if co-administration of isoniazid and rifampicin cannot be prescribed.^{130, level III}

Attempt should be made to resume the use of both isoniazid and rifampicin by slow sequential introduction to shorten the total duration of treatment. If symptoms recur or liver function tests become abnormal as the drugs are reintroduced, the last drug added should be stopped. Rifampicin can be introduced first as it is less likely than isoniazid or pyrazinamide to cause hepatotoxicity and is the most effective drug. In patients who have DIH but tolerate the reintroduction of rifampicin and isoniazid, it is advisable to avoid pyrazinamide.^{130, level III} After 3 - 7 days, isoniazid may be reintroduced. If pyrazinamide is not included in the intensive phase, the total duration of treatment should be extended to nine months.^{1, level III}

Liver transplantation may be required in the treatment of fulminant liver failure resulting from severe DIH.^{130, level III}

A suggested algorithm for treatment of patients with DIH is shown below:-

Algorithm 2: Management of DIH



E=Ethambutol
 S=Streptomycin
 H=Isoniazid
 R=Rifampicin
 F=Fluoroquinolone – ofloxacin, levofloxacin or moxifloxacin can be used

Recommendation 37

- Antituberculosis (antiTB) drugs should be stopped when the serum transaminase level reaches three times the upper limit of normal for symptomatic patients. **(Grade C)**
- AntiTB therapy can be recommenced by slow sequential introduction. **(Grade C)**
- Use of non-hepatotoxic regimens can be considered for patients with drug-induced hepatitis but will need a longer duration of therapy. **(Grade C)**
- Expert consultation is advisable in treating tuberculosis patients with drug-induced hepatitis. **(Grade C)**

b. Impact of ADR Towards Treatment Outcome

Adverse reactions occur frequently in MDR-TB patients but do not negatively impact treatment outcome ($p=0.11$).^{182, level III}

Compared with those without antiTB-induced liver injury (ATLI), ATLI patients have a 9.3-fold risk (95% CI 5.7 to 15.1) of unsuccessful antiTB treatment outcomes and a 2.1-fold risk (95% CI 1.2 to 3.6) of prolonged intensive treatment phase.^{171, level III}

Recommendation 38

- Hepatobiliary system should be monitored closely in patients with risk factors prescribed with antituberculosis drugs. **(Grade C)**

Refer to **Chapter 8** for the **Liver & Renal Impairment**.

11. MULTIDRUG-RESISTANT TUBERCULOSIS (MDR-TB)

WHO reports increasing numbers of MDR-TB and XDR-TB cases worldwide over the last few years. These pose huge public health threats and major challenges locally and globally due to their complicated and long treatment duration with high mortality rate. In Malaysia, 1.3% of all cultures performed was confirmed to be MDR-TB in 2011.^{2, level III}

MDR-TB is defined as *Mycobacterium tuberculosis* infection resistant to both isoniazid and rifampicin with or without resistance to other drugs.

Extensively drug-resistant tuberculosis (XDR-TB) is a condition when the *Mycobacterium tuberculosis* is resistance to isoniazid and rifampicin plus resistance to quinolones and at least one second-line aminoglycosides. Diagnosis of MDR-TB and XDR-TB can be confirmed by culture and sensitivity test or molecular methods.

Many countries have reported cases of TB infection caused by *Mycobacterium tuberculosis* resistance to all tested first-line and second-line antituberculous drugs. The term “totally drug resistant” or “extremely drug-resistance “ has been used by many countries to define this group of patients. However, it is not accepted globally yet.

Rapid diagnosis and prompt treatment as well as appropriate infection control measures are very crucial for better overall treatment outcome and prevention of disease transmission.

11.1 Risk Factors

The risk of MDR-TB in previously treated TB patient (secondary MDR-TB) had been reported high with OR of 9.1 (95% CI 6.3 to 13.2) to 10.2 (95% CI 7.6 to 13.7).^{139, level III; 183, level III}

Among previously treated patients, independent risk factors for MDR-TB as reported by Law WS et al. were:-^{184, level II-2}

- i. Smear-positive disease (OR=5.8, 95% CI 1.8 to 18.5)
- ii. New immigrants from a country with high MDR-TB prevalence (OR=6.9, 95% CI 1.4 to 34.1)
- iii. Frequent traveller to a country with high MDR-TB prevalence (OR=2.5, 95% CI 1.1 to 5.7)
- iv. Younger age group (OR=0.95, 95% CI 0.93 to 0.97)

HIV-positive patients have more than twice risk of primary MDR-TB.^{139 - 140, level III} In a study in Vietnam, mortality during TB treatment was increased in MDR-TB with a rate of 8.7% (95% CI 4.7 to 14.5).^{149, level II-2}

Recommendation 39

- Multidrug-resistant tuberculosis must be suspected in previously treated patient with tuberculosis and sputum samples for culture and sensitivity must be sent at diagnosis. (Grade C)

11.2 Treatment

The evidence presented in this section is based on WHO guidelines 2010¹, level III and WHO guidelines on drug-resistant TB.¹⁸⁵, level III AntiTB drugs are grouped according to efficacy, experience of use and drug class as shown in the the following **Table 9**.

Table 9: AntiTB drugs for MDR-TB

Group Name	AntiTB Drug	Description
Group 1	pyrazinamide ethambutol rifabutin	Group 1 drugs are the most potent and best tolerated. If laboratory evidence and clinical history suggests that a drug from this group is effective, it should be used. If a Group 1 drug was used in a previous regimen that fails, its efficacy should be questioned even if the DST result suggests susceptibility. The newer rifamycins, such as rifabutin, have very high rates of cross-resistance to rifampicin.
Group 2 - Injectable drugs	kanamycin amikacin	Group 2 - 5 (except streptomycin) are second-line or reserve drugs. All patients should receive a Group 2 injectable agent if susceptibility is documented or suspected. Kanamycin or amikacin is the first choice of an injectable agent. Amikacin and kanamycin have high frequency of cross-resistance. Hence if there is a resistance to both streptomycin and kanamycin, capreomycin should be used.
Group 3	levofloxacin moxifloxacin ofloxacin	The newer generation fluoroquinolones, such as levofloxacin or moxifloxacin, is the fluoroquinolone of choice.
Group 4	ethionamide cycloserine p-aminosalicylic acid (PAS)*	Drugs in this group can be added.
Group 5	clofazimine linezolid amoxicillin/ clavulanate clarithromycin imipenem	Group 5 drugs are not used routinely as their efficacy is uncertain. They may be needed in patients with XDR-TB.

* Drug not registered in Malaysia

a. **General Principles in Designing an MDR-TB Treatment Regimen**^{1, level III ; 185, level III}

Once MDR-TB is confirmed (by either type of laboratory method), patients can be treated with:

- a standard MDR-TB regimen (standardised approach) or
- an individually tailored regimen, based on DST of additional drugs

In the standard MDR-TB regimen:-

- a fluoroquinolone should be used with a later-generation fluoroquinolone (such as levofloxacin and moxifloxacin) rather than an earlier-generation fluoroquinolone (such as ofloxacin)
- ethionamide should be used in the regimen
- four second-line antiTB drugs that are most likely to be effective (including a parenteral agent), as well as pyrazinamide, should be included in the intensive phase
- regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide and either cycloserine or PAS (if cycloserine cannot be used)
- ethambutol and Group 5 drugs may be used but is not included among the drugs making up the standard regimen

The clinical effectiveness of a drug cannot be predicted by DST with 100% certainty. Previous antiTB drug exposure history and the DST of the source case if known should be taken into account. Each drug in an MDR-TB regimen is given as DOT throughout the treatment.

Patients who are highly likely to have MDR-TB may be commenced on an empirical MDR-TB regimen while waiting for laboratory confirmation. Once confirmed, the regimen may be continued or it may be adjusted based on DST. If rapid molecular-based DST is used, MDR-TB can be confirmed within 1 - 2 days and treatment with a standard MDR-TB regimen can be initiated immediately.

An individualised regimen will be based on DST for second-line drugs.

