



MINISTRY OF HEALTH  
SINGAPORE

# Prevention, Diagnosis and Management of Tuberculosis

MOH Clinical Practice Guidelines 1/2016



Academy of Medicine  
Singapore



College of Family  
Physicians, Singapore



Singapore Medical  
Association



Chapter of Infectious  
Disease Physicians,  
College of Physicians,  
Singapore



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Singapore

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## Levels of evidence and grades of recommendation

### Levels of evidence

Level	Type of Evidence
1+ +	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2+ +	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

### Grades of recommendation

Grade	Recommendation
<b>A</b>	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1+ + and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
<b>B</b>	A body of evidence including studies rated as 2+, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1+ + or 1+
<b>C</b>	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2+ +
<b>D</b>	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
<b>GPP</b> (good practice points)	Recommended best practice based on the clinical experience of the guideline development group.

**CLINICAL PRACTICE GUIDELINES**

**Prevention, Diagnosis  
and Management of  
Tuberculosis**

**MOH Clinical Practice Guidelines 1/2016**

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## Statement of Intent

These guidelines are not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case. These guidelines should neither be construed as including all proper methods of care, nor exclude other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient, in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

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## Foreword

Tuberculosis remains a serious global health problem according to the World Health Organisation Global Tuberculosis Report 2014. In 2013, an estimated 9 million people developed tuberculosis and 1.5 million died from the disease. The rise of drug-resistant TB poses an even greater challenge – World Health Organisation estimates that there were 480,000 new Multidrug-resistant (MDR) TB cases world-wide in 2013.

In Singapore, following the launch of the Singapore Tuberculosis Elimination Programme (STEP) in 1997, the incidence of tuberculosis declined to a low of 35 per 100,000 resident population in 2007. This declining trend however reversed in 2008. Although Singapore's tuberculosis rates and drug-resistance statistics are still lower than many of our neighbouring countries, this is no reason for complacency. Almost 50% of the new cases in Singapore are in foreigners.\* In the 5-year period from 2010 to 2014, there were 131 cases of MDR-TB (22 local-born, 109 foreign-born) compared to the previous 5-year period of 2005-2009, when there were 93 MDR-TB cases (14 local-born, 79 foreign-born).† All nine cases of extensively drug-resistant (XDR) tuberculosis cases were also in the foreign-born. Thus a substantial burden of tuberculosis in Singapore is imported.

The recent arrest in the decline of Singapore's tuberculosis incidence and the increasing number of MDR cases in the country pose serious challenges to our public health system. Singapore needs to meet these threats with a robust response in the form of a strong national tuberculosis control programme. MOH has recently made several significant enhancements to STEP in the areas of laboratory support, increased subsidies for patients, outreach directly observed therapy (DOT) for patients who are too frail or elderly to attend DOT at the Polyclinics, among others. This set of clinical practice guidelines was developed to familiarise the medical community with the various strategies of tuberculosis prevention, diagnosis, treatment and management. In this way, they will be equipped to provide the vital support to STEP which is necessary for the successful control of tuberculosis in Singapore.

\*Ministry of Health. Communicable diseases surveillance in Singapore 2013. Singapore: Ministry of Health; 2014.

†MOH STEP Registry (Unpublished data for 2014)

ASSOCIATE PROFESSOR BENJAMIN ONG  
DIRECTOR OF MEDICAL SERVICES

## Executive summary of recommendations

Details of recommendations can be found on the indicated pages.

Key recommendations are highlighted in green.

### 1. Tuberculosis transmission and pathogenesis

No.	Recommendation	Grade, Level of evidence	CPG Page No.
1	Healthcare providers must be aware of the individual and group risk factors for tuberculosis to ensure early diagnosis of tuberculosis.	GPP	24

### 2. Clinical diagnosis of tuberculosis

No.	Recommendation	Grade, Level of evidence	CPG Page No.
2	In patients presenting with unexplained cough of more than 3 weeks, pulmonary tuberculosis should be considered.	Grade A, Level 1+	26
3	Persons with prolonged cough of more than 3 weeks should undergo chest radiographic examination.	Grade D, Level 4	26
4	Persons presenting with cough and abnormal chest radiograph are often prescribed an empirical course of antibiotics for chest infection. As fluoroquinolones may mask or delay the diagnosis of pulmonary tuberculosis, these drugs should be avoided as empirical treatment for chest infection.	Grade B, Level 2++	26
5	Medical practitioners in primary care are urged to refer suspected tuberculosis cases to the Tuberculosis Control Unit or specialists with experience in tuberculosis management.	GPP	26

No.	Recommendation	Grade, Level of evidence	CPG Page No.
6	Two sputum samples – including one early morning sample – should be obtained for both microscopy and mycobacterial cultures for patients with suspected pulmonary tuberculosis. Recommendations for sputum collection are in Appendix 1 (page 91).	Grade D Level 4	27
7	In patients in whom it is difficult to obtain sputum specimens, e.g. children and stroke patients, other means of obtaining sputum should be utilised, including sputum induction and gastric lavage.	Grade D, Level 3	27
8	In patients presenting with extrapulmonary disease, a chest radiograph should also be done to determine if there is concomitant pulmonary tuberculosis and sputum samples obtained to determine if the case is infectious.	Grade D, Level 3	28
9	Patients with newly diagnosed tuberculosis should be screened for human immunodeficiency virus (HIV) and diabetes mellitus.	Grade D, Level 3	32

### 3. Imaging in tuberculosis

No.	Recommendation	Grade, Level of evidence	CPG Page No.
10	Patients with chest radiographic findings that suggest active* or inactive† disease should be referred without delay for further evaluation including two sputum samples for acid-fast bacilli (AFB) smear and culture.	*Grade D, Level 4 †GPP	36
11	A chest radiograph may be performed on pregnant patients (with lead shield protection when it is required for tuberculosis contact investigations and for evaluation of active disease.	Grade D, Level 4	38



## 4. Tuberculosis laboratory diagnosis

No.	Recommendation	Grade, Level of evidence	CPG Page No.
12	All tuberculosis suspects should have relevant clinical specimen(s) obtained and sent for mycobacterial cultures, regardless of the AFB smear results.	Grade B, Level 1++	43
<b>Nucleic acid amplification tests (NAATs)</b>			
13	In pulmonary tuberculosis, nucleic acid amplification tests (NAATs) need not be routinely performed on sputum in the Singapore context, when the clinical, radiological and epidemiological features are consistent with pulmonary tuberculosis.	GPP	44
14	Rapid molecular tests like the Genotype MTBDR <i>plus</i> and Xpert MTB/RIF should be used as the initial test on respiratory samples from individuals suspected of multidrug-resistant tuberculosis. Specimens should still be sent for mycobacterial culture and phenotypic drug susceptibility testing to first and second-line anti-TB drugs.	Grade A, Level 1++	45
15	The presence of <i>rpoB</i> gene mutation as detected by the Xpert MTB/RIF assay should be taken as a surrogate for the presence of multidrug-resistant tuberculosis (MDR-TB) until proven otherwise by phenotypic drug-susceptibility testing.	Grade D, Level 4	45
16	For extrapulmonary tuberculosis, nucleic acid amplification tests performed on the appropriate fluid and/or tissue samples are useful adjunctive tests for cases where the clinical suspicion of active tuberculosis is high.	Grade B, Level 1+	46
<b>Adenosine deaminase (ADA)</b>			
17	Testing for adenosine deaminase (ADA) in pleural and ascitic fluids may be useful in tuberculous pleurisy and peritonitis*. ADA testing in sputum samples <b>is not recommended</b> for pulmonary tuberculosis†.	*Grade A, Level 1++ †Grade D, Level 3	46

## 5. Treatment of tuberculosis

No.	Recommendation	Grade, Level of evidence	CPG Page No.
<b>Initiation of treatment</b>			
18	Patients with chest radiographic findings that suggest active disease may be commenced on tuberculosis treatment even before bacteriological results are available.	GPP	50
19	Tuberculosis treatment should be seriously considered in symptomatic patients despite the X-ray appearances of inactivity.	GPP	50
20	Before starting tuberculosis treatment, baseline liver enzymes should be performed in those over 15 years old. Adult patients to be commenced on ethambutol must have their visual acuity and colour vision checked at baseline.	GPP	50
<b>Treatment regimens for pulmonary tuberculosis</b>			
21	<b>6-month standard regimen</b> The 6-month standard treatment regimen comprising a 2-month intensive phase of ethambutol, isoniazid, rifampicin and pyrazinamide followed by a 4-month continuation phase of rifampicin and isoniazid is the regimen of choice for pulmonary tuberculosis.	Grade A, Level 1++	51
22	<b>9-month regimen</b> For patients who are unlikely to tolerate pyrazinamide (e.g. the elderly, those with liver disease), a 9-month regimen comprising ethambutol, rifampicin and isoniazid for 2 months followed by rifampicin and isoniazid for 7 months may be used.	Grade A, Level 1+	51
<b>Treatment of extrapulmonary tuberculosis</b>			
<b>Note:</b> Extrapulmonary tuberculosis is generally treated with the same regimen (6- or 9- month) as pulmonary tuberculosis. Please refer to additional recommendations below:			
	<b>Tuberculous meningitis</b>		
23	Tuberculous meningitis should be treated with the standard tuberculosis regimen but extended to 12 months. Steroids should be used as an adjunct.	Grade B, Level 2+	52

No.	Recommendation	Grade, Level of evidence	CPG Page No.
	<b>Musculoskeletal tuberculosis</b>		
24	The preferred treatment duration for musculoskeletal tuberculosis is 9 months with a rifampicin-containing regimen.	Grade A, Level 1+	53
	<b>Miliary tuberculosis</b>		
25	Miliary tuberculosis (in the absence of central nervous system or musculoskeletal involvement) may be treated with the standard 6-month treatment regimen.	Grade D, Level 4	53
	<b>Pleural tuberculosis</b>		
26	Pleural tuberculosis may be treated with the standard treatment regimen.	Grade B, Level 1+	53
	<b>Pericardial tuberculosis</b>		
27	Tuberculosis pericardial effusion can be treated with the standard tuberculosis regimen. Adjunctive steroids should be prescribed.	Grade C, Level 2+	54
	<b>Lymph node tuberculosis</b>		
28	The standard tuberculosis regimen can be used in tuberculous lymphadenitis.	Grade C, Level 2+	54
<b>Treatment under special circumstances</b>			
	<b>Pregnancy and breastfeeding</b>		
29	Standard tuberculosis treatment may be used during pregnancy and breastfeeding. Due to the small risk of relative pyridoxine deficiency, pyridoxine should be given to the breast-fed infant of a mother who is receiving standard anti-tuberculosis treatment.	Grade D, Level 4	55
	<b>Renal insufficiency and end stage renal failure</b>		
30	For tuberculosis patients on haemodialysis or with creatinine clearance of less than 30 ml/min, the recommended dose of pyrazinamide is 25 mg/kg three times a week. The dose should be given post-dialysis.	Grade D, Level 3	55

No.	Recommendation	Grade, Level of evidence	CPG Page No.
31	The recommended dose of ethambutol is 15 to 25 mg/kg three times a week in tuberculosis patients with end-stage renal disease or with creatinine clearance of $\leq 30$ ml/min.	Grade D, Level 3	56
32	Streptomycin should be used with great care in tuberculosis patients with renal impairment. If it must be used, the recommended dose of streptomycin is 12 to 15 mg/kg 2 to 3 times a week post-dialysis.	Grade D, Level 3	56
<b>Hepatic disease</b>			
33	Patients with hepatic disease should be monitored closely during treatment*. The 9-month regimen with rifampicin, isoniazid and ethambutol can be used if the tuberculosis patient with hepatic disease can tolerate this regimen. Pyrazinamide should generally be avoided in patients with hepatic disease†.	*GPP †Grade D, Level 4	57
<b>HIV co-infection</b>			
34	The standard six-month treatment regimen is recommended for HIV co-infected patients with pulmonary tuberculosis. As with non-HIV-infected patients, the treatment should be extended to 9 months in patients with tuberculous osteomyelitis and to 12 month in patients with central nervous system tuberculosis.	Grade A, Level 1++	58
35	Patients with HIV-related tuberculosis should, as far as possible, be treated with a regimen containing a rifamycin for the full course of tuberculosis treatment.	Grade D, Level 4	58
36	Intermittent dosing regimen for tuberculosis treatment is not recommended for patients with advanced HIV disease (CD4 counts less than 100 cells/mm <sup>3</sup> ) in view of the risk of acquiring rifamycin resistance.	Grade D, Level 4	58

No.	Recommendation	Grade, Level of evidence	CPG Page No.
<b>Monitoring of patients on tuberculosis treatment</b>			
37	Directly observed therapy (DOT) should be the standard of care for all infectious tuberculosis cases. Tuberculosis patients who are assessed to have difficulty adhering to treatment or who pose greater public risk of transmission, e.g. sputum-smear positive or working in institutional settings or settings with susceptible populations, or those at risk of or diagnosed with drug-resistant tuberculosis, are high priority for DOT.	Grade C, Level 2+	63
38	Before commencing the treatment, patients must be counselled regarding the importance of adhering to and completing the full course of treatments, as well as medication adverse effects.	GPP	64
39	The patient's weight should be documented at each visit and the drug dosages adjusted accordingly. Adult patients on ethambutol must have their visual acuity and colour vision checked at each visit. Those with risk factors for drug-induced hepatitis must be closely monitored.	GPP	64
40	Patients should be reviewed monthly by the specialist to monitor their clinical condition, adherence to treatment and adverse effects of tuberculosis medications.	Grade D, Level 4	65
41	Bacteriological response to treatment should be monitored in patients who are initially sputum acid-fast bacillus (AFB) and/or culture-positive.	Grade D, Level 4	66
42	Cigarette smokers with tuberculosis should be strongly advised and supported to stop smoking.	Grade D, Level 3	67
<b>Management of multidrug-resistant/extensively drug-resistant tuberculosis</b>			
43	A multidrug-resistant treatment regimen must contain at least four drugs, preferably more, (including a later-generation fluoroquinolone and a second-line injectable agent) to which the organism is shown to be susceptible and to which the patient has previously not been exposed.	Grade D, Level 3	68

No.	Recommendation	Grade, Level of evidence	CPG Page No.
44	Multidrug-resistant tuberculosis (MDR-TB) patients should be treated under strict programme conditions by physicians experienced in MDR-TB management. Directly observed therapy (DOT) should be utilised for the entire treatment duration.	Grade D, Level 4	68
45	Resectional surgery should be considered in high grade MDR-TB or XDR-TB patients with localised disease and adequate respiratory reserve, and for whom there are limited chemotherapeutic options, or who are not responding to chemotherapy.	Grade D, Level 4	69