Rapid DST of isoniazid and rifampicin or of rifampicin alone is recommended over conventional testing or no testing at the time of diagnosis of TB, subject to available resources. A rapid test is one that provides a diagnosis of resistance to isoniazid and rifampicin or rifampicin alone within two days of specimen testing. Molecular tests that can detect resistance quickly are the LPA and Xpert MTB/RIF. Conventional DST of cultured mycobacteria typically provides results within 1 - 3 months.

b. **Monitoring**

- Monthly sputum smears and cultures are done until smear and culture conversion occur. Conversion is defined as two consecutive negative smears and cultures taken 30 days apart. After conversion, smears are monitored monthly and cultures 3-monthly.
- Monitoring of MDR-TB patients by a clinician should be at least monthly until sputum conversion, then every 2 - 3 monthly. At each visit, patient's weight and side effects to antiTB drugs should be monitored.

c. Duration of treatment

- Intensive phase is defined by the duration of treatment with the injectable agent and an intensive phase of 8 months is suggested for most patients.
- In the treatment of patients newly diagnosed with MDR-TB (i.e. not previously treated for MDR-TB), a total treatment duration of 20 months is suggested for most patients.
- Treatment duration may be modified according to the response to treatment based on patient's cultures, smears, CXR and clinical status.

Recommendation 40

- Respiratory physician with experience in multidrug-resistant tuberculosis (MDR- TB) management should be consulted for all patients with MDR-TB and extensively drug-resistant tuberculosis. **(Grade C)**

12. PREVENTION

The primary emphasis of TB infection control plan should include:-

- prompt detection of infectious patients including screening
- airborne precautions (established control and prevention programme) and
- treatment of people who have suspected or confirmed disease

All TB cases must be notified by written notification within a week after diagnosis made using the standard notification form. Failure to comply is liable to be compounded under the Prevention and Control of Infectious Disease Act 1988 (Act 342).

12.1 Screening of TB Contacts

Screening of TB contacts is important among those exposed to patients with PTB for early detection of TB and to reduce its transmission. However, there is no universal definition of close contacts.

Index TB patients include both smear positive and negative cases.

The risk of acquiring all types of TB is higher amongst contacts compared to non-contacts (OR=4.5, 95% CI 4.3 to 4.8).^{186, level III} In a study in China, the rate was highest in the first three years.^{14, level II-2}

Contacts with diabetes are at higher risk of getting TB especially in the first three months compared to those without diabetes (OR=10.2, 95% CI 3.0 to 34.8).^{14, level II-2}

Certain factors increase the risk of TB in contacts. These include:^{187, level III}

- Presence of cavitation in index patients, OR=1.6 (95% CI 1.1 to 2.2)
- Having more than 100 AFB/field in the index patient, OR=1.8 (95% CI 1.2 to 2.8)
- Being a household contact at night, OR=2.1 (95% CI 1.3 to 3.2)
- Being a contact who is actively smoking, OR=1.6 (95% CI 1.1 to 2.4)

There is no uniform definition of contact and close contact. It is largely dependent on local understanding and practices. For example, Noertjojo K et al. defined contacts as family members living in the same room with the index cases for more than 30 days.^{188, level III} While Hou SY et al. defined contacts as family members or other people who lived with smear-positive pulmonary TB cases for more than half a year.^{189, level III}

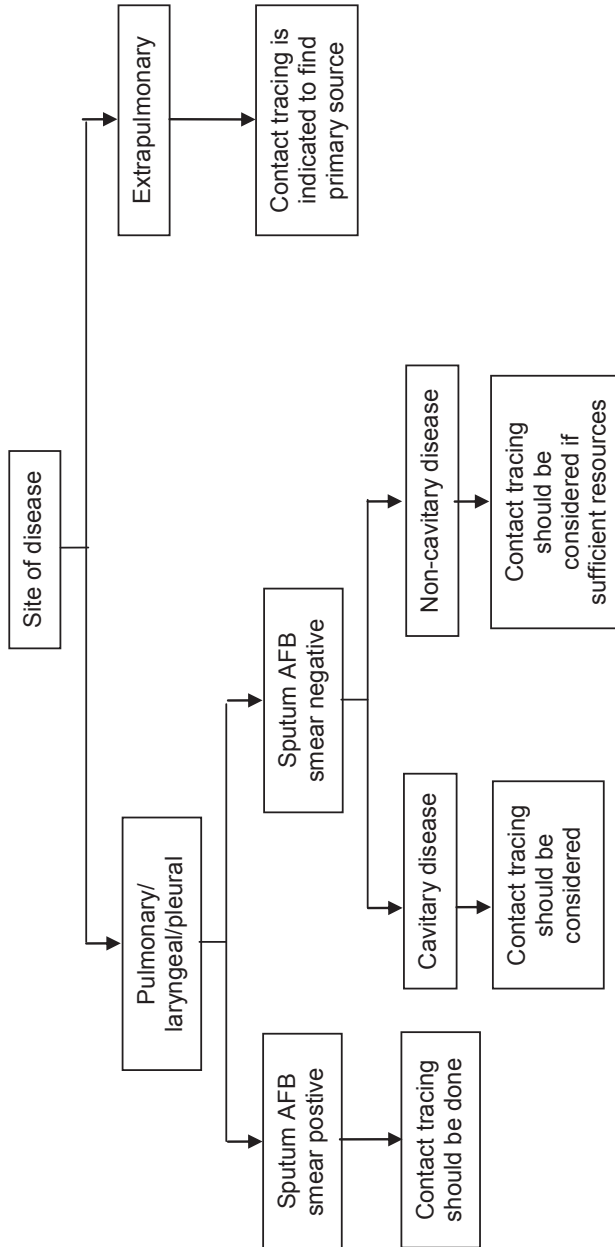
Recommendation 41

- Screening for tuberculosis should be done among all close contacts (especially household contacts) and high risk group*. **(Grade C)**

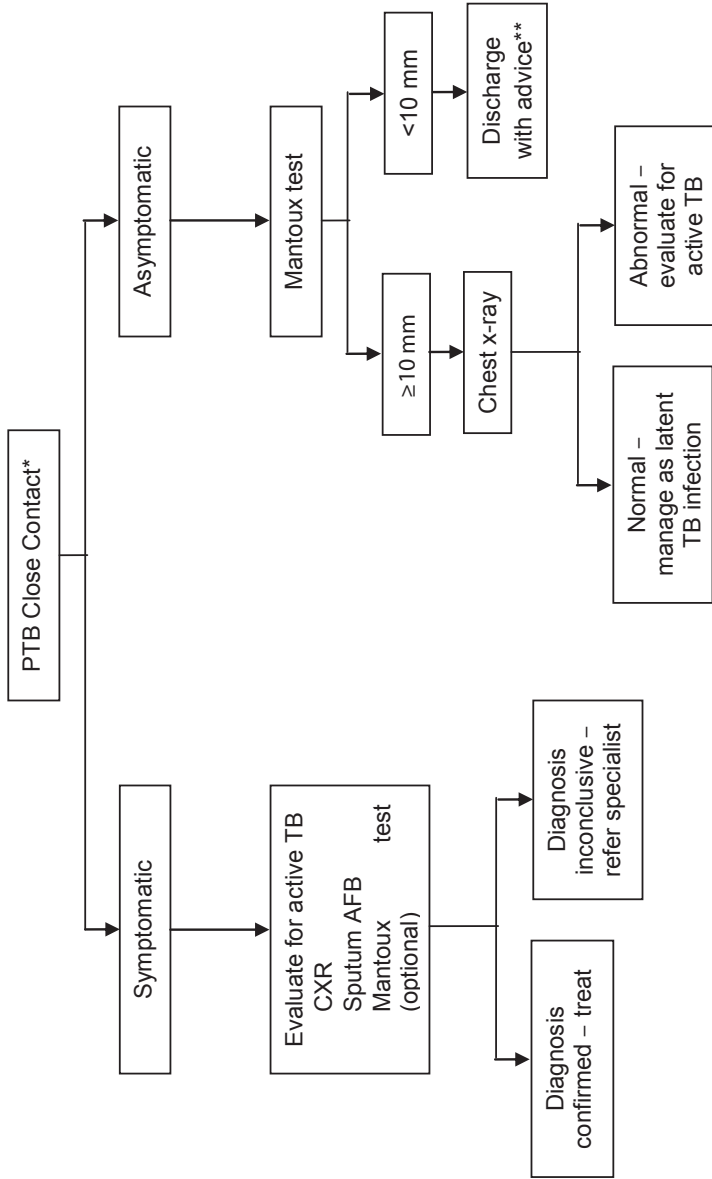
*Refer to **Chapter 2 on Epidemiology and High Risk Group**

Refer to the following algorithms on the proposed contact tracing:-

Algorithm 4: Contact Tracing



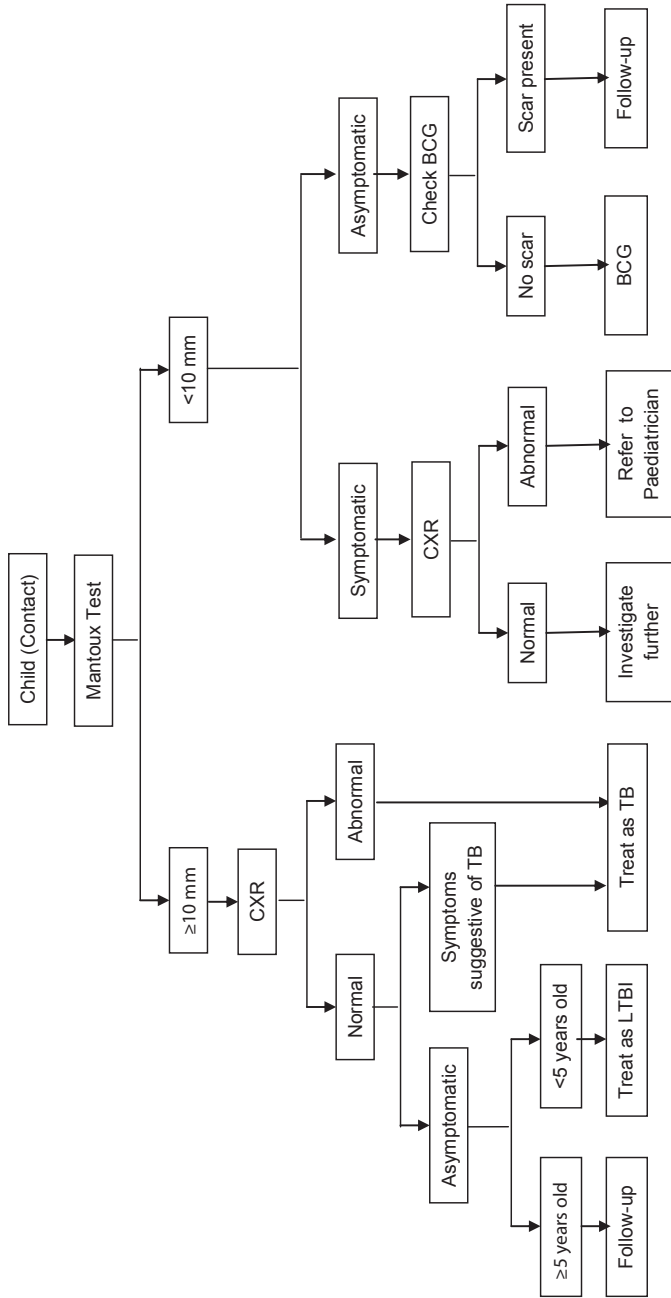
Algorithm 5: Investigations For Contact Tracing in Adults



*Immunocompetent close contacts

**To seek medical advice if patient has symptoms suggestive of TB such as fever, cough etc. for more than two weeks.

Algorithm 6: Management of Children with Positive History of Contact with Tuberculosis



Note:

- Mantoux test may be negative in children who are malnourished and immunocompromised.
 - Contact tracing and investigations in children are to be done **within six weeks** of diagnosis of the index patient.
- Source: World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. Geneva: WHO; 2006

12.2 Screening Tests for Contacts & High Risk Groups

TB screening tests are used to identify those most likely to have either an active disease or LTBI. TB screening should be targeted at high risk population (refer to **Chapter 2 on Epidemiology and High Risk Groups**).

In asymptomatic individuals, screening tools such as CXR, TST and IGRA may be used either alone or in combination. The effectiveness of these screening tools depends on the prevalence of TB and vaccination status of the population.

a. CXR

CXR is the preferred screening method when the primary objective is to identify persons with active PTB. Any form of pulmonary radiographic abnormality may suggest TB especially in immunosuppressed persons. Studies presented in this section were done on symptomatic cases.

CXR and symptom screening increases the number of active TB cases detected by 2.5-fold compared to symptom screening alone.^{41, level III} Any abnormality on CXR has higher sensitivity for detecting bacteriologically positive TB compared to screening based on symptoms.^{42, level III}

The addition of abnormal CXR findings into the screening combination of CFSW (cough, fever, night sweat and weight loss) was found to increase the sensitivity of the screening by 11.7% but reduce the specificity by 10.7%.^{157, level II-2} This is supported by another study on bacteriological positive TB, whereby the sensitivity of abnormal CXR was 0.97 (95% CI 0.90 to 1.00) while the sensitivity for symptoms was only 0.69 (95% CI 0.50 to 0.88). However the specificity of both was comparable.^{42, level III}

A clinical scoring system which includes CXR findings and clinical features (haemoptysis, age >45 years, loss of weight, expectoration, apical infiltrate and miliary infiltrate) can be useful for the diagnosis of smear negative TB (AUC=0.83, 95% CI 0.74 to 0.90).^{190, level III} It performs well in patients without previous history of TB.^{191, level III}

b. TST

TST has been used as a screening tool for TB for a long time. The most widely used is the Mantoux test. There is, however, no recent retrievable evidence to support its use.

The TST has the advantage of being cheap and relatively easy to perform. However, there is a timescale in interpreting the results and patients who do not return or delay returning, will have either no result or a possibly inaccurate one. The reading of the induration is also prone to subjective errors. Nonetheless, it is the preferred test in children <5 years of age.

False positive results may be caused by a NTM infection or previous BCG vaccination. False negative results may be seen in those who have compromised immune system. Extensive TB (pulmonary or miliary) itself can also temporarily depress the immunity and can lead to a paradoxically negative TST.

c. IGRA

This is a comparatively more recent but more expensive screening test than the TST. Its advantages are less frequent visits to the hospital, the results are available faster and there are no subjective errors in the reading compared to TST.

IGRA has less false positive results and thus has a higher positive predictive value than TST. This test, however, is not preferred in children.

A health economic study on elderly BCG-vaccinated population showed that the incremental cost-effectiveness ratio of IGRA resulted in a cost saving of US\$33,362.72 per QALY gained, when compared with CXR.^{192, level III}

A SR on cost-effectiveness of screening tools supports the use of IGRAs in screening high risk groups. The higher unit cost of the IGRAs compared to that of the TST is compensated for by cost savings through the more targeted performance of CXRs and offerings of chemoprevention. The most cost effective strategy was the 2-step strategy whereby a positive TST is followed by IGRA.^{193, level III}

12.3 TB Prevention Strategies for Healthcare Workers

Healthcare workers (HCWs) are exposed to patients with TB and are at risk of nosocomial infection. A TB programme should not only emphasise on detection and treatment but also on preventive measures of TB at the workplace.