## 6. Public health screening and infection control

No.	Recommendation	Grade, Level of evidence	CPG Page No.
<b>Air travel and tuberculosis</b>			
46	Physicians should inform persons with infectious or potentially infectious tuberculosis not to travel by commercial air transportation on a flight of any duration.	Grade D, Level 3	70
<b>Public health screening</b>			
47	Persons applying for long-term immigration passes should be screened for active tuberculosis to ensure early detection and access to treatment, and to reduce community risk of transmission. This is especially true for persons from high tuberculosis prevalence countries.	Grade D, Level 3	71
48	Chest radiograph examination should be used for the purpose of screening in long-term immigration pass applicants.	Grade C, Level 2+	71
49	Any chest radiograph abnormality compatible with tuberculosis (whether radiologically "active" or "inactive") should be evaluated further to rule out active tuberculosis.	Grade D, Level 4	72

No.	Recommendation	Grade, Level of evidence	CPG Page No.
50	Medical practitioners should have a high index of suspicion of drug-resistant tuberculosis in those who were previously treated, those who fail treatment, who are known contacts of multidrug-resistant tuberculosis (MDR-TB), or who come from countries with high prevalence of tuberculosis drug resistance.	Grade C, Level 3	72
<b>Infection control for tuberculosis in healthcare settings</b>			
51	Healthcare facilities that potentially receive tuberculosis patients should have an infection control plan for tuberculosis, comprising administrative controls, environmental controls and use of personal protective equipment to protect staff and patients from potential tuberculosis transmission.	Grade D, Level 4	75
52	Persons with tuberculosis symptoms should be promptly identified in healthcare settings and if necessary, separated from other patients.	Grade D, Level 4	76
53	A ventilation system (natural, mechanical or mixed mode) should be employed for health care facilities to ensure sufficient air exchange and control airflow direction to reduce the risk of tuberculosis exposure.	Grade D, Level 4	76
54	Where necessary, healthcare workers should use particulate respirators when caring for patients suspected or known to have infectious tuberculosis, especially drug-resistant tuberculosis patients and in situations where high-risk procedures are being performed.	Grade D, Level 4	76
<b>Infection prevention in the home and the community</b>			
55	Physicians should advise patients with suspected or confirmed tuberculosis to practise cough etiquette and respiratory hygiene (especially surgical mask use).	Grade D, Level 4	77

## 7. Tuberculosis contact investigations and screening

No.	Recommendation	Grade, Level of evidence	CPG Page No.
56	Contact investigations are carried out by the National Tuberculosis Programme. Persons with recent close exposure to infectious tuberculosis cases (i.e. bacteriologically positive cases of pulmonary tuberculosis, especially if acid-fast bacilli smear is positive) should be evaluated for active tuberculosis and Latent Tuberculosis Infection.	Grade B, Level 2++	80
57	Testing for Latent Tuberculosis Infection should be targeted at high-risk groups and should only be performed if there is an intention to treat for Latent Tuberculosis Infection if detected.	Grade D, Level 4	81
58	Low risk groups (i.e. casual contacts) should not be screened as they are more likely to throw up false positive test results for Latent Tuberculosis Infection.	GPP	81
<b>Testing for Latent Tuberculosis Infection</b>			
59	Either the tuberculin skin test or the interferon-gamma release assay may be used for the diagnosis of Latent Tuberculosis Infection in adults and children 5 years or older.	Grade A, Level 1+	83
60	The interferon-gamma release assay is the preferred test for adolescents and adults who have received Bacillus Calmette-Guerin (BCG) vaccination, while the tuberculin skin test is the preferred test for the diagnosis of latent tuberculosis in children <5 years of age.	Grade A, Level 1+	84
61	In significantly immunocompromised individuals, especially those with HIV/AIDS, the T-SPOT.TB may be preferable to the tuberculin skin test and QuantiFERON-TB Gold In-Tube (QFT-GIT) for the diagnosis of Latent Tuberculosis Infection.	Grade C, Level 2+	84
62	The interferon-gamma release assay (IGRA) should not be used to monitor response to preventive therapy.	Grade C Level 2+	84



## 8. Tuberculosis in children - specific considerations

No.	Recommendation	Grade, Level of evidence	CPG Page No.
63	Children with persistent, unremitting cough for 2 weeks, plus objective weight loss, together with fatigue, should be evaluated for tuberculosis.	Grade C, Level 2+	85
64	All children being evaluated for latent or active tuberculosis (pulmonary or otherwise) should have a frontal chest radiograph. Where tuberculosis is strongly suspected, a lateral radiograph should be performed even if the frontal view is normal.	Grade C, Level 2+	86
65	Currently available scoring systems for predicting tuberculosis in children lack sensitivity and/ or specificity, and are not recommended to be used for diagnosis.	Grade B, Level 2++	87
66	In children younger than 5 years old suspected of having tuberculosis infection or disease, the tuberculin skin test (TST) is the preferred mode of initial immunological assessment.	Grade B, Level 2++	88
67	When interferon-gamma release assay (IGRA) testing is performed in children <4 years old, the T-SPOT.TB is preferred over the QFT-GIT due to a lower incidence of indeterminate results.	Grade C, Level 2+	88
68	Because of its excellent specificity, children with a positive interferon-gamma release assays (IGRA) are considered to have tuberculosis infection or disease, and should be offered treatment.	Grade B, Level 2++	88
69	For children with a clinical suspicion of tuberculosis disease with a negative tuberculin skin test (TST), the interferon-gamma release assay (IGRA) may be performed to increase sensitivity. However, treatment for tuberculosis should be considered when other factors are strongly supportive of tuberculosis (epidemiologic, radiologic, histologic, microbiologic), and neither a negative TST nor IGRA should delay treatment.	Grade D, Level 4	88

# 1 Introduction

Tuberculosis continues to be a disease of public health importance in Singapore and worldwide. According to the World Health Organisation's Global Tuberculosis Report 2014, an estimated 9 million people developed tuberculosis and 1.5 million died from the disease.<sup>1</sup> Issues like delayed detection and missed opportunities for treatment, and the emergence of drug-resistance are also of increasing concern.

## 1.1 Aim

The target audience is all healthcare practitioners in Singapore. These guidelines aim to

1. Increase knowledge and awareness of tuberculosis as to facilitate the early detection of active tuberculosis
2. Serve as an evidence-based resource to provide guidance on the use of tuberculosis diagnostic tools and treatment regimens
3. Inform regarding the public health measures necessary for the control of tuberculosis control in Singapore

## 1.2 Scope

These guidelines will cover tuberculosis referral and diagnosis, treatment of active and latent tuberculosis, and public health actions required on the part of treating physicians. The standards of diagnosis and treatment, which are outlined in the International Standards for Tuberculosis Care, will also be referenced in the clinical practice guideline.

## 1.3 Target group

The content of the guidelines will be useful for all healthcare professionals and public health service providers who encounter patients with tuberculosis. The CPG will be applicable to the diagnosis and management of both adult and paediatric patients. The doctor evaluating the patient is ultimately responsible for clinical decisions made after reviewing the individual patient's history, clinical presentation and treatment options available.

## **1.4 Development of guidelines**

These guidelines have been produced by a committee of respiratory physicians, infectious disease consultants, and representatives from polyclinics and the College of Family Physicians Singapore, as well as representatives from MOH and Tuberculosis Control Unit appointed by the Ministry of Health. They were developed by the adaptation of existing guidelines, by the review of relevant literature and by expert clinical consensus with consideration of local practice.

The following principles underlie the development of these guidelines:

- Treatment recommendations are supported by scientific evidence and expert clinical consensus.
- Treatment should maximise therapeutic and public health benefits and minimise side effects.

## **1.5 Review of guidelines**

Evidence-based clinical practice guidelines are only as current as the evidence that supports them. Users must keep in mind that new evidence could supersede recommendations in these guidelines. The workgroup advises that these guidelines be scheduled for review five years after publication, or when new evidence appears that requires substantive changes to the recommendations.

## 2 Epidemiology of tuberculosis in Singapore

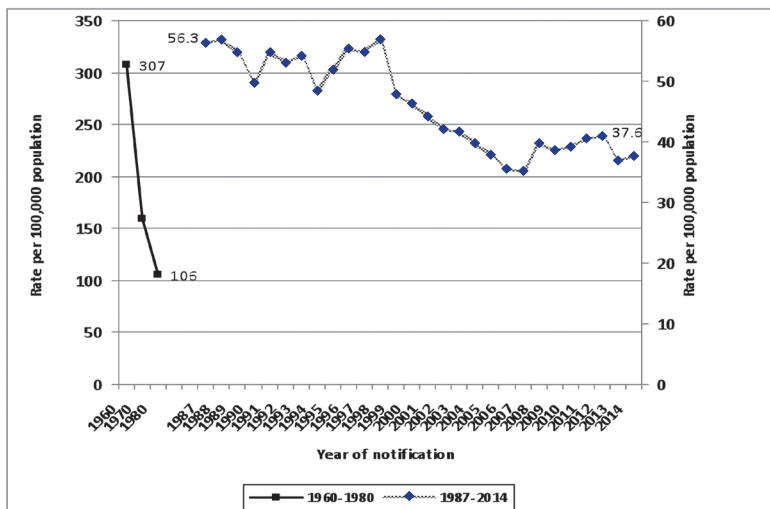
### 2.1 Overview of tuberculosis

Tuberculosis is an infectious disease which is caused by the bacterium, *Mycobacterium tuberculosis* and is spread from person to person via airborne droplets (e.g. when an infected person coughs or sneezes). Tuberculosis primarily affects the lungs (causing pulmonary tuberculosis), but it can also affect other organs, e.g. central nervous system, lymphatic system, and circulatory system among others, resulting in extrapulmonary tuberculosis. When a person first becomes infected, the tuberculosis bacteria generally lay dormant in the body and the person will not manifest any symptoms (this is termed “Latent Tuberculosis Infection”. Persons with Latent Tuberculosis Infection are not infectious. However, in about 10% of healthy individuals with Latent Tuberculosis Infection, active tuberculosis disease may eventually develop over their lifetime. The highest risk of progressing to active tuberculosis disease is in the first two years after initial infection. In persons who are immunocompromised (e.g. the elderly or those who are human immunodeficiency virus (HIV) positive), the rate of progressing to active tuberculosis disease will be higher than in healthy individuals. For example, individuals with untreated HIV co-infection may progress from Latent Tuberculosis Infection to active tuberculosis disease at the rate of 5-8% per year, with a lifetime risk of approximately 30%.

### 2.2 Tuberculosis in Singapore residents (citizens and permanent residents)

The incidence of tuberculosis declined from 307 cases per 100,000 populations in 1960 to 56 cases per 100,000 in 1987. From 1987 to 1998, the rate of tuberculosis among residents was fairly static ranging from 49-57 per 100,000 resident populations. Following the launch of the Singapore Tuberculosis Elimination Programme (STEP) in 1997, the incidence of tuberculosis declined to a low of 35 per 100,000 resident populations in 2007. However, between 2008 and 2012, tuberculosis incidence rates amongst Singapore residents rose to between 39 and 41 per 100,000 before dipping to 37.6 per 100,000 in 2014.

**Figure 1** Incidence rate of tuberculosis among Singapore residents, 1960-1980 and 1987-2014



Source: Communicable diseases surveillance in Singapore 2013. Singapore: Ministry of Health; 2014.

In 2014, the incidence of tuberculosis was 37.6 cases per 100,000 resident population (1454 cases). 83.9% of new resident tuberculosis cases notified in 2014 had pulmonary tuberculosis with or without extrapulmonary involvement while the remainder (16.1%) had exclusively extrapulmonary tuberculosis. The most common site of extrapulmonary tuberculosis was the pleura (134 cases) followed by the lymphatic system (119 cases). There were no cases of tuberculous meningitis reported in residents below 15 years of age. In 2013, there were 46 deaths from tuberculosis among Singapore residents, giving us a mortality rate of 1.2 cases per 100,000 population.

The incidence rate of tuberculosis was higher in males compared to females (53.5 per 100,000 in males compared to 22.2 per 100,000 in females). The incidence rate increased with age, with the highest incidence rate in persons aged 80+ years (139.8 per 100,000), followed by persons aged 70-79 years (118.5 per 100,000) and those aged 60-69 years (78.7 per 100,000). In terms of ethnic group, Malays had the highest incidence rate of tuberculosis (56.1 per 100,000) compared to Chinese (35.6 per 100,000) and Indians (25.8 per 100,000).

In 2014, there were 137 relapsed cases of tuberculosis.

Persons with HIV are known to be particularly susceptible to tuberculosis, both from the reactivation of latent tuberculosis and from new infection with rapid progression to active disease. In 2013, 3.1% of the 1420 new tuberculosis cases among Singapore residents had prior diagnosis of HIV. Most of these TB-HIV co-infections were observed in older age groups and in the male Chinese population.

### **2.3 Tuberculosis in non-residents**

In 2014, there were 1287 new cases of tuberculosis among non-residents in Singapore. The largest group of tuberculosis cases among non-residents were work permit holders (409), followed by work permit applicants (391) and short term social visitors (215). The number of new tuberculosis cases who were long-term visit pass holders rose from 524 in 2009 to 564 in 2014 (accounting for one-fifth of all new tuberculosis cases notified in Singapore). Similarly, the number of new tuberculosis cases contributed by short-stay non-residents increased from 551 in 2009 to 723 in 2014 (constituting more than one-quarter of all new tuberculosis cases notified in Singapore). Chest radiograph is carried out to detect cases of active pulmonary tuberculosis among pass applicants. While this may not pick up all cases of active tuberculosis, effective screening can nonetheless reduce the likelihood of imported tuberculosis and enable appropriate public health actions to be taken to avoid further spread within the local community. The medical practitioner's role in ensuring accurate and effective screening for active tuberculosis in work pass and immigration pass applicants is therefore critical to reducing the threat of imported tuberculosis.