In a meta-analysis of 14 studies in low-and middle-income countries, the pooled prevalence of LTBI among all HCWs was 54% (95% CI 53 to 55). Risk factors for LTBI were increasing age and duration of employment in the healthcare facility in most of the primary studies.^{194, level II-2} These are supported in a recent study in Henan province, China which identified with working in departments with increased contact with TB patients as another risk factor.^{195, level III}

Prevalence of TB infection in a hospital in Hanoi estimated by IGRA, one- and two-step TST differed greatly (47.3%, 61.1% and 66.3% respectively).^{196, level III} In a local study on four hospitals in Klang Valley, the overall prevalence of LTBI using Quantiferon TB Gold was 10.6% (95% CI 8.6 to 12.6). Kappa values between Quantiferon TB gold in-tube and TST were poor for both cut-off points (0.12 for ≥ 10 mm and 0.31 for ≥ 15 mm TST).^{197, level III}

Although there was no specific TB infection control programmes used in the healthcare facilities, multiple strategies showed a drop in TB/LTBI incidence. Failure to use personal protection was associated with a 2.6-fold (95% CI 1.06 to 6.64) increased risk of TB among HCWs.^{194, level II-2} Studies in many parts of the world (including those in resource-limited, high-burden countries) had shown that simple administrative and engineering measures were helpful to reduce the risk of TB among HCWs.^{198 - 199, level II-2; 200, level III}

A cost-effectiveness study in among HCWs at different risk of TB exposure showed that regular tuberculin screening among them is cost-effective and result in a net cost-savings. However, this study is done in a country with low TB incidence.^{201, level III}

Prevention of TB infection among HCWs is done via risk assessment, risk category and risk control. Risk assessment is done to determine the risk of TB transmission at workplace. Once

risk level has been determined, control measures should be taken to reduce the risk. The risk should be re-evaluated. The risk controls are administrative controls, engineering controls and personal protective equipment.

NICE recommends reminders of TB symptoms, and prompt reporting of such symptoms should be included with annual reminders about occupational health for staff who are at high risk of TB contact.⁸⁵ NZGG states that staff at high risk of TB exposure should complete an annual questionnaire on TB symptoms and exposure.¹⁰⁵

Recommendation 42

- All healthcare facilities should have administrative, engineering and personal protective measures in place to reduce tuberculosis occupational risk of healthcare workers*. **(Grade C)**

*Refer to Guidelines on Prevention and Management of Tuberculosis for Health Care Workers in Ministry of Health Malaysia.^{202, level III}

13. REFERRAL CRITERIA

There is lack of primary evidence in the recommendation for specialist referral of TB. However, various guidelines have certain referral criteria for the management of TB.^{1, level III; 85; 203, level III} Extrapolating from other parts of the CPG, certain TB cases or TB-related conditions would need to be referred to the specialists with substantial experience in treating the conditions as shown in the recommendation box below.

Recommendation 43

- The following conditions should be referred to specialists with experience in tuberculosis (TB) management:-
 - Unsure of TB diagnosis
 - Retreatment of TB
 - Adverse events following antiTB drugs
 - Multidrug-resistant and extremely drug-resistant TB
 - Extrapulmonary TB except for tuberculous lymphadenitis
 - Renal and/or liver impairment with TB
 - HIV-TB co-infection
 - Smear negative TB
 - Smear positive after two months of treatment
 - All children diagnosed with TB
 - Maternal TB
 - Complex TB cases requiring surgical intervention (**Grade C**)

14. IMPLEMENTING THE GUIDELINES

It is important to standardise the management of TB at all healthcare levels in Malaysia using an evidence-based CPG in order to prevent the emergence of MDR-TB. The incidence of TB has not decreased and it poses a huge challenge to healthcare policy makers. It is therefore crucial for healthcare providers to understand the implications of poor TB management of TB.

14.1 Facilitating & Limiting Factors

Existing facilitators for application of the recommendations in the CPG include:-

1. Wide dissemination of the CPG to healthcare providers (hard- and soft-copies)
2. Regular TB update for healthcare providers
3. National TB registry
4. TB control programme indicators

Existing barriers for application of the recommendations of the CPG are:-

1. Poor understanding/limited knowledge of the TB issues
2. Insufficient resources in the management of TB particularly in the expertise and diagnostic tools
3. Poor communication between primary and secondary/tertiary health care
4. Variation in treatment practice and preferences

14.2 Potential Resource Implications

To implement the CPG, there must be strong commitment to:-

1. Ensure widespread distribution of the CPG to healthcare providers via printed and electronic copies.
2. Re-inforce training (with adequate funding) of healthcare providers by regular seminars or workshops to ensure information is up-to-date
3. Availability of highly specialised diagnostic tools and trained manpower in TB management including multidisciplinary team at different levels of healthcare
4. Ensure availability of second-line TB drugs to treat MDR-TB
5. Ensure widespread distribution of updated patient education materials

To assist in the implementation of the CPG, the following are proposed as clinical audit indicators for quality management:-

- TB Sputum Conversion Rate (Target 85%) = $\frac{\text{Number of TB cases with positive sputum convert to negative sputum after two month treatment}}{\text{Number of TB cases with positive sputum eligible for analysis}} \times 100\%$
- TB Cure Rate (Target 85%) = $\frac{\text{Number of cured sputum-positive TB cases in a year}}{\text{Number of registered sputum-positive TB cases in the same period}} \times 100\%$
- TB Treatment Success* Rate (Target 85%) = $\frac{\text{Number of successfully treated TB cases in a year}}{\text{Number of notified TB cases (all forms) in the same period}} \times 100\%$
*Cure & Completed Treatment
- TB Mortality Rate (Target ≤ 5 in 100,000 population) = $\frac{\text{Number of TB deaths in a year}}{\text{Estimated mid-year population in the same period}} \times 100,000$

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APPENDIX 1

SEARCH TERMS

The following MeSH terms or free text terms were used either singly or in combination:

tuberculosis/, tuberculos\$.tw., tb.tw., tuberculos*, tuberculosis, pulmonary/, pulmonary tuberculosis\$.tw., pulmonary phthisis.tw., tuberculosis, lymph node/, lymph node tuberculosis\$.tw., tuberculous lymphadenitis.tw., scrofula*, mycobacterial cervical, cervical lymphadenitis, cervical tuberculosis, tuberculosis, meningeal/, meningeal tuberculos\$.tw., tubercul\$ meningitides.tw., tubercul\$ meningitis.tw., tuberculos\$ meningeal.tw., tubercular meningitis, tuberculosis, pleural/, tuberculo\$ pleur\$.tw., tuberculosis, spinal/, spinal tuberculos\$.tw., pott's disease.tw., potts disease, peritonitis, tuberculous/, tuberculos\$ peritoneal.tw., pericarditis, tuberculous/, tuberculous pericarditis.tw., tuberculous pericarditides, tuberculosis, endobronchial.tw., tuberculosis, renal/, miliary/, miliary tuberculos\$.tw., latent tuberculosis/, latent tuberculosis infection\$.tw., latent tuberculos\$.tw., epidemiology/, epidemiology.tw., risk factors/, risk adj1 factor\$.tw., laboratory techniques and procedures/, laboratory technic\$ and procedure\$.tw., laboratory technique\$ and procedure\$.tw., laboratory examination\$ adj1 diagnos\$.tw., diagnos\$ and laboratory examination\$.tw., laboratory procedure\$.tw., laboratory diagnos\$.tw., laboratory examination\$ adj1 diagnos\$.tw., diagnostic test, routine.tw., rapid molecular method.tw., microscopy fluorescence/, molecular diagnostic techniques/, susceptibility testing.tw., rapid susceptibility testing.tw., drug resistant/, multi-drug resistance.tw., rapid detection.tw., immunology and serology.tw., diagnosis/, diagnos\$.tw., sputum/, smear negative\$.tw., induced sputum\$.tw.. sputum induction\$.tw., gastric lavage/, gastric lavage\$.tw., bronchoalveolar lavage/, bronchial lavage\$.tw., bronchoscopy/, bronchoscop\$.tw., thoracoscopy/, pleuroscopy.tw., adenosine deaminase/, adenosine deaminase\$.tw., polymerase chain reaction/, polymerase chain reaction\$.tw., cerebrospinal fluid/, cerebrospinal fluid.tw. diagnostic imaging/, medical imaging.tw., diagnostic imaging.tw., fine-needle aspiration.tw., biopsy, fine-needle/; fine needle biopsy\$.tw./, biopsy/, biops\$.tw., radiography/, radiography.tw., diagnostic x-ray.tw., diagnostic x-ray radiology.tw., ultrasonography/, ultrasonography.tw., medical sonography.tw., ultrasonic diagnosis.tw., ultrasonic imaging.tw., tomography, x-ray computed/, x-ray ct scan.tw., x-ray computed tomography.tw., magnetic resonance imaging/, imaging, nmr.tw., magnetic resonance imaging.tw., tomography, mr.tw., mri scan.tw., newly diagno\$.tw., therapeutics/, treatment\$.tw., therapeutic\$.tw., antibiotics, antitubercular/, antitubercular agents/, antitubercular drug\$.tw., tuberculostatic agent\$.tw., antitubercular agent\$.tw., antituberculosis, anti tuberculous, isoniazid/, pyrazinamide/, rifampin/, rifampicin.tw., ethambutol/, recurrence/, recurrence\$.tw., relapse\$.tw., recrudescence\$.tw., duration.tw., period.tw., drug administration schedule/, drug administration schedule\$.tw., dosing.tw., regimen.tw., drug combinations/, drug combination\$.tw., directly observed therapy/, dots.tw., steroids/, catatoxic steroids, BCG vaccine/, bacillus calmette guerin vaccine\$.tw., BCG vaccine\$.tw., calmette guerin bacillus vaccine\$.tw., calmette\$ vaccine\$.tw., lymphadenitis/, lymphadeniti\$.tw., congenital.tw., perinatal, gastric lavage/, pregnancy/, pregnanc\$.tw., gestation\$.tw., breast feeding/, breast feeding.tw., breastfeeding.tw., lactation/, lactation\$.tw., contraceptives, oral, combined/, combined oral contraceptive\$.tw., combined contraceptive agent\$.tw., hepatic insufficiency/, liver impair\$.tw., renal insufficiency/, renal impair\$.tw., HIV infections/, HIV infection\$.tw., prevalence/, prevalence\$.tw., incidence/, incidence\$.tw., diagnostic reagent kit/, diagnostic reagent kit\$.tw., diagnostic test kit\$.tw., time factors/, time factor\$.tw., prophylaxis.tw., antiretroviral therapy, highly active/, highly active antiretroviral therapy.tw., haart.tw.,

office visits/, office visit\$.tw., follow-up.tw., adverse drug reaction reporting systems/, adverse drug reaction reporting system.tw., drug therapy/, drug therapie\$.tw., pharmacotherapy.tw., chemotherapie\$.tw., medication therapy management/, drug therapy management.tw., medication therapy management.tw., drug toxicity/, drug toxicit*, drug safety, adverse drug reaction*, adverse drug event*, tuberculosis, multidrug-resistant/, multidrug resistance\$.tw., multi-drug resistance\$.tw., multiple drug resistance\$.tw., drug resistant/, drug resistance\$.tw., contact\$.tw., contact trac\$.tw., screen\$.tw., case find\$.tw., radiography, thoracic/, thoracic adj1 radiograph\$.tw., chest radiograph*. tuberculin test/, (tuberculin adj1 test\$.tw., mantoux test\$.tw., "health personnel"[MeSH Terms], health care provider*, healthcare provider*, fieldworker*, field worker*, "prevention and control"[Subheading], prevent*, preventive therap*, preventive measure*, prevention strateg*, control*, "infection control"[MeSH Terms], infection control, referral and consultation/, specialist/, specialist\$.tw., referral/, referral\$.tw., consultation\$.tw., second opinion.tw.

(For details of search strategies used, contact the CPG Secretariat, MoH)

APPENDIX 2

CLINICAL QUESTIONS

1. What is the epidemiology of TB?
2. Who are the high risk groups for TB?
3. What is the role of fluorescence microscopy in the diagnosis of TB?
4. What is the role of molecular methods in diagnosing TB?
5. What are the optimal methods to rapidly detect drug resistant *Mycobacterium tuberculosis*?
6. What are the roles of rapid methods (immunology and serology) to detect TB?
7. When are procedures performed to diagnose TB?
8. What is the role of imaging in TB diagnosis?
9. What is the treatment of choice for newly diagnosed PTB cases?
10. What is the treatment of choice for previously treated PTB cases?
11. What is the optimal duration of PTB treatment?
12. In maintenance phase for PTB treatment, is intermittent dosing regimen as effective as daily regimens?
13. Is fixed-dose combination (FDC) regimen as effective as separate-drug regimen in PTB treatment?
14. How is directly observed therapy (DOT) best implemented in PTB treatment?
15. What is the optimal duration of extrapulmonary TB (EPTB) treatment?
16. In which type of EPTB are corticosteroids effective in reducing mortality and morbidity?
17. How is latent TB diagnosed?
18. Who should get chemoprophylaxis in latent TB?
19. What is the optimal regimen in latent TB?
20. What are reliable diagnostic tests/procedures for PTB in children?
21. What are the effective treatments for PTB and EPTB in children?
22. What are reliable diagnostic tests for latent TB in children?
23. What are the effective antiTB drugs to treat latent TB in children?
24. What is the effective management for BCG lymphadenitis?
25. What is the best management for congenital and perinatal TB?
26. What is the management of TB in pregnancy, lactation and oral contraceptive use?
27. What is the management of TB in liver and renal impairment?
28. What is the prevalence/incidence of TB-HIV co-infections?
29. What are reliable diagnostic tests in diagnosing TB in HIV-positive patients?
30. What are the effective antiTB drugs/regimens in treating TB-HIV?
31. What is the optimal duration of antiTB in HIV positive patients?
32. Is IPT effective in patients with HIV?
33. What is the best timing for commencing ART in patients with HIV and TB co-infection?
34. What are the options/regimens for ARV in patients with HIV and TB co-infection?
35. How should follow-up be done during and after treatment of TB?
36. What are the drug adverse events and their management in TB?
37. What are the risk factors for MDR-TB?
38. What is the effective management of MDR-TB?
39. Among TB contacts, who should be screened?
40. What types of screening are most effective in TB?
41. What are the TB prevention strategies for health care workers?
42. When should referral of TB cases to specialist be done?

GLOSSARY

1	Definition of TB Cases	
1.1	A case of TB	A patient in whom TB has been bacteriologically confirmed or has been diagnosed by a clinician. Any person given treatment for TB should be recorded.
1.2	All forms	The sum of new smear-positive pulmonary, relapse, new smear-negative pulmonary and extrapulmonary cases.
1.3	New smear-positive PTB	A patient who has never received treatment for TB, or who has taken anti-TB drugs for less than 30 days and who has one of the following: <ul style="list-style-type: none"> • two or more initial sputum smear examinations positive for AFB; • one sputum examination positive for AFB plus radiographic abnormalities consistent with active PTB as determined by a clinician; or • one sputum specimen positive for AFB and at least one sputum specimen that is culture-positive for AFB
1.4	New smear-negative PTB	A case of PTB that does not meet the above definition for smear-positive TB.
1.5	EPTB	TB of organs other than the lungs, such as pleura, lymph nodes, abdomen, genito-urinary tract, skin, joints, bones and meninges. Diagnosis should be based on one culture-positive specimen, or histological or strong clinical evidence consistent with active EPTB, followed by a decision by a clinician to treat with a full course of antiTB chemotherapy. (A patient diagnosed with both pulmonary and extrapulmonary TB should be classified as a case of PTB)
1.6	Previously treated	Patient previously treated for TB including relapse, failure and default cases
1.7	Relapse	A patient whose most recent treatment outcome was “cured” or “treatment completed”, and who is subsequently diagnosed with bacteriologically positive TB by sputum smear microscopy or culture.
1.8	Treatment failure	A patient who has received Category I treatment for TB and in whom treatment has failed.
1.9	Treatment after default	A patient who returns to treatment, bacteriologically positive by sputum smear microscopy or culture, following interruption of treatment for two or more consecutive months.