**Figure 2 Distribution of non-residents with new tuberculosis by pass category/status, 2009-2014**

Pass category / status	No. of new tuberculosis cases notified					
	2009	2010	2011	2012	2013	2014
<b>Long-Term Immigration Pass Holders Residing in Singapore</b>						
Work Permit Holders	403	403	442	458	434	409
Employment Pass Holder	32	41	47	53	52	27
Other Pass Holders *	89	106	104	132	122	128
<b>Sub-total</b>	<b>524</b>	<b>550</b>	<b>593</b>	<b>643</b>	<b>608</b>	<b>564</b>
<b>Short Stay Foreigners</b>						
Work Permit Applicants	218	329	462	528	389	391
Visitors†	220	253	237	238	216	215
Others ‡	113	181	207	151	168	117
<b>Sub-total</b>	<b>551</b>	<b>763</b>	<b>906</b>	<b>917</b>	<b>773</b>	<b>723</b>
<b>Total</b>	<b>1,075</b>	<b>1,313</b>	<b>1,499</b>	<b>1,560</b>	<b>1,381</b>	<b>1287</b>

Source: Communicable diseases surveillance in Singapore 2013. Singapore: Ministry of Health; 2014.

\* Professional pass holder, dependent pass holder, long-term social visit pass holder and student pass holder and S pass holder

† Short-term social visitor

‡ Professional visit pass applicant, dependent pass applicant, long-term social visit pass applicant, student pass applicant, employment pass applicant, S pass applicant and illegal immigrant

## 2.4 Emergence of MDR and XDR-TB

Another emerging area of concern to the control of tuberculosis in Singapore is the threat of multidrug-resistant tuberculosis (MDR-TB)<sup>2</sup> which can put considerable strain on the healthcare system to manage and treat these patients. Drug resistance is a man-made problem that is caused by poor treatment monitoring and sub-optimal patient compliance, as well as the inappropriate use of anti-tuberculosis drugs. Previous drug treatment is the largest single risk factor for the presence of MDR-TB.<sup>3</sup> The number of cases of local MDR-TB remained low in 2014. There was one new case of pulmonary MDR-TB among Singapore residents.

There were no cases of extensively drug-resistant tuberculosis (XDR-TB)<sup>2</sup> among Singapore residents in 2014. We have however encountered one foreigner who was found to have XDR-TB. The threat of MDR-TB is also high among non-residents in Singapore, especially those who are originally from high-tuberculosis burden countries (see Figure 3). In 2014, there were 9 new pulmonary MDR-TB cases among non-residents, compared to one new pulmonary case among Singapore residents. In this regard, effective screening among non-residents at entry will be paramount in allowing us to identify suspect cases of MDR-TB for early management.

The key to the control of MDR-TB and XDR-TB is to prevent their emergence in the first place. MDR-TB and XDR-TB are “man-made”. They arise from ineffective treatment protocols and poor treatment compliance.

**Figure 3 Proportion of MDR-TB cases among culture positive pulmonary tuberculosis cases according to country of birth, 2002-2014**

Country of Birth	New cases (%)	Previously treated cases (%)
Myanmar	7.7	22.0
Vietnam	4.4	50.0
China	3.2	2.9
Philippines	2.5	4.5
Indonesia	2.2	26.6
India	0.9	18.2
Bangladesh	1.1	33.3
Singapore or Malaysia	0.3	1.2

Source: MOH STEP Registry (Unpublished data for 2002-2014).

## 2.5 Reasons for increasing tuberculosis trend in Singapore

We believe that there are multiple factors that may be contributing to the rise in tuberculosis incidence in Singapore. Firstly, like many developed countries, Singapore’s rapidly ageing population represents a sizable reservoir of tuberculosis infection, and not surprisingly, the risk of tuberculosis is highest in those aged 65 years and above due to the “cohort effect” (i.e. there is a higher proportion of Latent Tuberculosis Infection in this age group as they were born



in the era of very high tuberculosis incidence rates). Reactivation of primary tuberculosis infection may also occur as result of age-associated chronic diseases and weakened immune status.<sup>4</sup> Diagnosis and treatment of tuberculosis in the elderly can also be challenging due to atypical presentation of symptoms and greater likelihood of adverse drug effects.<sup>5</sup> Secondly, ongoing community transmission continues to contribute significantly to new infections. Delays in diagnosis and issues with treatment compliance increase the duration that infectious cases can remain in the community to propagate transmission. Thirdly, greater population flux and mobility in recent years have increased our vulnerability to imported tuberculosis. The number of non-resident tuberculosis cases increased from 1075 in 2009 to 1381 in 2013.

## **2.6 National tuberculosis control programme**

MOH established the National Tuberculosis Programme in 1957 with the setting up of the Tuberculosis Control Unit and a National Tuberculosis Register in 1958.

Mass BCG vaccination started in Singapore in the mid-1950s and has been part of the national childhood immunisation programme. Under this programme, BCG vaccination was administered at birth, and re-vaccination was carried out at ages 12 or 16 years for tuberculin non-reactors. The practice of BCG revaccination was discontinued on 1 July 2001 based on the recommendations of the Ministry's Expert Committee on Immunisation, STEP Committee, and the International Advisory Committee on tuberculosis, for the following reasons:

- i) There was no scientific basis for the protective effect of BCG revaccination.
- ii) WHO had recommended discontinuation of this practice in 1995.
- iii) BCG re-vaccination confounded the interpretation of the tuberculin skin test (TST), which is used for the identification of people with Latent Tuberculosis Infection amongst close contacts of tuberculosis Index cases.

BCG vaccination at birth is still useful for the protection of infants and young children from tuberculous meningitis. Over the last decade, we have maintained a high BCG coverage among infants of close to 100%.

While the incidence of tuberculosis fell dramatically in the decades after the National Tuberculosis Programme was established till the late 1980s, there was a plateau in the incidence rate from 1987 to 1996 at about 50-60 cases per 100,000 population. In response to the plateau in tuberculosis incidence rate, the National Tuberculosis Programme was enhanced into the Singapore Tuberculosis Elimination Programme (STEP) in April 1997.

## 2.7 **Singapore Tuberculosis Elimination Programme (STEP)**

STEP focused on the following strategies to control tuberculosis in Singapore:

- (a) Promotion of directly observed therapy (DOT) for tuberculosis patients;
- (b) Implementation of a National Treatment Surveillance Registry to monitor treatment progress and outcome for all tuberculosis patients; and
- (c) Contact investigations to identify recently infected close contacts of infectious tuberculosis cases, and offering of preventive therapy to reduce their risk of progression to active tuberculosis.

### **Case finding and epidemiological surveillance**

Tuberculosis is diagnosed mainly by passive case finding when the patient presents with symptoms. The National Tuberculosis Notification Registry, established in 1957, continues to collect and collate data on incidence of tuberculosis disease in Singapore. All medical practitioners and laboratories that make a diagnosis of tuberculosis are required by law to notify the Ministry. Notification is mandatory for both confirmed and suspected cases of tuberculosis.

STEP also monitors tuberculosis treatment. This involves a computerised National Treatment Surveillance Registry in which treatment progress for every notified tuberculosis patient is monitored until completion of treatment. This allows for the early detection of treatment defaulters so that they can be traced and followed-up closely to ensure completion of their treatment.

## **Identifying all tuberculosis contacts with Latent Tuberculosis Infection**

Under STEP, contact tracing is prioritized according to the infectiousness of the Index case. Identified contacts of bacteriologically positive pulmonary cases are interviewed and offered testing for Latent Tuberculosis Infection using the interferon-gamma release assay (IGRA) or TST. Those found to have positive results are followed up with chest radiography for the exclusion of active tuberculosis as prelude to preventive treatment. Contacts found to have Latent Tuberculosis Infection are offered preventive therapy to reduce their risk of progression to active disease. Contact screening includes household and family members, as well as close contacts in the workplace, and in congregate settings such as childcare centres, schools, prisons, drug rehabilitation centres, nursing homes for the elderly and the mental institution. Close contacts of tuberculosis Index cases with Latent Tuberculosis Infection are given outpatient preventive treatment.

## **Preventing the emergence of drug-resistant tuberculosis**

Poorly managed treatment practices are the root cause of drug-resistant tuberculosis. Drug resistance can develop when patients take the wrong drugs or when patients stop taking their medicines because they feel better. The main strategies employed to increase treatment compliance and to prevent the emergence of drug resistant tuberculosis locally include the use of directly observed therapy (DOT) and close monitoring.

Legal enforcement using the Infectious Diseases Act (IDA) to ensure treatment completion in recalcitrant treatment defaulters has been applied since July 2004 in order to control community transmission of the disease, and to prevent the emergence of drug resistant tuberculosis.

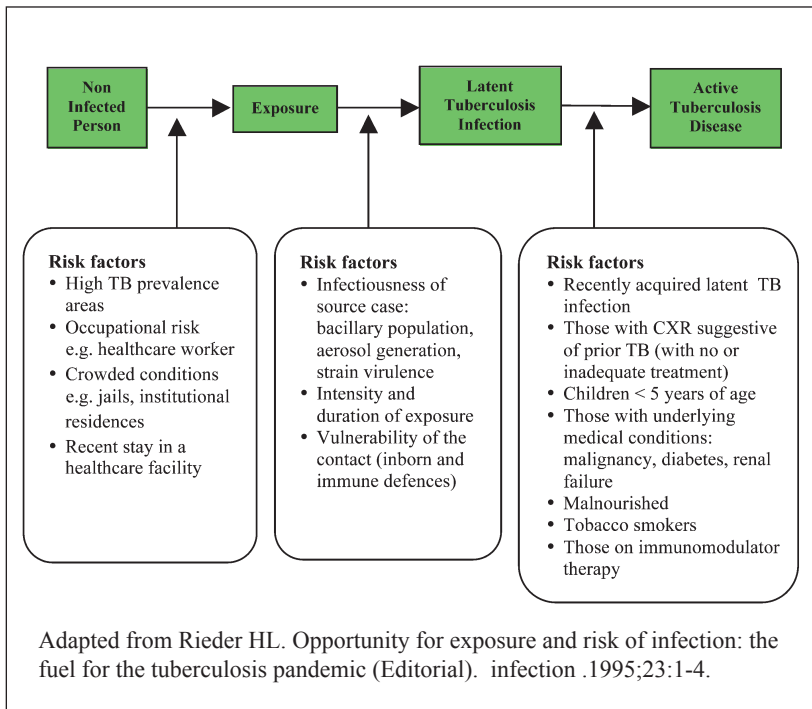
### 3.1 Tuberculosis: transmission and pathogenesis

The vast majority of patients with tuberculosis acquire the infection through inhalation of airborne droplet nuclei containing *Mycobacterium tuberculosis* complex (MTC).<sup>6</sup> Transmission via direct inoculation or oral ingestion is rare, particularly in developed countries in the case of the latter route owing to pasteurisation of dairy products and improving control of *Mycobacterium bovis* (a zoonotic member of MTC) transmission among cattle herds.<sup>7, 8</sup> Whereas only patients with active tuberculosis involving the respiratory tract are infectious, the likelihood of successful person-to-person transmission is affected by a variety of factors including source patient and exposed person characteristics, aspects of the exposure, and virulence of the infecting strain of MTC (Table 1).<sup>9</sup>

**Table 1 Factors involved in the person-to-person transmission of tuberculosis**

	<b>Factors affecting transmission</b>
Source patient	Sputum smear positivity (increased) <sup>10, 11</sup> Cavitary pulmonary disease (increased) <sup>12</sup> Higher frequency of cough (increased) <sup>9</sup>
Exposed person	BCG vaccination (protective in children) <sup>13</sup> Previous MTC infection (protective) <sup>14</sup> Innate immunity (protective) <sup>15, 16</sup> Genetic susceptibility (increased) <sup>17</sup>
Exposure	Higher frequency and duration of exposure (increased) <sup>12</sup> Poor ventilation (increased) <sup>9, 18</sup>
MTC strain	Beijing genotype (increased) <sup>19</sup>

**Figure 4 The risk factors for transmission of tuberculosis and the development of active tuberculosis disease**



A systematic review by Nava showed that at a population level, the risk factors associated with recent transmission of MTC include: being a member of an ethnic minority, being a native of the country, homelessness, prior imprisonment, HIV infection, young age, sputum smear positivity, and male gender.<sup>20</sup> Healthcare facilities are also associated with higher rates of tuberculosis transmission among both patients and healthcare workers compared to the general population.<sup>9, 21, 22</sup> Published guidelines recommend a combination of administrative and engineering controls as well as personal respiratory protection to reduce the risk of transmission in the healthcare setting.<sup>22-24</sup>

When MTC within droplet nuclei reach the alveoli, they are engulfed by either alveolar macrophages or epithelial type II pneumocytes, forming phagolysosomes.<sup>6</sup> The ensuing surviving bacteria within these phagolysosomes trigger off a local immune reaction resulting in the formation of granulomas, which effectively contain the spread of infection.<sup>6</sup> <sup>25</sup> Within the granuloma, which eventually becomes a calcified and fibrotic lesion, MTC may remain dormant but viable for decades, establishing a state of latent infection.<sup>6, 25</sup> In immunocompetent persons with latent tuberculosis, approximately 10% will develop clinical tuberculosis in their lifetime,<sup>25</sup> half of whom will develop it in the first two years following acquisition of the infection. However, in immunosuppressed patients, the risk is higher. For example, up to 30% of patients co-infected with HIV will eventually develop active tuberculosis, with an annual risk of 5-8%,<sup>26</sup> while patients on biologics had a greater than fourfold risk of reactivating latent tuberculosis compared to controls on meta-analysis of clinical trials involving these agents.<sup>27</sup>

When latent tuberculosis progresses into active tuberculosis, or when primary infection cannot be controlled, MTC escapes from the granuloma and spread within the lungs and/or to other tissues via the blood or lymphatics.<sup>6</sup> In an era prior to the development of effective therapy for tuberculosis, the disease followed a general pattern, with hematogenous dissemination – occasionally with the development of miliary or meningitic tuberculosis – occurring after the formation of the primary Ghon complex; after which pleurisy followed by pulmonary (majority of cases) or other extrapulmonary (minority of cases) reactivation of tuberculosis occurred.<sup>28</sup> Among untreated HIV-negative patients, the overall mortality is estimated to be 70% and 20% for smear-positive and smear-negative active pulmonary tuberculosis respectively.<sup>29</sup>

**GPP** Healthcare providers must be aware of the individual and group risk factors for tuberculosis to ensure early diagnosis of tuberculosis.

**GPP**

*Mycobacterium tuberculosis* is transmitted primarily by the airborne route. Screening for tuberculosis in migrant population, especially international students and foreign workers from countries where there is a high incidence of tuberculosis, has led to earlier detection of cases and reduced infectiousness.<sup>30</sup>

The relative risk for developing tuberculosis is higher in patients with the following conditions:<sup>31</sup>

1. Diabetes mellitus
2. HIV and other immunocompromised states (e.g. post-transplant, on immunosuppressive agents)
3. Chronic renal failure
4. Patients on immunomodulators (e.g. TNF – alpha inhibitors)
5. Gastrectomy, jejunioileostomy
6. Exposure to individuals with sputum smear positive pulmonary tuberculosis
7. Individuals in institutional settings (e.g. in-mates in drug rehabilitation facilities, prison in-mates, healthcare workers)

Pulmonary tuberculosis is the most common and infectious form of tuberculosis. Diagnosis of pulmonary tuberculosis is based on a combination of clinical symptoms and signs, radiological changes, characteristic histopathological changes, positive culture of *Mycobacterium tuberculosis* complex (MTC) in bodily tissues or fluid.

Several studies in which patients diagnosed with pulmonary tuberculosis based on positive sputum culture reveal that chronic cough and weight loss were the predominant symptoms.<sup>32-35</sup> Haemoptysis, though present in only 25% of patients with pulmonary tuberculosis, was associated with respiratory diseases other than pulmonary tuberculosis in the majority.<sup>36</sup> 5-14% of patients may remain asymptomatic at presentation. These are generally older patients (>50years).<sup>32, 33</sup>

## KEY RECOMMENDATION

**A** In patients presenting with unexplained cough of more than 3 weeks, pulmonary tuberculosis should be considered.

**Grade A, Level 1+**

Chest radiographic examination is a useful initial investigation for persons with prolonged cough of more than 3 weeks to identify those who will require further evaluation for causes of radiographic abnormalities including tuberculosis (refer to 5.1.1 Chest radiography in the clinical evaluation of symptomatic patients ).<sup>37</sup>

**D** Persons with prolonged cough of more than 3 weeks should undergo chest radiographic examination.

**Grade D, Level 4**

Fluoroquinolones should be avoided as empirical treatment for chest infection in persons with symptoms or radiological manifestations which may be compatible with pulmonary tuberculosis. This may mask or delay the diagnosis of pulmonary tuberculosis and generate organisms resistant to the fluoroquinolones which are a key second-line anti-tuberculosis drug.<sup>38</sup>

**B** Persons presenting with cough and abnormal chest radiograph are often prescribed an empirical course of antibiotics for chest infection. As fluoroquinolones may mask or delay the diagnosis of pulmonary tuberculosis, these drugs should be avoided as empirical treatment for chest infection.

**Grade B, Level 2++**

**GPP** Medical practitioners in primary care are urged to refer suspected tuberculosis cases to the Tuberculosis Control Unit or specialists with experience in tuberculosis management.

**GPP**



For patients with suspected pulmonary tuberculosis, two consecutive sputum specimens should be obtained, one being an early morning collection. A third specimen should be collected if acid-fast bacilli (AFB) smears are negative and the clinical suspicion of tuberculosis is high. The specimens can be collected on the same day and each should ideally contain at least 5 ml of well-expectorated sputa (refer to 6.3.1.1 Two versus three sputum samples and recommendations for sputum collections in Appendix 1<sup>39-42</sup>). In children, gastric lavage may be useful.<sup>39-44</sup>

It should be noted that sputum samples in pulmonary tuberculosis patients may not yield mycobacterial growth for reasons such as inadequate specimen sampling, intermittent bacterial excretion or low bacillary load. The diagnosis of culture-negative pulmonary tuberculosis may be based on characteristic radiological features in the appropriate clinical and epidemiological setting.

## KEY RECOMMENDATION

**D** Two sputum samples – including one early morning sample – should be obtained for both microscopy and mycobacterial cultures for patients with suspected pulmonary tuberculosis. Recommendations for sputum collection are in Appendix 1 (Page 91).

**Grade D, Level 4**

**D** In patients in whom it is difficult to obtain sputum specimens, e.g. children and stroke patients, other means of obtaining sputum should be utilised, including sputum induction and gastric lavage.

**Grade D, Level 3**

In immunocompromised hosts, especially in HIV-infected patients, extrapulmonary disease is a more common presentation than in immunocompetent individual. Nevertheless, pulmonary tuberculosis is still a common manifestation of tuberculosis in HIV patients. Cough and haemoptysis are less frequently reported in these patients. This is probably due to the reduction in inflammatory response as a result of the immunocompromised state.<sup>45</sup>

Clinical presentation of patients with extrapulmonary tuberculosis varies widely in both immunocompetent and immunocompromised hosts. In general, the presentation in HIV patients is similar to that seen in non-HIV patients, although the signs and symptoms (such as fevers, weight loss, and malaise) may be attributed to HIV itself and the possibility of tuberculosis overlooked. Pathogenesis is primarily lympho-haematogenous dissemination following primary tuberculosis infection. The incidence of extrapulmonary tuberculosis in advanced HIV disease is much higher than in non-HIV patients.<sup>35</sup> Patients with extrapulmonary tuberculosis may present with signs and symptoms specific to the involved site, such as lymphadenopathy, headache, meningismus, pyuria, abscess formation, back pain, and abdominal pain. These findings in HIV-infected patients can present a diagnostic challenge. In HIV patients, low CD4 cell counts are associated with an increased frequency of extrapulmonary tuberculosis, positive mycobacterial blood cultures, and atypical chest radiographic findings, reflecting an inability of the impaired immune response to contain infection.<sup>46</sup> The most common extrapulmonary site in HIV patients is the lymph node. Neurological, pleural, pericardial and abdominal involvement has also been seen commonly in HIV patients. Every attempt should be made to obtain diagnostic specimens for the presence of acid-fast bacilli (AFB) and cultured for mycobacteria.

**D** In patients presenting with extrapulmonary disease, a chest radiograph should also be done to determine if there is concomitant pulmonary tuberculosis and sputum samples obtained to determine if the case is infectious.

**Grade D, Level 3**

## **Tuberculous lymphadenitis**

Tuberculous lymphadenitis is the most common manifestation of extrapulmonary tuberculosis.<sup>47</sup> It usually presents as a painless swelling of one or more lymph nodes in the anterior or posterior cervical chain or those in the supraclavicular fossa. These lymph nodes can rupture leading to the formation of sinus tracts. This manifestation is particularly common in children. In HIV-infected patients, tuberculous lymphadenitis can be associated with disseminated disease.<sup>48</sup> Fine-needle aspirate or surgical biopsy of the enlarged node should be performed to obtain diagnostic material for histological and mycobacterial culture.

## **Pleural tuberculosis**

This is the second most common form of extrapulmonary tuberculosis. Patients may present with an acute febrile illness with pleuritic chest pain. If the effusion is large enough, dyspnea may occur, although the effusions generally are small. Tuberculous empyema is a much less common occurrence. Diagnosis of pleural tuberculosis would involve the analysis of pleural fluid and pleural biopsy specimens which should be sent for mycobacterial culture and drug susceptibility testing in addition to histopathological examination. It is usually a self-limiting disease with resolution of the effusion in 4-16 weeks. If left untreated, it progresses to overt pulmonary tuberculosis in the majority (43%-60%) of cases.<sup>49</sup>

## **Genitourinary tuberculosis**

Common symptoms of genitourinary tuberculosis include flank pain, haematuria, dysuria and frequency of micturition. There may be associated renal impairment at the time of diagnosis due to destruction of the renal parenchyma.<sup>50</sup> However, many patients with any form of genitourinary tuberculosis remain asymptomatic and are detected because of an evaluation for an abnormal routine urinalysis.<sup>51</sup> Majority of these patients do have abnormalities on the chest radiograph. Urine microscopic examination, mycobacterial culture and radiological imaging studies are needed for diagnostic confirmation.

## **Abdominal tuberculosis**

Tuberculosis involving the abdominal organs tends to present with non-specific symptoms and signs and can be difficult to diagnose. Symptoms at presentation include abdominal pain, pronounced weight loss followed by loss of appetite, nausea, vomiting or diarrhea.<sup>52</sup> Most common sites of involvement are the terminal ileum, caecum and less commonly the peritoneum. Appropriate tissue specimens, e.g. ascitic fluid and surgical biopsy specimens taken from the affected organ, should be sent for histological evaluation, microscopic examination and mycobacterial culture, for confirmation of the disease.

## **Skeletal tuberculosis**

Pain and swelling of the affected joint are the common symptoms at presentation.<sup>53</sup> There may be associated limitation of joint mobility with sinus tract formation in the advanced stage of the disease. Approximately 1% of young children with tuberculosis disease will develop a bony focus.<sup>10</sup> The most common site of bony tuberculosis is the spine, followed by weight-bearing joints (hip and knee) and, lastly, the other skeletal sites.<sup>54</sup> The predilection for spinal disease may be explained by the fact that the vertebrae are extremely well vascularised, even in adulthood. Spinal disease is most frequently located in the lower thoracic and lumbar spine, with thoracic disease being more common in children and adolescents, whereas lumbar disease is found more commonly in adults. Most cases of tuberculous bone and joint disease are isolated to one area, but multifocal disease has also been described.<sup>54</sup> Computed tomographic scans and magnetic resonance imaging of the affected joint or skeletal region should be obtained if there is a high index of suspicion of tuberculosis. Bone biopsy should be performed for histological and mycobacterial culture to if the chest radiograph is normal and the sputum smear and culture are negative.<sup>48</sup>

## **Tuberculous meningitis**

Tuberculous meningitis is the most common manifestation of tuberculosis affecting the central nervous system.<sup>10</sup> If not treated promptly, it is associated with high mortality and in those who survive, a high frequency of neurologic sequelae is seen.<sup>55</sup> It usually presents as a sub-acute illness in adults with symptoms of low-grade fever, malaise, headaches, dizziness, vomiting, cranial neuropathies and / or personality change. These are the result of meningeal fibrosis and vascular inflammation.<sup>55</sup> Classic features of photophobia, neck stiffness and high fever may be absent.<sup>10</sup> In immunocompromised hosts and in children tuberculous meningitis can present as acute meningitis. In the case of suspected tuberculous meningitis, cerebrospinal fluid is sent for FEME

(Full and microscopic examination), AFB smear, TB PCR and AFB culture. In persons from high MDR-TB prevalence countries, the Xpert® MTB/RIF is the preferred molecular test.

### **Miliary tuberculosis**

Miliary tuberculosis is the pathological name describing the millet seed-sized (1-2 mm) granulomas in various organs by tubercle bacilli.<sup>56</sup> It results from massive lympho-haematogenous dissemination of a *Mycobacterium tuberculosis* laden focus. Clinical presentation is variable but broadly classified as either acute or sub-acute forms.<sup>57</sup> However, symptoms are non-specific which often leads to delay in diagnosis.<sup>58</sup> In the more common sub-acute form, patients usually complain of weight loss, loss of appetite, fever, night sweats lasting several months.<sup>57</sup> The acute form is fulminant with multi-organ failure, septic shock and acute respiratory distress syndrome.<sup>59</sup>

### **MDR-TB (Multidrug-resistant tuberculosis)**

This is defined by the presence of *Mycobacterium tuberculosis* isolate demonstrating resistance to at least isoniazid and rifampicin. Managing patients with MDR-TB is challenging and should be undertaken by individuals with expertise in this field.

#### **Risk factors for MDR-TB<sup>60</sup>**

1. Previous self-administered therapy for active tuberculosis
2. Contact with individuals known to have MDR-TB
3. Non-compliance with previous anti-tuberculosis treatment
4. Individuals originating from areas where MDR-TB is common

Managing patients suspected of MDR-TB will involve good infection control measures, rapid and accurate diagnosis, appropriate drug treatment associated with close monitoring of patients.

The diagnosis of MDR-TB is dependent on culture and sensitivity profile of the *Mycobacterium tuberculosis* isolates from the sputum, bodily fluids or tissue specimens.<sup>16</sup> However drug susceptibility testing results for MDR-TB may take several weeks to months to be available.

The Xpert MTB/RIF and GenoType® MTBDR*plus* are two available nucleic acid amplification tests (NAAT; refer to 6.3.3) which can speed up the diagnosis of drug resistant tuberculosis. These tests should be used on respiratory samples obtained from persons who are failing or have failed anti-tuberculosis therapy with first line agents, patients who come from countries with high prevalence of MDR-TB, individuals who have been non-adherent to treatment and those who are exposed to a known MDR-TB case.<sup>61</sup>

### **Screening for HIV and diabetes mellitus in tuberculosis patients**

Human immunodeficiency virus (HIV) infection is the strongest predisposing risk factor for tuberculosis HIV infection influences the clinical manifestation, course and outcome of tuberculosis. It is vital to ascertain the HIV status of all tuberculosis patients as the early institution of anti-retroviral treatment (ART) in those with HIV co-infection has been shown to decrease mortality and improve tuberculosis treatment outcome.<sup>62</sup>

Persons with diabetes mellitus have a two to three times higher risk of developing tuberculosis than non-diabetics, a four times higher risk of death during tuberculosis treatment, and a higher risk of tuberculosis relapse.<sup>63, 64</sup> International health authorities recommend that all persons diagnosed with tuberculosis be screened for diabetes mellitus.<sup>65</sup>

**D** Patients with newly diagnosed tuberculosis should be screened for human immunodeficiency virus (HIV) and diabetes mellitus.

**Grade D, Level 3**

## 5 Imaging in tuberculosis

### 5.1 The utility of chest radiography in the diagnosis of tuberculosis

#### 5.1.1 Chest radiography in the clinical evaluation of symptomatic patients

Chest radiography has long been used as a tool in the diagnosis of pulmonary tuberculosis. A posterior-anterior radiograph of the chest is the standard view used for the detection of chest abnormalities. A lateral view may be helpful in some cases.

Tuberculosis affects the lungs in disease patterns that are a reflection of a combination of factors ranging from the host's immune status, the existence of hypersensitivity from previous infection, the method of spread of the disease and the predilection of tuberculosis to affect certain regions of the lungs.

The radiographic appearance may be divided into two broad categories:

- **Primary tuberculosis**  
In primary tuberculosis, the predominant radiographic feature is the presence of hilar and/or mediastinal adenopathy in the appropriate lymph drainage pathways. The primary focus of tuberculous pneumonia may or may not be visible.
- **Reactivation (postprimary) tuberculosis**  
The apical/posterior segments of the upper lobes and the superior segments of the lower lobes are most often involved. The possible radiographic findings are elaborated in the following section.