2 Definition of Treatment Outcome		
2.1	Cured	Former smear-positive patient who was smear-negative in the last month of treatment and on at least one previous occasion.
2.2	Completed treatment	A patient who has completed treatment but who does not meet the criteria to be classified either as a cure or a failure.
2.3	Treatment success	The sum of patients who are cured and those who have completed treatment.
2.4	Died	A patient who dies for any reason during the course of treatment.
2.5	Failure	A patient whose sputum smear positive at five months or later during treatment.
2.6	Defaulted	A patient who has interrupted treatment for two consecutive months or more.
2.7	Transferred out	A patient who has been transferred to another recording and reporting unit and for whom the treatment outcome is not known.
2.8	Not evaluated	A patient who did not have the treatment outcome evaluated.
3 Indicators to assess treatment outcome		
3.1	Cure rate	Proportion of cured cases out of all cases registered in a given period.
3.2	Treatment success rate	The sum of the proportion of patients who were cured and patients who completed treatment out of all cases registered in a given period. The global target is an 85% cure rate and a greater treatment success rate.

4. Case detection rate and DOTS detection rate

Directly observed treatment, short-course (DOTS)

The 5 Strategy for TB control are	
1	Political commitment with increased and sustained financing
2	Case detection through quality-assured bacteriology
3	Standardised treatment with supervision and patient support
4	An effective drug supply and management system
5	Monitoring and evaluation system, and impact measurement
Targets for TB control established by the World Health Assembly (1991)	
1	To cure 85% of the sputum smear-positive TB cases detected.
2	To detect 70% of the estimated new sputum smear-positive TB cases.

Definition of Case Detection Rate		
4.1	Case Detection Rate (%)	Annual new smear-positive notifications (country and area)
		Estimated annual new smear-positive incidence (country and area)
4.2	DOTS Detection Rate (%)	Annual new smear-positive notifications under DOTS
		Estimated annual new smear-positive incidence (country and area)

Note: The case detection rate and DOTS detection rate are identical when a country or area has a 100% DOTS enrolment rate.

5 About DOTS		
5.1	Population with access to DOTS	The country and area's population who live in administrative areas where DOTS services are available.
5.2	DOTS enrolment rate (%)	This rate indicates a proportion of cases enrolled in DOTS, out of notified cases.
5.3	DOTS enrolment rate (all forms) (%)	Annual notifications of all forms under DOTS
		Total annual notifications of all forms
5.4	DOTS enrolment rate (new ss+) (%)	Annual notification of new ss+ under DOTS
		Total annual notifications of new ss+
6 Definitions of MDR-TB and XDR-TB		
6.1	MDR-TB, or multidrug-resistant TB	Strains of TB that are resistant to at least two main first-line anti-TB drugs i.e. isoniazid and rifampicin.
6.2	XDR-TB	TB that is resistant to any fluoroquinolone, and at least one of three injectable second-line drugs (capreomycin, kanamycin, and amikacin), in addition to MDR-TB. The WHO Global Task Force on XDR-TB agreed on this definition of XDR-TB in October 2006.
7 Indicator to assess laboratory performance		
7.1	Satisfactory performance	Zero error

Source: Sistem Maklumat Tibi Kementerian Kesihatan Malaysia

APPENDIX 4

CXR FEATURES OF PTB

a. Primary TB

- Parenchymal disease
 - Dense homogenous consolidation, predominantly in the lower lobes, middle lobe, lingula and anterior segments of the upper lobes. Occurs in 73% of cases.
 - Lobar or segmental atelectasis (segmental collapse)
 - Calcified granuloma is a sequelae of primary TB. The organism may remain quiescent within this nodule, serving as a possible source of reactivation
- Lymphadenopathy
 - Mediastinal lymphadenopathy is the hallmark of primary TB and it occurs in 96% maybe sole radiographic feature especially in infants
 - Typically unilateral and right-sided, but maybe bilateral in about 1/3 of cases
- Pleural effusion
 - Maybe the sole manifestation except in infants
 - Usually unilateral
 - May result in pleural thickening and calcification
- Miliary disease
 - involvement of both lungs with slight lower lobe predominance
 - evenly distributed diffuse 2 – 3 mm nodules

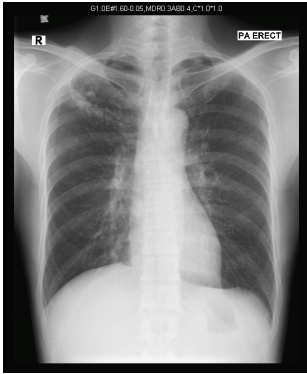
Post-primary TB

- Parenchymal disease
 - Patchy heterogenous consolidation predominantly in the apical and posterior segments of the upper lobes and the superior segments of the lower lobes
 - Poorly defined linear and nodular opacities in approximately 25% of patients
 - In majority of cases, more than one pulmonary segment of lung involvement with bilateral disease seen in 1/3 - 2/3 of cases
 - Cavitation is the hallmark of reactivation in up to 50%, usually multiple, within consolidation, sometimes with air-fluid levels
 - Tuberculoma, a well-defined round 0.5 - 4.0 cm density, is seen in 5% of patients. Satellite nodules around the tuberculoma may be present in as many as 80% of cases.
 - Architectural distortion and fibrosis
- Lymphadenopathy
 - Hilar and mediastinal lymphadenopathy is uncommon (about 5 - 10%)
- Pleural effusion
 - Occurs less frequently in approximately 15 - 20%
 - Typically unilateral and septated
 - Usually small and associated with parenchymal disease
 - Residual pleural thickening ± calcification
- Airway involvement
 - Bronchial stenosis seen in 10 - 40% cases resulting in lobar collapse or hyperinflated lung fields
 - Traction bronchiectasis particularly of upper lobe

Source:

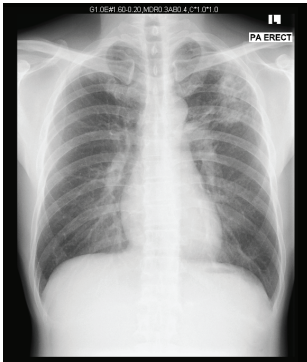
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GRADING OF SEVERITY IN CXR FEATURES OF PTB



a. Minimal

- Slight lesions with no cavity. Confined to small parts of one or both lungs but the total extent not exceeding the upper zone.



b. Moderate

- Dense confluent lesions not exceeding one third of one lung OR disseminated slight to moderate density in one or both lungs not exceeding the volume of one lung
- Total diameter of cavity should not exceed 4 cm



c. Advanced

- Lesions are more extensive than moderately advanced

APPENDIX 5

MANTOUX TESTING PROCEDURE

1. Wipe the arm with a sterile cotton swab.
2. Use 2 TU (0.1ml) of Purified Protein Derivative (PPD) RT 23 SSI which is given by intradermal injection to left forearm (at the junction of middle and lower third of the volar aspect), using a specific TB needle/syringe. If done correctly there should be a bleb, raised about 7 mm in diameter, which disappears within an hour.
3. Read at 48 – 72 hours and record the diameter of induration, in mm, (not simply “positive” or “negative”).

PROCEDURES FOR OBTAINING CLINICAL SAMPLES FOR TB SMEAR & CULTURE

Strict infection control policy must be adhered to during collection, storage and transportation of specimen.

A. Expectoration

Children who can produce a sputum specimen may be infectious. Thus the expectoration must be performed in a room that has adequate infection control precautions (negative pressure, ultraviolet light [turned on when room is not in use] and extractor fan). If there is no adequately equipped room, it should be done outdoor. The procedure should not be performed in enclosed spaces (such as toilets).

The expectorate produced must be directly collected into sterile sputum container.

B. Gastric Aspiration/Lavage

Gastric aspiration should be performed on three consecutive mornings for each patient. The child must be fasted for at least 4 hours (3 hours for infants) prior to the procedure and children with a low platelet count or bleeding tendency should not undergo the procedure.

Gastric aspiration is generally not an aerosol-generating procedure, hence considered a low risk procedure for TB transmission and can safely be performed at the child's bedside or in a routine procedure room.

1. Prepare the child and equipments as standard requirement for nasogastric tube insertion.
2. Attach a syringe to the nasogastric tube.
3. Aspirate gastric contents (2 – 5 ml) using the syringe attached to the nasogastric tube.
4. If no fluid is aspirated, insert 5 – 10 ml sterile water or normal saline and attempt to aspirate again.
5. Transfer gastric fluid from the syringe into a sterile sputum container.