## **The chest radiographic findings in the evaluation of clinical disease**

### **Chest radiographic findings that can suggest ACTIVE tuberculosis disease<sup>66</sup>**

This category comprises all findings typically associated with active pulmonary tuberculosis. A person with any of the following findings must be further evaluated and submit sputum specimens for acid-fast bacilli (AFB) smears and cultures.

- **Consolidation**  
Opacification of airspaces within the lung parenchyma. Consolidation can be dense or patchy and may have irregular, ill-defined, or hazy borders.
- **Any cavitary lesion**  
Lucency (darkened area) within the lung parenchyma, with or without irregular margins that may be surrounded by air-space consolidation, or by nodular or reticular opacities, or both. The walls surrounding the lucent area can be thick or thin. Calcification can exist around a cavity.
- **Nodule with poorly defined margins**  
Round opacity within the lung parenchyma, consistent with a tuberculoma. Nodules included in this category are those with margins that are indistinct or poorly defined. The surrounding haziness can be either subtle or readily apparent, suggesting coexisting air-space consolidation.
- **Pleural effusion**  
Presence of a significant amount of fluid within the pleural space. This finding must be distinguished from blunting of the costophrenic angle, which may or may not represent a small amount of fluid within the pleural space (except in children, for whom even minor blunting must be considered a finding that can suggest active tuberculosis).



- **Hilar or mediastinal lymphadenopathy**  
Enlargement of lymph nodes in one or both hila and/or within the mediastinum, with or without associated atelectasis (volume loss) or consolidation.
- **Other**  
Any other finding suggestive of active tuberculosis, such as miliary tuberculosis.  
Miliary tuberculosis demonstrates nodules that are uniform in size, measuring 1 to 2 mm (millet size), distributed throughout the parenchyma.

### **Chest radiographic findings that can suggest INACTIVE tuberculosis disease<sup>66</sup>**

This category includes findings that are suggestive of prior tuberculosis disease that is inactive. Assessments of the activity of tuberculosis disease cannot be made accurately on the basis of a single radiograph. A person with any of the following findings must be further evaluated and submit sputum specimens for AFB smears and cultures.

- **Discrete fibrotic scar or linear opacity**  
Discrete linear or reticular opacity within the lung. The edges of the opacity should be distinct, and there should be no suggestion of airspace opacification or haziness between or surrounding the linear or reticular lesion. Calcification can be present within the lesion.
- **Discrete nodule(s) without calcification**  
One or more nodular opacities with distinct borders and no surrounding airspace consolidation. Nodules are generally round or have rounded edges, features that distinguish them from airspace consolidation. To be included here, these nodules must be non-calcified. A solitary calcified nodule is included in the section 5.1.3 ‘Chest radiographic findings which do not require further evaluation for pulmonary tuberculosis’.

- **Discrete fibrotic scar with volume loss or retraction**  
Discrete linear opacities with reduction in the space occupied by the upper lobe. Associated signs include upward deviation of the fissure or hilum on the corresponding side, plus/minus asymmetry of the volumes of the two thoracic cavities.
- **Other**  
Any other finding suggestive of prior tuberculosis, such as upper lobe bronchiectasis. Bronchiectasis is bronchial dilation with bronchial wall thickening.

### **Stable chest radiographic findings<sup>67</sup>**

The lack of radiographic change on a chest radiograph, especially over a period of years, generally indicates inactive disease. However, as culture positive disease may still be found in patients with stable radiographic findings, further evaluation should still have to be carried out in such patients particularly those with no prior history of adequate tuberculosis treatment.

**D&GPP** Patients with chest radiographic findings that suggest active\* or inactive† disease should be referred without delay for further evaluation including two sputum samples for acid-fast bacilli (AFB) smear and culture.

\*Grade D, Level 4

†GPP

## **5.1.2 The public health role of chest radiographic screening in an asymptomatic person**

The aim of screening of persons from countries with a high prevalence of tuberculosis is to prevent the importation of the disease into Singapore. Thus the screening chest radiograph should be read with a high index of suspicion for pulmonary tuberculosis. This is opposed to the more specific approach for the clinical diagnosis of tuberculosis in a symptomatic patient.

The purpose of the screening chest radiograph is to determine if there are findings suggestive of active or prior pulmonary tuberculosis disease (e.g., cavities, consolidation, effusions, nodules, or linear opacities).<sup>66</sup>

It has been recognised that no particular radiographic pattern is specific for tuberculosis. Other pulmonary diseases may mimic the appearance of pulmonary tuberculosis. Screening chest radiography is therefore, to detect ‘any abnormality’ suggesting active or prior tuberculosis.<sup>35, 68</sup>

### 5.1.3 Chest radiographic findings which do not require further evaluation for pulmonary tuberculosis<sup>66</sup>

The following findings do not suggest active pulmonary tuberculosis and will not need further evaluation.

- **Pleural thickening**  
Irregularity or abnormal prominence of the pleural margin, including apical capping (thickening of the pleura in the apical region). Pleural thickening can be calcified.
- **Diaphragmatic tenting**  
A localised accentuation of the normal convexity of the hemidiaphragm as if “pulled upwards by a string.”
- **Blunting of costophrenic angle (in adults)**  
Loss of sharpness of one or both costophrenic angles. Blunting can be related to a small amount of fluid in the pleural space or to pleural thickening and, by itself, is a nonspecific finding. In contrast, a larger pleural effusion suggests active tuberculosis disease. Note: In children, minor blunting of the costophrenic angle may suggest active tuberculosis disease.
- **Solitary calcified nodule or lymph node**  
Discrete calcified nodule (granuloma) within the lung, or calcified lymph node. The calcified lymph node can be within the hilum or mediastinum. The borders must be sharp, distinct, and well defined.

## 5.1.4 Chest radiographic screening in children

Refer to 10.2 Chest radiographic screening in children<sup>69-74</sup>

## 5.1.5 Chest radiographic screening in pregnancy<sup>75</sup>

With the very low foetal dose of radiation associated with a chest radiograph, the associated risks of childhood cancer is very low (< 1 in 1,000,000) and judged to be acceptable when compared to the natural risk (of around 1 in 500). Consequently a chest radiograph can be carried out on pregnant women, as long as it is clinically justified and the dose is kept to a minimum consistent with the diagnostic requirements. A lead shield placed over the abdomen and pelvis should be used if a chest radiograph is performed. Thus pregnancy is not a contraindication to a chest radiograph particularly when it is required for tuberculosis contact investigations.

The chest radiograph may be deferred if the purpose is for non-urgent screening.

**D** A chest radiograph may be performed on pregnant patients (with lead shield protection) when it is required for tuberculosis contact investigations and for evaluation of active disease.

**\*Grade D, Level 4**

## 5.2 Utility of other imaging modalities and image guided interventional procedures in the diagnosis of tuberculosis

### 5.2.1 Computed tomography (CT)

Computed tomography (CT) is more sensitive than chest radiography in the detection and characterisation of subtle parenchymal disease, mediastinal lymphadenopathy and pleural disease.

CT thorax is not utilised as a first line imaging test for screening of pulmonary tuberculosis due to availability and cost considerations.

A CT thorax may be performed if the chest radiograph is normal or shows nonspecific findings in a patient suspected to have active or latent tuberculosis on screening. Subtle disease not seen on the chest radiograph may be detected on CT.

A CT thorax can be useful in determining disease activity. A presumptive radiological diagnosis of active tuberculosis may be made on the CT finding of consolidation, presence of cavitations or evidence of endobronchial spread such as tree-in-bud opacities or centrilobular nodules. Definitive diagnosis still requires isolation and identification of *Mycobacterium tuberculosis* in clinical specimens.

CT is also useful for evaluation of thoracic complications including tuberculous effusion, empyema, bronchopleural fistula and chest wall extension as well as for imaging of extrapulmonary tuberculosis.

## 5.2.2 Ultrasound

Ultrasound is not useful in the screening of pulmonary tuberculosis or in the imaging of pulmonary disease. This modality is useful for the characterisation of a pleural effusion, guidance in thoracentesis and for the evaluation of the pericardium in secondary tuberculous involvement.

Ultrasound is also useful in the imaging of extrapulmonary tuberculosis and in image guided tissue sampling.

## 5.2.3 Imaging of extrapulmonary tuberculosis<sup>76, 77</sup>

Tuberculosis can affect any organ system in the body.

Ultrasound, CT, MRI and nuclear imaging are useful in the evaluation extrapulmonary tuberculous involvement. However, tuberculosis has a variety of radiologic appearances and may mimic numerous other disease entities. A familiarity with the varied radiologic features of tuberculosis coupled with a high degree of clinical suspicion aids in the early diagnosis and initiation of treatment in these patients.

## 5.2.4 Image guided procedures

Image guided tissue sampling is commonly performed with ultrasound or CT imaging guidance. Occasionally tissue sampling is performed using MRI guidance if the lesion is only visualised on MRI.

Often, the clinical indication for a biopsy would be for the confirmation of a neoplasm. However, if tuberculosis is a potential differential diagnosis in the clinical scenario, a sample should be obtained for AFB smears and mycobacterial cultures.

## 6 Tuberculosis laboratory diagnosis

### 6.1 Tuberculosis: laboratory aspects

Various laboratory tests are being used for the diagnosis, management and control of latent and active tuberculosis and are discussed below, and classified according to the use for each test.

### 6.2 Laboratory testing for latent tuberculosis

Refer to 9.2 Testing for Latent Tuberculosis Infection.

### 6.3 Laboratory testing for active tuberculosis

The culture of *Mycobacterium tuberculosis complex* (MTC) from a clinical specimen remains the gold standard test for both the diagnosis and antimicrobial susceptibility testing for active tuberculosis. All clinical specimens, except blood for which special transport / culture bottles should be used, must be collected in sterile, rigid, leak-proof, screw-capped containers that are promptly delivered to the laboratory, ideally within one working day. Prolonged delivery may lead to overgrowth of the sample with commensal bacteria or deterioration of the mycobacteria, thus compromising the sample quality.

Refer to Chapter 4 Clinical diagnosis of tuberculosis for further details on specimen collection.

#### 6.3.1 Acid-fast bacillus (AFB) smears

Direct microscopy is a relatively inexpensive and rapid test for active tuberculosis. However, smears only provide a preliminary diagnosis as sensitivity is low and false positives may occur with the presence of environmental or commensal nontuberculous mycobacteria.

##### 6.3.1.1 Two versus three sputum samples

Studies have shown that an average of 85.8% of all smear-positive cases is detected with the first sputum specimen. With a second

specimen, the average incremental yield was 11.9%.<sup>42, 78</sup> Consistent with this review, other groups have shown that the benefit of a third sputum sample is minimal, increasing the sensitivity by 2 to 5%.<sup>79</sup> These findings have resulted in the World Health Organization (WHO) recommending two, rather than three, specimens be used for screening tuberculosis patients, but only for settings with a well-established laboratory network, a fully functional External Quality Assurance programme for smear microscopy including on-site evaluation with the feedback mechanism and where the workload is very high and human resources are limited.<sup>42</sup> Since less than 50% of cases will have positive smear results,<sup>80</sup> this recommendation is not applicable if the patient's smears are negative and if there is a strong likelihood of active tuberculosis.

### **6.3.1.2 Same day microscopy**

The sensitivity and specificity of same-day microscopy for pulmonary tuberculosis (64 and 98% respectively) has been shown to be similar to that for standard microscopy i.e. obtaining sputum samples over 2 or more days.<sup>43</sup>

Fluorescent staining is the preferred method as it is faster and more sensitive compared to traditional Ziehl-Neelson or Kinyoun staining methods.

## **6.3.2 AFB cultures**

Culture examination should be performed on all patients with suspected active tuberculosis, regardless of the AFB smear results. The sensitivity is greater than that of smears. In Singapore, drug susceptibility testing is performed against to first-line tuberculosis drugs, should the culture be positive. If the drug-susceptibility testing shows resistance to the first-line drugs, further drug-susceptibility testing is performed against the second-line drugs. Cultures are inoculated into a liquid broth and solid medium, and monitored for growth for 6-8 weeks.<sup>81</sup> Once the mycobacteria have been isolated in culture, MTC can be identified using nucleic acid probes, antigen-detection, high performance liquid chromatography (HPLC) or nucleic acid amplification test for NAAT-based line probe assays. Except for HPLC and some of the NAAT-based assays, these methods do not differentiate BCG from the rest of the MTB complex.



- It is imperative to collect clinical samples for AFB cultures as a positive culture for *Mycobacterium tuberculosis* complex confirms the diagnosis of tuberculosis, and susceptibility testing of the isolate is important for appropriate treatment. Of note, tuberculosis may also be diagnosed on the basis of clinical signs, symptoms or other radiological and laboratory findings, even in the absence of a positive culture.

## KEY RECOMMENDATION

**B** All tuberculosis suspects should have relevant clinical specimen(s) obtained and sent for mycobacterial cultures, regardless of the AFB smear results.

**Grade B, Level 1++**

### 6.3.3 Nucleic acid amplification tests (NAAT)

These tests detect nucleic acids and do not determine if the organism is viable unless ribonucleic acid (RNA) is detected. There are several tests available including BD ProbeTec Strand Displacement Amplification DTB, HAIN GenoType MTBDR*plus*, GeneXpert and in-house polymerase chain reaction (PCR). The pooled sensitivities and specificities, compared to that of cultures, may range between 48.4 to 98% and 84.7 to 100% respectively;<sup>82-88</sup> the performance being better for smear-positive and sputum specimens.<sup>83-86, 89, 90</sup> As the test can be rapidly performed, the detection of MTC DNA can provide the empiric basis for initiation of treatment. However, nucleic acids may still be detected up to several years following treatment. The result may be falsely negative when there is a mixed culture, inhibitors in the sample or genetic mutation in the gene target of the isolate. Conversely, cross-contamination from the environment and inanimate objects may lead to a false positive result. Therefore, these molecular tests should be used as an adjunct to other investigations such as culture or histology.

## Pulmonary tuberculosis

**GPP** In pulmonary tuberculosis, nucleic acid amplification tests (NAATs) need not be routinely performed on sputum in the Singapore context, when the clinical, radiological and epidemiological features are consistent with pulmonary tuberculosis.

**GPP**

### 6.3.3.1 Genotypic detection of drug-resistant tuberculosis in sputum

Some of these tests provide the additional advantage of detecting resistance to isoniazid and rifampicin (Genotype MTBDR*plus*, Hain Lifescience GmbH) or to rifampicin alone (Xpert MTB/RIF, GeneXpert; INNO-LiPA Rif.TB, Innogenetics).