C. Sputum Induction Guidelines (Adults and Children)

Sputum induction is a simple and non-invasive procedure, often precludes the need for bronchoscopy if done properly. It is an aerosol-generating procedure and should be performed in a room that has **adequate infection control precautions** by trained staffs with strict **airborne respiratory precautions**.

Indication

1. Patients who are unable to spontaneously expectorate adequate sputum specimens
2. May be useful in the diagnosis of miliary TB and tuberculous pleural effusion

Contraindications/Precautions

1. Patients in whom severe coughing may be harmful including patients with:
 - haemoptysis of unknown origin
 - acute respiratory distress
 - unstable cardiovascular status (arrhythmias, angina)
 - thoracic, abdominal or cerebral aneurysms
 - hypoxia (SaO₂ <90% on room air)
 - lung function impairment (FEV₁ < 1.0 litre)
 - pneumothorax
 - pulmonary emboli
 - fractured ribs or other chest trauma
 - recent eye surgery
 - bleeding disorders

The risks and benefits of the procedure should be discussed with patient before proceeding with it.

2. Patients who are unable to follow instructions or having reduced level of consciousness.
3. Inadequate fasting (<3 hours)

As hypertonic saline (3%) causes bronchoconstriction, the procedure should only be performed after pre-medication with salbutamol and under medical supervision in patients with asthma, suspected asthma or severely impaired lung function (FEV₁ <1 litre)

Preparation For The Procedure

Assess the patient for potential risk and explain the procedures to patient.

1. Patient should rinse their mouth and gargle with water (to prevent specimen contamination).
2. Fill the nebuliser (preferably ultrasonic nebuliser) with 3% saline (such as 5 ml for children and 20 – 30 ml for adult).
3. Patient should sit upright, place the mouthpiece in the patient's mouth, (apply nose clip) and turn nebuliser on.
4. Inhale and exhale through the mouthpiece only.
5. Gentle chest physiotherapy may be carried out during the procedure.
6. The procedure should be stopped when:
 - patient has produced 1 – 2 ml of sputum for each specimen collected
 - 15 minutes of nebulisation is reached
 - patient complains of dyspnoea, chest tightness or wheeze
7. Transport the specimen (in a cool box) to the laboratory for processing as soon as possible (within 4 hours).
8. If it is likely to take >4 hours for the specimens to be transported, place them in the refrigerator (4 – 8 °C) and stored until transported.
9. The specimen should be labelled as induced-sputum sample.

APPENDIX 6

SUGGESTED FIRST-LINE ANTITB MEDICATION DOSAGES & SIDE EFFECTS

Drug	Recommended Dose						Common Side Effects	Drug-Drug Interactions	AntiTB & HAART Concern
	Adult			Paediatric					
	Daily		3 Times Per Week		Daily				
	Dose (Range) in mg/kg body weight)	Max. Dose in mg	Dose (Range) in mg/kg body weight	Max. Dose in mg	Dose (Range) in mg/kg body weight	Max. Dose in mg			
Isoniazid*	5 (4 – 6)	300	10 (8 – 12)	900	10 (10 – 15)	300	Skin rash, jaundice, hepatitis, anorexia, nausea, abdominal pain, burning, numbness or tingling sensation in the hands or feet	<ul style="list-style-type: none"> Reduction in phenytoin & diazepam levels Increase the toxicity of carbamazepine, benzodiazepines, paracetamol, serotonergic antidepressants, warfarin & theophylline 	Care is needed when taking with HAART medications that can cause peripheral neuropathy, particularly stavudine (d4T) & didanosine (ddI)
Rifampicin	10 (8 – 12)	600	10 (8 – 12)	600	15 (10 – 20)	600	Skin rash, jaundice, hepatitis, anorexia, nausea, abdominal pain, orange or red urine, flu syndrome (fever, chills, malaise, headache, bone pain)	Reduction in plasma level of: <ul style="list-style-type: none"> - anti-infectives - hormone therapy, including ethinylestradiol, norethindrone, tamoxifen, levothyroxine - methadone - warfarin - cyclosporine - corticosteroid - anticonvulsants 	<ul style="list-style-type: none"> Reduces levels of protease inhibitors & NNRTIs in the blood.

Drug	Recommended Dose						Common Side Effects	Drug-Drug Interactions	AntiTB & HAART Concern
	Adult			Paediatric					
	Daily		3 Times Per Week	Daily		Max. Dose in mg			
	Dose (Range) in mg/kg body weight)	Max. Dose in mg		Dose (Range) in mg/kg body weight	Max. Dose in mg				
							- cardiovascular agents - HMG-CoA reductase inhibitors - antipsychotics - azole antifungal drug		
Pyrazinamide	25 (20 – 30)	2000	35 (30 – 40)	3000	35 (30 – 40)	2000	Skin rash, jaundice, hepatitis, anorexia, nausea, abdominal pain & joint pains Visual impairment	Excretion may be blocked by probenecid Should be taken two hours before didanosine (ddl)	
Ethambutol	15 (15 – 20)	1600	30 (25 – 35)	2400	20 (15 – 25)	1000	Absorption delayed or reduced by aluminium hydroxide	-	
Streptomycin	15 (12 – 18)	1000	15 (12 – 18)	1500	-	-	Skin rash, deafness (no wax on otoscopy), dizziness (vertigo & nystagmus), decreased urine output May increase ototoxicity & nephrotoxicity when use with: - aminoglycoside - amphotericin B - cephalosporins - cyclosporin - cisplatin - furosemide - vancomycin	-	

* Pyridoxine 10 - 20 mg need to be added when isoniazid is prescribed

SUGGESTED SECOND-LINE ANTI-TB MEDICATION DOSAGES & SIDE EFFECTS

Drug	Adult		Paediatric		Common Side Effects	Drug-drug Interactions
	Daily Dose (mg/kg body weight)	Max. Dose (mg)	Daily Dose (mg/kg body weight)	Max. Dose (mg)		
Kanamycin	15 – 20	1000	15 – 30	1000	Nephrotoxicity, peripheral neuropathy, rash, auditory damage	<ul style="list-style-type: none"> - Loop diuretic (increase auditory ototoxicity) - Non-depolarising muscle relaxants (respiratory depression) - Nephrotoxic agents (additive nephrotoxicity)
Amikacin	15 – 20	1000	15 – 22.5	1000	Nephrotoxicity, tubular dysfunction, azotaemia, proteinuria, urticaria or maculopapular rash	<ul style="list-style-type: none"> - Non-depolarising muscle relaxants (respiratory depression) - Nephrotoxic agents (additive nephrotoxicity)
Capreomycin	15 – 20	1000	15 – 30	1000		
Cycloserine*	15 – 20	1000	10 – 20	1000	Neurological and psychiatric disturbances including headaches, irritability, sleep disturbances, aggression and tremors, gum inflammation, pale skin, depression, confusion, dizziness, restlessness, anxiety, nightmares, severe headache, drowsiness.	<ul style="list-style-type: none"> - Ethionamide and isoniazid (additive nervous system side effects) - Phenytoin (may increase cycloserine level)

* All patients receiving cycloserine should be given 50 mg pyridoxine for every 250 mg of cycloserine.

Drug	Adult		Paediatric		Common Side Effects	Drug-drug Interactions
	Daily Dose (mg/kg body weight)	Max. Dose (mg)	Daily Dose (mg/kg body weight)	Frequency		
Ethionamide	15 – 20	1000	15 – 20	Twice daily	Severe gastrointestinal intolerance, psychotic disturbances, neurotoxicity, gynecomastia	<ul style="list-style-type: none"> - Cycloserine (increase neurotoxicity) - PAS (increase liver toxicity)
<i>p</i> -aminosalicylic acid (PAS)	150	12000	200 – 300	3 – 4 equally divided doses	Gastrointestinal intolerance, careful use in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency.	<ul style="list-style-type: none"> - Ethionamide (increase risk of hypothyroidism)
Clofazimine	100 – 300 mg daily (not in mg/kg)	300	Safety and efficacy not established	-	Ichthyosis, dry skin; pink to brownish-black discoloration of skin, cornea, retina and urine; anorexia, abdominal pain	<ul style="list-style-type: none"> - Rifampicin (decrease absorption rate) - Isoniazid (increase clofazimine serum concentration)
Ofloxacin	15 – 20	1000	15 – 20	Twice daily	Gastrointestinal intolerance, headache, malaise, insomnia, restlessness, dizziness, allergic reactions, diarrhoea, photosensitivity	<ul style="list-style-type: none"> - Should not be given to patients receiving class Ia antiarrhythmic drugs (such as quinidine and procainamide) or Class III antiarrhythmics (such as amiodarone and sotalol) - Antacids (decrease absorption and loss of therapeutic efficacy)
Levofloxacin	7.5 – 10	1000	7.5 – 10	Daily		
Moxifloxacin	7.5 – 10	400	7.5 – 10	Daily		

HAART – Refer to Ministry of Health Malaysia. Guidelines for the Management of Adult HIV Infection with Antiretroviral Therapy. Putrajaya: Ministry of Health; 2011

Source:

1. World Health Organization. Treatment of tuberculosis Guidelines Fourth Edition. Geneva: WHO; 2010
2. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis 2011 Update. Geneva: WHO; 2011
3. Drugs, diseases & procedures. Medscape Reference. Available at <http://www.eMedicine.medscape.com>

SUGGESTED STEROID REGIMEN FOR TB MENINGITIS & TB PERICARDITIS

a. TB meningitis

Severity	Regimen
Grade I disease	Week 1: IV dexamethasone sodium phosphate 0.3 mg/kg/day Week 2: 0.2 mg/kg/day Week 3: Oral dexamethasone 0.1 mg/kg/day Week 4: Oral dexamethasone a total of 3 mg/day, decreasing by 1 mg each week
Grade II and III disease	Week 1: IV dexamethasone sodium phosphate 0.4 mg/kg/day Week 2: 0.3 mg/kg/day Week 3: 0.2 mg/kg/day Week 4: 0.1 mg/kg/day, then oral dexamethasone for 4 weeks, decreasing by 1 mg each week

Source: Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. Cochrane Database of Systematic Reviews 2008, Issue 1. Art. No.: CD002244. DOI: 10.1002/14651858.CD002244.pub3

b. TB pericarditis

Week 1 - 4: Oral prednisolone 60 mg daily Week 5 - 8: Oral prednisolone 30 mg daily Week 9 - 10: Oral prednisolone 15 mg daily Week 11: Oral prednisolone 5 mg daily IV hydrocortisone can be used if patients cannot take orally: IV hydrocortisone 300 mg bolus, then 100 mg daily for 1 - 2 weeks b, continued with oral prednisolone as above

Source: Mayosi BM. Interventions for treating tuberculous pericarditis. Cochrane Database of Systematic Reviews 2002, Issue 4. Art. No.: CD000526. DOI: 10.1002/14651858.CD000526

SUGGESTED ANTITB DOSING FOR ADULT PATIENTS WITH REDUCED RENAL FUNCTION

Drug	AntiTB dose and frequency with CrCl <30 ml/min or for patients receiving intermittent hemodialysis*
First-Line Drugs	
Isoniazid	No dosing changes are required
Rifampin	No dosing changes are required
Pyrazinamide	25 - 35 mg/kg (ideal body weight) per dose PO 3 times/week; max. 2.5 g per dose
Ethambutol	15 - 25 mg/kg (ideal body weight) per dose PO 3 times/week; max. 1.6 g per dose
Streptomycin	12 – 15 mg/kg/dose IV/IM 3 times/week; max. 1.5 g per dose
Second-Line Drugs	
Cycloserine	250 mg PO once daily or 500 mg/dose 3 times/week
Ethionamide	250 - 500 mg/dose PO daily
Amikacin/kanamycin	12 - 15 mg/kg/dose (ideal body weight) IV/IM 3 times/week; max. 1.5 g per dose
Capreomycin	12 - 15 mg/kg/dose (ideal body weight) IV/IM 3 times/week; max. 1 g per dose
Para-aminosalicylic acid (PAS)	4 g/dose, PO twice daily
Levofloxacin	750 - 1000 mg per dose PO 3 times/week
Moxifloxacin	400 mg PO daily

*On the day of hemodialysis, medications should be administered after hemodialysis/

Source: Blumberg HM, Burman WJ, Chaisson RE et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med. 2003 Feb 15;167(4):603-62

LIST OF ABBREVIATIONS

ADA	Adenosine Deaminase
ADR(s)	adverse drug reaction(s)
AFB	acid fast bacilli
ALT	alanine aminotransferase
AntiTB	antituberculosis
ART	antiretroviral treatment
ARV	antiretroviral
ATLI	antiTB-induced liver injury
BCG	Bacille Calmette-Guérin
CD4	cluster of differentiation 4
CI	confidence interval
cm	centimetre
CNS	central nervous system
CPG(s)	clinical practice guidelines
CSF	cerebrospinal spinal fluid
CSF-ADA	cerebrospinal spinal fluid-Adenosine Deaminase
CT	computerised tomography
CTX	co-trimoxazole
CXR	chest x-ray
DG	Development Group
DIH	drug-induced hepatitis
DOT	directly observed therapy
DOTS	directly observed therapy, short course
DRESS	Drug Rash with Eosinophilia and Systemic Symptoms
DST	drug sensitivity test
EPTB	extrapulmonary tuberculosis
FDC(s)	fixed-dose combination(s)
FM	fluorescence microscopy
FNA	needle aspiration
g	gram
HAART	Highly Active Antiretroviral Therapy
HCWs	Healthcare workers
HIV	Human Immunodeficiency Virus
HR	hazard ratio

HRCT	high resolution computerised tomography
IGRA(s)	Interferon Gamma Release Assay(s)
IM	intramuscular
IPT	Isoniazid Prophylaxis Therapy
IQR	interquartile range
IRIS	Immune Reconstitution Inflammatory Syndrome
IRR	incidence rate ratio
IV	intravenous
kg	kilogram
LFT	liver function test
LPA	Line Probe Assay
LR	likelihood ratio
LTBI	latent TB infection
Max.	Maximum
MDR-TB	Multidrug-resistant tuberculosis
mg	milligram
ml	millilitre
mm	millimetre
MoH	Ministry of Health
MRI	magnetic resonance imaging
NAAT	Nucleic Acid Amplification Test
NICE	National Institute for Health and Clinical Excellence
NNT	number needed to treat
NPV	negative predictive value
NNRTIs	Non-Nucleoside Reverse Transcriptase Inhibitors
NRTIs	Nucleoside Reverse Transcriptase Inhibitors
NTM	Nontuberculous Mycobacteria
OR	odds ratio
PAS	p-aminosalicylic acid
PCR	Polymerase Chain Reaction
PIs	protease inhibitors
PO	per oral
PPV	positive predictive value
PTB	pulmonary tuberculosis
RC	Review Committee
RCT(s)	randomised controlled trial(s)

RR	relative risk
SAT	self-administered therapy
SJS	Steven-Johnson Syndrome
SR	systematic review
TB	tuberculosis
TEN	Toxic Epidermal Necrolysis
TST	tuberculin skin test
U/L	Unit per litre
US	ultrasonography
VATS	video-assisted thoracoscopy surgery
vs	versus
WHO	World Health Organization
XDR-TB	extensively drug-resistant TB

ACKNOWLEDGEMENT

The members of development group of these guidelines would like to express their gratitude and appreciation to the following for their contributions:

- Panel of external reviewers who reviewed the draft
- Ms Sin Lian Thye (Nursing Matron) and Ms Loong Ah Moi (Nursing Sister)
- Technical Advisory Committee for CPG for their valuable input and feedback
- All those who have contributed directly or indirectly to the development of the CPG

DISCLOSURE STATEMENT

The panel members of both Development Group and Review Committee had completed disclosure forms. None held shares in pharmaceutical firms or acts as consultants to such firms. (Details are available upon request from the CPG Secretariat)

SOURCES OF FUNDING

The development of the CPG on Management of Tuberculosis (3rd Edition) was supported financially in its entirety by the Ministry of Health Malaysia and Malaysian Thoracic Society.

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