Mono-resistance to rifampicin is rare and resistance to rifampicin is an indicator that a MTC isolate is multidrug resistant (resistant to both isoniazid and rifampicin). The sensitivity and specificity of these tests range between 85.7 to 100%, and 96.6 to 100% respectively.<sup>82, 83, 85, 86, 91</sup> Both tests are sensitive and specific for the detection of MTC and rifampin resistance in smear-positive respiratory samples; however, the sensitivity and specificity of the Genotype MTBDR*plus* is lower for smear-negative samples and for the detection of isoniazid resistance.<sup>82, 83, 85, 91, 92</sup> Therefore, the Genotype MTBDR*plus* should not be used on smear-negative specimens.<sup>82, 90</sup>

WHO has recommended that these tests be used to screen patients suspected of having multidrug-resistant tuberculosis. These would include treatment failure cases, previously treated cases, patients who come from countries with high prevalence of MDR-TB and patients who have been non-adherent to treatment. These tests cannot determine the infectivity of the individual, the susceptibility to other drugs and cannot be used to replace smears and cultures. They should not be used for monitoring treatment response.<sup>82, 83</sup>

For the Xpert MTB/RIF, controlled clinical validation trials involving individuals suspected of tuberculosis or MDR-TB have shown a pooled sensitivity and specificity of 92.2% and 99% respectively, when compared to culture results.<sup>83</sup> The sensitivity of a single Xpert MTB/RIF test in smear-negative/culture-positive patients was 72.5% and increased to 90.2% when three samples were tested. Xpert MTB/RIF detected rifampicin resistance with 99.1% sensitivity and excluded resistance with 100% specificity. The GeneXpert system provides rapid results within 2 hours of specimen reception in the laboratory and WHO has advocated it as an initial diagnostic tool test in individuals suspected of MDR-TB or HIV-associated tuberculosis.<sup>83</sup>

**A** Rapid molecular tests like the Genotype MTBDR*plus* and Xpert MTB/RIF should be used as the initial test on respiratory samples from individuals suspected of multidrug-resistant tuberculosis. Specimens should still be sent for mycobacterial culture and phenotypic drug susceptibility testing to first and second-line anti-TB drugs.

**Grade A, Level 1++**

**D** The presence of *rpoB* gene mutation as detected by the Xpert MTB/RIF assay should be taken as a surrogate for the presence of multidrug-resistant tuberculosis (MDR-TB) until proven otherwise by phenotypic drug-susceptibility testing.

**Grade D, Level 4**

### **6.3.3.2 Detection of tuberculosis DNA in extrapulmonary tuberculosis**

Although the data for the use of these tests in extrapulmonary tuberculosis are limited, WHO has recently recommended the use of Xpert MTB/RIF as the initial diagnostic test for testing cerebrospinal fluid specimens from patients presumed to have tuberculous meningitis. The Xpert MTB/RIF may also be used for testing

specific nonrespiratory specimens (lymph nodes and other tissues) from patients presumed to have extrapulmonary tuberculosis.<sup>93, 94</sup>

Notwithstanding, it must be emphasised that specimens must also be sent for culture and full drug sensitivity testing.

### Extrapulmonary tuberculosis

**B** For extrapulmonary tuberculosis, nucleic acid amplification tests performed on the appropriate fluid and/or tissue samples are useful adjunctive tests for cases where the clinical suspicion of active tuberculosis is high.

**Grade B, Level 1+**

### 6.3.4 Interferon- $\gamma$ release assays (IGRAs)

Refer to 9.2 Testing for Latent Tuberculosis Infection

### 6.3.5 Adenosine deaminase (ADA)

Adenosine deaminase (ADA) is an enzyme involved in purine metabolism, and is present in most cells. An increase in ADA concentrations in various tissue fluids, especially pleural fluid, represents the presence of activated lymphocytes and monocytes, and is particularly pronounced in active tuberculosis.<sup>95</sup> Other conditions can also affect ADA levels, such as advanced HIV infection and other immuno-compromised states may lower ADA levels.<sup>96, 97</sup> Whereas cancer, other infection and lymphoma may raise ADA levels giving rise to false-positive results.<sup>96-98</sup> The sensitivity of ADA in sputum is poor and the test is not recommended for routine use in pulmonary tuberculosis.<sup>99, 100</sup> For tuberculous pericarditis and meningitis, the supporting evidence is more variable, depending on the testing method and disease prevalence in the population.<sup>101-103</sup> It may be useful for tuberculous pleurisy and peritonitis.<sup>104, 105</sup>

**A&D** Testing for adenosine deaminase (ADA) in pleural and ascitic fluids may be useful in tuberculous pleurisy and peritonitis\*. ADA testing in sputum samples is not recommended for pulmonary tuberculosis†.

**\*Grade A, Level 1++**

**†Grade D, Level 3**

### 6.3.6 Lipoarabinomannan (LAM)

Lipoarabinomannan (LAM) is a MTC cell wall glycolipid that is also a virulence factor for the organism.<sup>106, 107</sup> It is shed by metabolically active MTC cells and can be detected in the urine. A commercial ELISA assay for detecting urinary LAM – Clearview™ tuberculosis ELISA (Alere Inc, USA) – is in existence but is not currently available in Singapore. LAM urinary assays have not been clinically proven to be very useful in diagnosing active tuberculosis, though there appears to be potential for its use in HIV patients<sup>108, 109</sup> with advanced immunosuppression.

## 7.1 Principles of tuberculosis treatment

In an active tuberculosis patient, there are several subpopulations of *Mycobacterium tuberculosis* with different rates of metabolic activity. Although the majority of organisms are rapidly reproducing (and thus rapidly killed by appropriate chemotherapy), some reproduce slowly or are semi-dormant with occasional spurts of metabolism. Because of this, treatment of tuberculosis needs to be prolonged to ensure the killing of these slowly growing / semi-dormant organisms which, if not fully eradicated, may cause relapse.

Within each population of *Mycobacterium tuberculosis* complex are spontaneously occurring mutants resistant to the first-line anti-tuberculosis drugs. Giving a single drug will select for a population that is resistant to this drug after a period. Hence, a combination of multiple effective drugs must be given. Monotherapy i.e. treatment with only one effective drug, must be avoided at all cost. In the presence of drug resistance, unintentional monotherapy may occur even if multiple drugs are prescribed. Therefore, in situations where drug resistance is suspected, all measures must be taken to give an adequate number of drugs pending the full drug susceptibility test results.

Drugs have to be taken regularly and in the correct dosages according to the given regimen. Failure to do so may cause resistance.

The first-line antimycobacterial agents are isoniazid, rifampicin, ethambutol, pyrazinamide and streptomycin.

**Table 2 Dosages of first-line anti-tuberculosis drugs<sup>110, 111</sup>**

Drug	Available preparations	Dosing for adults (i.e. persons age ≥15 years)	Dosing for children (i.e. persons age <15 years)
Isoniazid	100 mg, 300 mg	5 mg/kg daily, maximum 300 mg/day  15 mg/kg, max 900 mg 3x/wk	10-15 mg/kg daily max 300 mg/day  20 mg/kg max 900 mg 3x/ week
Rifampicin	150 mg, 300 mg	10 mg/kg, max 600 mg daily or 3x/week	10-20 mg/kg daily max 600 mg daily  20 mg/kg max 600 mg 3x/ week
Ethambutol	100 mg, 400 mg	15-20mg /kg daily for 1 <sup>st</sup> 2 months then 15 mg/kg daily. Maximum 1600 mg/day	15-25 mg/kg max 1600 mg daily
Pyrazinamide	500 mg	25 mg/kg daily, maximum 2g/day	25-35 mg/kg max 2g daily
Streptomycin i/m	1 g vial	15mg/kg daily, maximum 1g/d in persons ≤ 59 years of age  10 mg/kg daily, maximum 0.75 g/day in persons > 59 years of age	15-20 mg/kg max 1g daily

Adapted from American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America. *Am J Respir Crit Care Med.* 2003 Feb 15;167(4):603-62 & Centers for Disease Control and Prevention. *MMWR recommendations and reports:* 52(RR11);1-77.

The standard six-month tuberculosis treatment regimen comprises a 2-month intensive phase of daily ethambutol, isoniazid, rifampicin and pyrazinamide followed by a 4-month continuation phase of daily rifampicin (R) and isoniazid.<sup>110, 112</sup> Rifampicin and isoniazid may be dosed thrice weekly in the continuation phase to facilitate the supervision of treatment (i.e. under directly observed therapy (DOT)). The majority of the organisms are eliminated in the intensive phase. However to achieve cure, it is important that the entire course, including the continuation phase, is completed.

In summary, tuberculosis treatment requires a combination of effective drugs given at the correct dosages and for an adequate duration.

## 7.2

### Initiation of treatment

**GPP** Patients with chest radiographic findings that suggest active disease may be commenced on tuberculosis treatment even before bacteriological results are available.

**GPP**

**GPP** Tuberculosis treatment should be seriously considered in symptomatic patients despite the X-ray appearances of inactivity.

**GPP**

**GPP** Before starting tuberculosis treatment, baseline liver enzymes should be performed in those over 15 years old. Adult patients to be commenced on ethambutol must have their visual acuity and colour vision checked at baseline.

**GPP**

#### Treatment regimens for pulmonary tuberculosis

##### 6-month standard regimen

Once the clinical diagnosis of pulmonary tuberculosis has been made, treatment must be started while awaiting the sputum mycobacterial culture and drug susceptibility results.

Patients should be started on the standard 6-month treatment regimen. Streptomycin may be used as the fourth drug in place of ethambutol. While it had previously been acceptable to start treatment with three drugs, i.e. rifampicin, isoniazid and pyrazinamide in areas where primary isoniazid resistance is below 4%<sup>112</sup>, WHO recommends 4 drugs in the intensive phase as, worldwide, isoniazid resistance is 7.8%.<sup>113</sup> The intensive phase is given for two months after which treatment is continued with



rifampicin and isoniazid for 4 months if there is no drug resistance detected. Before reducing to rifampicin and isoniazid in the continuation phase, it is essential to ascertain that the patient's MTC isolate is susceptible to both these drugs. In patients diagnosed with culture negative pulmonary tuberculosis, the standard 6 month treatment should be given. To facilitate DOT, the medications may be given thrice weekly in the continuation phase. The dose of isoniazid must be adjusted to 15 mg /kg for thrice weekly dosing.

## KEY RECOMMENDATION

**A** The 6-month standard treatment regimen comprising a 2-month intensive phase of ethambutol, isoniazid, rifampicin and pyrazinamide followed by a 4-month continuation phase of rifampicin and isoniazid is the regimen of choice for pulmonary tuberculosis.<sup>112</sup>

**Grade A, Level 1++**

## 9-month regimen

**A** For patients who are unlikely to tolerate pyrazinamide (e.g. the elderly, those with liver disease), a 9-month regimen comprising ethambutol, rifampicin and isoniazid for 2 months followed by rifampicin and isoniazid for 7 months may be used.<sup>114</sup>

**Grade A, Level 1+**

## Other regimens

In the event of isoniazid intolerance or mono-resistance, rifampicin, ethambutol and pyrazinamide given daily for 6 months is an alternative regimen although this regimen should be used only by experienced tuberculosis clinicians.<sup>115</sup>

## 7.3 Treatment of extrapulmonary tuberculosis

Extrapulmonary tuberculosis is generally treated with the same regimen as pulmonary tuberculosis. However, in tuberculous meningitis and musculoskeletal tuberculosis, a longer duration is needed and in tuberculous meningitis and pericarditis, evidence suggests that steroid use may be a beneficial adjunct.

### 1) Tuberculous meningitis

Tuberculous meningitis is treated with an initial regimen of 4 drugs. Isoniazid, rifampicin, ethambutol and pyrazinamide are the recommended agents for initiation of treatment. After 2 months and adequate clinical response, ethambutol and pyrazinamide may be stopped, and isoniazid and rifampicin continued for 10 months.<sup>116-119</sup>

A Cochrane systematic review showed that adjunctive corticosteroids reduced death and disability from tuberculous meningitis in HIV-negative persons.<sup>120</sup>

**B** Tuberculous meningitis should be treated with the standard tuberculosis regimen but extended to 12 months. Steroids should be used as an adjunct.

**Grade B, Level 2+**

### 2) Musculoskeletal tuberculosis

Musculoskeletal tuberculosis includes conditions such as osteomyelitis, arthritis as well as involvement of joint tissues alone. It can occur in any part of the skeletal system but the spine is the most frequent site.

A rifampicin-containing regimen of 9 months duration is favored by some authorities<sup>121-123</sup> as there is evidence that the standard 6 month treatment may be inadequate.<sup>124</sup> In most cases, medical treatment was shown to be as effective as surgery, even with myelopathy.<sup>121, 125</sup> Hence, surgery should only be reserved for exceptional cases.

**A** The preferred treatment duration for musculoskeletal tuberculosis is 9 months with a rifampicin-containing regimen.

**Grade A, Level 1+**

### 3) Miliary tuberculosis

Miliary or disseminated tuberculosis is treated with the standard 6 month regimen. Its course can be acute and treatment must be started as soon as possible. Steroids may be beneficial but there are no controlled trials to support this practice in the absence of CNS or pericardial involvement.

It is important to exclude CNS involvement in persons with miliary tuberculosis. In the presence of CNS tuberculosis, the treatment should be extended to 12 months, and adjunctive steroids prescribed [refer to the section on 7.3 1) Tuberculous meningitis for the recommendation].<sup>126</sup>

**D** Miliary tuberculosis (in the absence of central nervous system (CNS) or musculoskeletal involvement) may be treated with the standard 6-month treatment regimen.

**Grade D, Level 4**

### 4) Pleural tuberculosis

The standard 6 month treatment regimen is recommended for pleural tuberculosis.<sup>112</sup>

Tuberculous empyema is a persistent active purulent infection of the pleural space with high bacterial load. Surgery may be needed and should only be performed by experienced surgeons.

**B** Pleural tuberculosis may be treated with the standard treatment regimen.<sup>112</sup>

**Grade B, Level 1+**

#### 5) Pericardial tuberculosis

Tuberculosis of the pericardium is treated with the standard 6-month regimen. Steroids are recommended in the earlier part of treatment. There is evidence that steroids may reduce morbidity and mortality.<sup>127, 128</sup> On 10 year follow up, the group receiving prednisolone appeared to have had a less adverse outcome.<sup>129</sup>

**C** Tuberculosis pericardial effusion can be treated with the standard tuberculosis regimen. Adjunctive steroids should be prescribed.

**Grade C, Level 2+**

#### 6) Lymph node tuberculosis

Tuberculosis adenitis is treated with the standard 6-month regimen.<sup>130-132</sup> It is to be noted that the nodes can enlarge during treatment. Drainage of peripheral lymph nodes that are about to rupture may be needed but surgical excision is rarely needed unless the nodes are very bulky.

**C** The standard tuberculosis regimen can be used in tuberculous lymphadenitis.

**Grade C, Level 2+**

## 7.4 Treatment under special circumstances

### Pregnancy and breastfeeding

Rifampicin, isoniazid and ethambutol have not been shown to be teratogenic.<sup>133</sup> Although there is less data regarding the use of pyrazinamide in pregnancy, it is generally deemed safe. Therefore the standard 6-month regimen is recommended by the World Health organization (WHO)<sup>134</sup> and International Union Against Tuberculosis and Lung Disease (IUATLD)<sup>135</sup> for routine use in pregnant women. Streptomycin may cause foetal ototoxicity and should be avoided in pregnancy.

Breastfeeding should not be discouraged as the small drug concentrations in breast milk are not toxic to the infant.<sup>136</sup>

**D** Standard tuberculosis treatment may be used during pregnancy and breastfeeding. Due to the small risk of relative pyridoxine deficiency, pyridoxine should be given to the breast-fed infant of a mother who is receiving standard anti-tuberculosis treatment.

**Grade D, Level 4**

## Renal insufficiency and end stage renal failure

Rifampicin and isoniazid, the two main tuberculosis drugs, are not cleared by the kidneys or by haemodialysis. Hence no dose adjustment is needed in patients with renal impairment.<sup>137, 138</sup>

Pyrazinamide is metabolised by the liver but its metabolites are cleared by the kidney. As such, for patients on haemodialysis or with creatinine clearance of less than 30 ml/min, the recommended dose is 25 mg/kg three times a week. The dose should be given post-dialysis.<sup>137, 139</sup>

**D** For tuberculosis patients on haemodialysis or with creatinine clearance of less than 30 ml/min, the recommended dose of pyrazinamide is 25 mg/kg three times a week. The dose should be given post-dialysis.

**Grade D, Level 3**

Ethambutol is cleared mainly by the kidneys and not very much by haemodialysis. The recommended dose is 15 to 25 mg/kg three times a week in patients with end-stage renal disease or with creatinine clearance of  $\leq 30$  ml/min.<sup>140</sup>

**D** The recommended dose of ethambutol is 15 to 25 mg/kg three times a week in tuberculosis patients with end-stage renal disease or with creatinine clearance of  $\leq 30$  ml/min.

**Grade D, Level 3**

Streptomycin is almost solely cleared by the kidneys and should be used with great care in patients with renal impairment. If it must be used, doses have to be adjusted in renal disease. The recommended dose is 12 to 15 mg/kg 2 to 3 times a week post-dialysis. Even so some drug accumulation should be expected. Dialysis removes about 40% of the drug if given before dialysis.<sup>141</sup>

**D** Streptomycin should be used with great care in tuberculosis patients with renal impairment. If it must be used, the recommended dose of streptomycin is 12 to 15 mg/kg 2 to 3 times a week post-dialysis.

**Grade D, Level 3**

No data is available for patients with renal impairment but with creatinine clearance of more than 30 ml/min. No dependable data exists for peritoneal dialysis and it should not be assumed that the above recommendations for hemodialysis can apply.

As patients on haemodialysis are regularly present at their dialysis centre, it is convenient for the patient to undergo DOT there. Co-ordination of treatment with the dialysis centre is crucial and correct timing of the drug dosages must be informed to the patient and the dialysis centre.

## Hepatic disease

Treatment of tuberculosis in patients with underlying hepatic disease presents several difficulties: 1) isoniazid, rifampicin and pyrazinamide are potentially hepatotoxic, and the risk of drug-induced hepatotoxicity may be greater when there is underlying liver disease 2) drug-induced hepatotoxicity in patients with

marginal hepatic reserve is potentially very serious, and 3) the underlying liver disease may confound monitoring for tuberculosis drug hepatotoxicity.

Chronic hepatitis C infection is associated with an increased risk of tuberculosis drug hepatotoxicity.<sup>142, 143</sup> Some studies have shown that chronic hepatitis B infection is also associated with an increased risk of tuberculosis drug hepatotoxicity<sup>142, 144, 145</sup> whereas this was not borne out in other studies.<sup>146</sup> Nonetheless, chronic hepatitis B infection is considered as a risk factor for tuberculosis drug-induced hepatotoxicity in international guidelines.<sup>147</sup>

Pyrazinamide should generally be avoided in patients with hepatic disease. The 9-month regimen with rifampicin, isoniazid and ethambutol can be used if the patient can tolerate this regimen. In all cases of hepatic disease, close monitoring for potential drug induced liver injury is needed. If treatment is not tolerated, then expert consultation is advised.<sup>110</sup>

#### **GPP&D**

Patients with hepatic disease should be monitored closely during treatment\*. The 9-month regimen with rifampicin, isoniazid and ethambutol can be used if the tuberculosis patient with hepatic disease can tolerate this regimen. Pyrazinamide should generally be avoided in patients with hepatic disease†.

**\*GPP**

**† Grade D, Level 4**

## **HIV co-infection**

The standard six-month regimen is the recommended treatment for HIV co-infected patients with pulmonary tuberculosis.<sup>110</sup> As with non-HIV infected patients, the treatment should be extended to 9 months in patients with tuberculous osteomyelitis and to 12 months in patients with central nervous system (CNS) tuberculosis.

**A** The standard six-month treatment regimen is recommended for HIV co-infected patients with pulmonary tuberculosis. As with non-HIV-infected patients, the treatment should be extended to 9 months in patients with tuberculous osteomyelitis and to 12 months in patients with central nervous system (CNS) tuberculosis.

**Grade A, Level 1++**

Concurrent treatment of tuberculosis and HIV poses several challenges: 1) the need for adherence to multiple medications, 2) the overlapping side effect profiles of the anti-tuberculosis and antiretroviral drugs, 3) the immune reconstitution syndrome and 4) drug-drug interactions.

Of particular importance is the drug-drug interaction between the rifamycins (rifampicin, rifabutin and rifapentine) and four classes of antiretroviral drugs: protease inhibitors, non-nucleoside reverse transcriptase inhibitors (NNRTIs), CCR5-receptor antagonists, and integrase inhibitors. However, as rifamycins are an essential component of successful tuberculosis treatment, patients with HIV-related tuberculosis should, as far as possible, be treated with a regimen containing a rifamycin for the full course of tuberculosis treatment. A preferred strategy for co-treatment of HIV and tuberculosis is efavirenz 600 mg with 2 NRTIs, together with a rifampicin-based tuberculosis treatment regimen.<sup>148</sup>

**D** Patients with HIV-related tuberculosis should, as far as possible, be treated with a regimen containing a rifamycin for the full course of tuberculosis treatment.

**Grade D, Level 4**

**D** Intermittent dosing regimen for tuberculosis treatment is not recommended for patients with advanced HIV disease (CD4 counts less than 100 cells/mm<sup>3</sup>) in view of the risk of acquiring rifamycin resistance.

**Grade D, Level 4**



### **Timing of initiation of antiretroviral treatment (ART)**

There is evidence that providing ART to HIV-infected adults during tuberculosis treatment reduces mortality particularly in those with advanced HIV disease. The WHO 2012 guidelines recommend that HIV-infected patients should start ART as soon as possible within 8 weeks of starting tuberculosis treatment, and that patients with CD4 counts  $< 50$  cells/mm<sup>3</sup> should commence ART two weeks after initiation of tuberculosis treatment.<sup>62</sup> However, a large scale study published in 2014 has shown that, for HIV-positive patients with CD4 counts  $> 220$  cells/mm<sup>3</sup>, ART may be safely delayed till after completion of 6 months tuberculosis treatment.<sup>149</sup>

**Table 3 Adverse effects of first-line anti-tuberculosis drugs<sup>35, 110, 150</sup>**

Drug	Adverse Effects	Remarks
All first-line anti-TB drugs	<u>Cutaneous reactions</u> Pruritis with or without rash may occur.	This is generally self-limiting and amenable to anti-histamine therapy, allowing continuation of the anti-TB drugs. <i>Be alert for the rare occurrence of severe cutaneous reactions e.g. Stevens-Johnsons Syndrome, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) or Toxic Epidermal Necrolysis (TEN)</i>
	<u>Gastrointestinal symptoms</u> Anorexia, nausea, abdominal discomfort	To administer drugs after light meal or before bedtime. <i>Exclude hepatotoxicity if symptoms severe or persistent</i>
Isoniazid	<u>Peripheral neuropathy</u> Paresthesia, pricking pain, burning sensation in feet and hands  Hepatitis  Rarely, toxic psychosis, convulsions, haematologic reactions, lupus-like syndrome, hypersensitivity reactions  Drug interactions	More common in HIV-infected, diabetic, uraemic or malnourished patients, and alcohol users. Frequency increases with higher doses of isoniazid; prevented by supplemental pyridoxine 10 mg daily  Risk of hepatotoxicity increases with age, alcohol use, and the concomitant use of other hepatotoxic agents. Reversible if isoniazid is stopped early  Increases the serum concentrations of phenytoin and carbamazepine
Rifampicin	<u>Cutaneous syndrome</u> Flushing and/or pruritis, with or without rash, often with redness and watering of the eyes  <u>Flu-like syndrome</u> Fever, chills, malaise, headache and bone pains  <u>Respiratory syndrome</u> Shortness of breath; rarely shock  Rarely, severe immune-mediated reactions such as thrombocytopenic purpura, haemolytic anaemia, acute renal failure  Hepatitis  Drug interactions due to induction of hepatic microsomal enzymes	Occurs with intermittent therapy  Rifampicin must be stopped and never given again  Rifampicin is less hepatotoxic than isoniazid or pyrazinamide  Decreases the serum concentration and hence effectiveness of oral contraceptives, warfarin, corticosteroids, methadone, protease inhibitors, cyclosporine

### Continuation to Table 3

Drug	Adverse Effects	Remarks
	Orange discolouration of bodily fluids	Universal effect of Rifampicin; to reassure patient
<b>Ethambutol</b>	<u>Optic neuritis</u> Decrease in visual acuity, red-green colour blindness, blurring, central scotoma	Toxicity is dose-dependent, recovery dependent on early withdrawal of the drug
<b>Pyrazinamide</b>	Hepatitis  Arthralgia  Hyperuricemia  Hypersensitivity reaction	Pyrazinamide increases the risk of hepatotoxicity appreciably when added to Isoniazid and Rifampicin-containing regimens. Should be withheld, or used cautiously in the elderly, persons who use alcohol and those with underlying chronic liver disease  May be managed with analgesics, while continuing the drug. Rarely, classic gout may occur and this can be treated with colchicine.  Asymptomatic hyperuricemia does not require any treatment or withdrawal of the drug
<b>Streptomycin</b>	<u>Ototoxicity</u> Vertigo and ataxia; tinnitus and hearing loss  <u>Neurotoxicity</u> Transient circumoral paresthesia and tingling occurring soon after injection  Nephrotoxicity	Risk increases with dose and age (over 40 years) Causes fetal ototoxicity  Potentiates neuromuscular blocking agents and should be avoided in patients with myasthenia gravis

Adapted from Toman K, Freiden T (ed.). World Health Organization, 2004; Blumberg HM, Burman WJ, Chaisson RE et al. Am J Respir Crit Care Med. 2003 & Girling D J. Journal of Antimicrobial Chemotherapy 1977; 115-132.

## 7.5 Monitoring of patients on tuberculosis treatment

The tuberculosis patient is required to take many drugs over several months, making adherence to the full course of treatment a major challenge. Irregular, interrupted treatment or premature cessation of treatment may result in continued infectiousness and transmission of the disease in the community, the generation of drug resistant strains, and an increased risk of relapse. It is not possible to predict which patients will or will not adhere to their treatment. As tuberculosis is a major public health threat, international guidelines clearly state that the responsibility for successful treatment is assigned to the healthcare provider and not the patient.<sup>110, 151</sup> Physicians who treat tuberculosis patients must therefore also have the means to assure treatment adherence.

Directly observed therapy (DOT) has been shown to reduce the risk of relapse and development of drug resistance. DOT is the internationally recommended standard of care for tuberculosis patients.<sup>152, 153</sup>

Directly observed therapy (DOT) has been the internationally recommended standard of care for tuberculosis patients for decades.<sup>110, 151</sup> DOT refers to a healthcare worker or trained volunteer supervising the patient ingesting each dose of tuberculosis medication. The DOT worker must be fully accountable to the public healthcare system. Although a Cochrane systematic review concluded that DOT administered by healthcare/community workers or family members did not result in improved treatment completion rates as compared to self-administered therapy,<sup>154</sup> this review failed to analyse the all-important outcome of prevention of drug (rifampicin) resistant tuberculosis, which was the rationale for and purpose of DOT as originally conceptualised by Styblo.<sup>153</sup> The introduction of universal DOT has been shown in a non-randomised, controlled trial to result in significant reductions in the rates of primary drug resistance, acquired drug resistance and relapse.<sup>152</sup> Frieden and Sbarbaro have further challenged the validity of trials which support self-administration of treatment, noting that no large scale programme without direct observation of treatment has achieved global targets, while most programmes using direct observation of treatment achieve or nearly achieve these targets.<sup>155</sup> DOT also enhances patient monitoring for adverse effects of

medication. At its core, DOT demonstrates society's and the healthcare provider's responsibility and commitment to successful treatment of the individual patient and to the protection of the community. As far as possible, DOT should be patient-centred, with the provision of incentives and enablers for the patient to achieve a successful treatment outcome.

In Singapore, outpatient DOT is carried out at the 18 polyclinics nation-wide and at the Tuberculosis Control Unit (TBCU). TBCU healthcare workers also administer outreach DOT to selected patients e.g., the frail or elderly, in their homes.

**C** Directly observed therapy (DOT) should be the standard of care for all infectious tuberculosis cases. Tuberculosis patients who are assessed to have difficulty adhering to treatment or who pose greater public risk of transmission, e.g. sputum-smear positive or working in institutional settings or settings with susceptible populations, or those at risk of or diagnosed with drug-resistant tuberculosis, are high priority for directly observed therapy (DOT).

**Grade C, Level 2+**

The patients' progress during tuberculosis treatment is assessed by their clinical, bacteriological and radiographic response.

Patients usually experience symptomatic improvement (i.e. resolution of cough, fever and constitutional symptoms), and weight gain within a few weeks of commencing appropriate treatment. The importance however of adhering to and completing the full course of treatment must be emphasised. The patient's weight should be documented at each visit and the drug dosages adjusted accordingly. As the results of phenotypic drug susceptibility testing are not usually known at the time of treatment initiation, the treating physician must ensure that these results are noted in a timely manner, and that appropriate action is taken should the patient have drug-resistant tuberculosis.

Patients should be counselled regarding the potential adverse effects of anti-tuberculosis medications (Table 3). Particularly important are the symptoms and signs of hepatitis (e.g. unexplained fatigue, poor

appetite, abdominal pain, jaundice, tea-coloured urine) which must be specifically sought at each clinic review. Routine baseline liver function testing should be performed, and monitoring of liver enzymes carried out should there be any clinical suspicion of hepatitis. Patients should be instructed to abstain from alcohol while on anti-tuberculosis treatment. Those who are elderly, who have pre-existing liver disorders (e.g. chronic hepatitis B or C infection), who abuse alcohol, are HIV-infected or who have abnormal baseline liver function are at risk of drug-induced hepatitis and should have their liver function monitored closely. Internationally recommended thresholds for treatment interruption (with subsequent modification of treatment regimen) are alanine transaminase (ALT) elevation more than three times the upper limit of normal in the presence of hepatitis symptoms and / or jaundice, or with ALT elevation five times the upper limit of normal.<sup>147</sup> The reader is referred to the American Thoracic Society (ATS)'s 2006 guideline for the management of patients with antituberculosis drug-induced hepatitis.<sup>147</sup>

Adult patients on ethambutol must have their visual acuity and colour vision checked at baseline and each visit.

**GPP** Before commencing the treatment, patients must be counselled regarding the importance of adhering to and completing the full course of treatments, as well as medication adverse effects.

**GPP**

**GPP** The patient's weight should be documented at each visit and the drug dosages adjusted accordingly. Adult patients on ethambutol must have their visual acuity and colour vision checked at each visit. Those with risk factors for drug-induced hepatitis must be closely monitored.

**GPP**

**D** Patients should be reviewed monthly by the specialist to monitor their clinical condition, adherence to treatment and adverse effects of tuberculosis medications.

**Grade D, Level 4**

Minor drug side-effects such as itch, joint pains, lethargy and gastrointestinal upset are not uncommon. These are usually self-limiting and can be overcome with symptomatic treatment (e.g. antihistamines and moisturisers for itch, analgesics for joint pain), taking the medications with small meals (for gastrointestinal reactions) and reassurance, without the need for major modification of the treatment regimen. Nonetheless, the treating physician should always be alert for signs and symptoms which indicate serious adverse events such as hepatitis, rash with mucosal involvement, respiratory distress, shock, and haematological events.

The World Health Organization (WHO) defines “cure” of an initially sputum AFB smear or culture positive patient as the demonstration of negative sputum smear or culture in the last month of treatment and on at least one previous occasion.<sup>134</sup> Treatment failure is defined as positive sputum bacteriology at or after 5 months of treatment.<sup>134</sup> Approximately 85% of initially sputum positive patients convert their cultures at two months of treatment. Non-conversion of sputum cultures at two months is a good surrogate marker for risk of relapse.<sup>156, 157</sup> The American Thoracic Society (ATS) recommends monthly sputum AFB smear and cultures until bacteriological conversion is demonstrated, and extension of the continuation phase by three months for sputum AFB smear-positive patients with cavitary disease who do not show bacteriological conversion at two months of treatment.<sup>110</sup> At the very least, initially sputum positive patients should undergo repeat sputum AFB smears and tuberculosis cultures at two months (to identify those at risk of relapse for whom the continuation phase should be extended); as well as in the last month of treatment to demonstrate “cure”.

**D** Bacteriological response to treatment should be monitored in patients who are initially sputum acid-fast bacillus (AFB) and/or culture-positive.

**Grade D, Level 4**

As repeat sampling for microbiological testing is often not feasible in extrapulmonary disease sites, treatment response in these cases is therefore assessed clinically.

Radiological clearing of tuberculous lesions is relatively slow compared to that of other infectious aetiology such as bacterial pneumonia. Radiographic improvement at two months of treatment (i.e. end of intensive phase) provides evidence of treatment response. Pulmonary tuberculosis lesions usually heal with sequelae of fibrosis and scarring. The end-of-treatment chest radiograph is therefore useful to serve as a new baseline for future comparison. The presence of cavitation in the end-of-treatment chest radiograph has been shown to be associated with increased risk of relapse.<sup>158</sup>

Radiological worsening or the appearance of new lesions during treatment should prompt the treating physician to consider the possibilities of treatment non-adherence, drug resistance, concomitant pulmonary infection, mis-diagnosis or dual pathology (e.g. co-existing lung carcinoma). Rarely, new lesions may be due to a paradoxical reaction (i.e. the immune reconstitution inflammatory syndrome), which is a diagnosis of exclusion.

Patients with diabetes mellitus are at risk for tuberculosis.<sup>64</sup> Diabetes is a common co-morbid condition which was present in 30% of tuberculosis patients above the age of 50 years in Singapore (unpublished data).

Tuberculosis patients with diabetes have an increased risk of tuberculosis treatment failure, death and disease relapse.<sup>63</sup> It is therefore all the more important that diabetic tuberculosis patients be closely monitored for adherence and treatment response with consideration given to extending treatment duration in persons with high bacillary burden and cavitary disease. Close attention should also be paid to the control of diabetes in these patients.



Cigarette smoking increases the risk for tuberculosis.<sup>159</sup> Cigarette smoking has also been shown adversely affect sputum culture conversion at two months of tuberculosis treatment. To improve treatment outcomes, patients with tuberculosis should be strongly advised and supported to stop smoking.<sup>160</sup>

**D** Cigarette smokers with tuberculosis should be strongly advised and supported to stop smoking.

**Grade D, Level 3**

## 7.6 Management of multidrug-resistant/extensively drug-resistant tuberculosis

Multidrug-resistant tuberculosis (MDR-TB) is defined as tuberculosis resistant to rifampicin and isoniazid, the two most potent anti-tuberculosis drugs contained in the standard short course treatment regimen. Treatment of MDR-TB requires multiple second-line drugs which are less potent but more toxic and much more costly than the first-line drugs. As the second-line drugs are less effective, they have to be given for an extended period of time. The reported treatment success rate for MDR-TB is approximately 60% compared to more than 95% for drug-susceptible cases.<sup>161</sup>

Extensively drug resistant tuberculosis (XDR-TB) refers to MDR-TB with additional resistance to any fluoroquinolone and second-line injectable agent, which are the two key second-line drugs in MDR-TB treatment regimens. The reported treatment success rate for non-HIV XDR-TB patients ranges from 34% to 67%.<sup>161, 162</sup>

To date, there have been no large randomised, controlled trials evaluating MDR-TB treatment regimens. According to expert opinion and consensus, an MDR treatment regimen must contain at least four drugs (preferably more) to which the organism is shown to be susceptible and to which the patient has previously not been exposed.<sup>163, 164</sup> It is thus crucial to obtain a meticulous history of the patient's past tuberculosis treatment. It is important for the regimen to include the two key second-line drugs (i.e. a later-generation

fluoroquinolone and a second-line injectable agent. Experts advise that the injectable be continued for 6 months after culture conversion, and the oral drugs continued for 18 months after culture conversion. A systematic review and meta-analysis showed that treatment success rates improved when treatment duration was at least 18 months and if patients received DOT throughout treatment.<sup>165</sup> Another systematic review and meta-analysis noted high rates of default among MDR-TB patients and identified factors associated with worse outcome to be male gender, alcohol abuse, low BMI, smear positivity at diagnosis, fluoroquinolone resistance and the presence of an XDR resistance pattern. Factors associated with successful outcome were surgical intervention, no previous treatment and fluoroquinolone use.<sup>166</sup> A recent retrospective cohort study reported that an aggressive regimen (one containing at least five effective drugs including a fluoroquinolone and injectable) was associated with decreased mortality.<sup>167</sup>

**D** A multidrug-resistant treatment regimen must contain at least four drugs, preferably more, (including a later-generation fluoroquinolone and a second-line injectable agent) to which the organism is shown to be susceptible and to which the patient has previously not been exposed.<sup>163, 164</sup>

**Grade D, Level 3**

**D** Multidrug-resistant tuberculosis (MDR-TB) patients should be treated under strict programme conditions by physicians experienced in MDR-TB management. Directly observed therapy (DOT) should be utilised for the entire treatment duration.

**Grade D, Level 4**

In parts of the world where second-line drug-susceptibility testing is not performed, and where patients have had no previous exposure to second-line anti-tuberculosis drugs, WHO recommends a standardised MDR treatment regimen containing pyrazinamide, a fluoroquinolone (preferably later generation), a parenteral agent,

ethionamide (or prothionamide), and cycloserine, or else para-amino-salicylic acid if cycloserine cannot be used.<sup>163, 168</sup> An intensive phase (during which an injectable is included) of 8 months, and a total treatment duration of at least 20 months is suggested. Recognising the tremendous challenge in terms of drug toxicity and cost which this regimen poses to patients and tuberculosis programmes in developing countries, the International Union Against TB and Lung Disease (IUATLD)<sup>164</sup> 2013 guidelines recommend a shortened, standardised treatment regimen of at least 9 months which contains kanamycin, prothionamide and isoniazid in the 4 month intensive phase, with moxifloxacin, ethambutol, pyrazinamide and clofazimine throughout the 9 months (the so-called “Bangladesh regimen”).<sup>165, 169</sup>

As the majority of patients will experience side-effects to the second-line anti-tuberculosis medications, the skilful management of drug side-effects and psychosocial support are essential to achieve a successful treatment outcome. International experts advocate that these patients be treated by MDR-TB specialists under strict programmatic conditions.<sup>165</sup> The use of DOT for the entire treatment duration to prevent amplification of drug resistance and ensure treatment completion cannot be over-emphasised.

### **Role of surgery in MDR and extensively drug-resistant tuberculosis (XDR-TB)**

**D** Resectional surgery should be considered in high grade MDR-TB or XDR-TB patients with localised disease and adequate respiratory reserve, and for whom there are limited chemotherapeutic options, or who are not responding to chemotherapy.<sup>170</sup>

**Grade D, Level 4**

## 8 Public health screening and infection control

### 8.1 Air travel and tuberculosis

Although the risk of transmission of infectious diseases onboard aircraft is limited, airborne and droplet borne diseases such as tuberculosis are potentially transmissible onboard aircraft due to prolonged contact in closed environment. Case studies involving tuberculosis exposure on flight have demonstrated the possibility of transmission (including that of drug-resistant forms of tuberculosis) among close contacts on long flights.<sup>171</sup> To reduce the potential risk of transmission, persons with infectious or potentially infectious tuberculosis<sup>172</sup> should be advised not to travel by commercial air transportation on a flight of any duration, until their infectious status have been determined. Patients with MDR-TB or XDR-TB will require a longer period of adequate treatment and detailed follow-up, with satisfactory clinical response to treatment, and sputum-culture conversion to negative before being confirmed as non-infectious and allowed to travel.<sup>1</sup>

**D** Physicians should inform persons with infectious or potentially infectious tuberculosis not to travel by commercial air transportation on a flight of any duration.<sup>192</sup>

**Grade D, Level 3**

### 8.2 Public health screening

One of the ways to safeguard community health is to pro-actively screen new incoming foreigners from high tuberculosis prevalence settings to reduce the risk of spread in the local community. Immigrants from settings with a high prevalence of tuberculosis are considered one of the possible risk groups to consider for screening for tuberculosis, and may be recommended to be screened on a conditional basis.<sup>37</sup> Systematic screening of high risk populations for tuberculosis can reduce the risk of poor treatment outcomes and health sequelae of migrants. At the same time, migrant screening can also reduce tuberculosis transmission within local communities by shortening of the duration of infectiousness.

**D** Persons applying for long-term immigration passes should be screened for active tuberculosis to ensure early detection and access to treatment, and to reduce community risk of transmission. This is especially true for persons from high tuberculosis prevalence countries.

**Grade D, Level 3**

In Singapore, foreigners applying for work pass (work permit and S-pass), student pass and long-term social visit pass are required to undergo a medical examination which includes screening for tuberculosis via chest radiography. The aim is to detect active pulmonary tuberculosis. Work permit and S-pass holders are also required to undergo a repeat screening for active tuberculosis at first renewal of their passes (refer to Chapter 5 Imaging in tuberculosis for guidelines on diagnosis and screening of patients.).

Compared to symptom screening, chest X-ray screening generally showed greater accuracy and less heterogeneity. The pooled sensitivity of chest X-ray reading was higher than of symptom screening (i.e. 98% for ‘any chest X-ray abnormality’, with 75% specificity, and 87% pooled sensitivity for ‘tuberculosis abnormalities’, with 89% specificity).<sup>172, 173</sup>

**C** Chest radiograph examination should be used for the purpose of screening in long-term immigration pass applicants.

**Grade C, Level 2+**

As the objective of medical screening for immigration pass applicants is to prevent the importation of tuberculosis into Singapore, medical practitioners should maintain a high degree of vigilance even in the absence of reported symptoms. Medical practitioners who conduct these screenings should exercise public health responsibility and report results conservatively. Applicants with tuberculosis-related abnormality in their chest x-ray should be referred to the Tuberculosis Control Unit for further tests and evaluation to exclude active tuberculosis. Medical practitioners who

conduct medical screenings for foreigners should therefore ensure that any anomalous results are accurately reflected in the medical examination form, and complete the form accordingly to indicate unequivocal radiological findings.

**D** Any chest radiograph abnormality compatible with tuberculosis (whether radiologically “active” or “inactive”) should be evaluated further to rule out active tuberculosis.

**Grade D, Level 4**

**C** Medical practitioners should have a high index of suspicion of drug-resistant tuberculosis in those who were previously treated, those who fail treatment, who are known contacts of multidrug-resistant tuberculosis (MDR-TB), or who come from countries with high prevalence of tuberculosis drug resistance.<sup>174</sup>

**Grade C, Level 3**

Refer to Chapter 4 Clinical diagnosis of tuberculosis and Chapter 6 Tuberculosis laboratory diagnosis for more information on MDR-TB diagnosis and clinical management.

### **8.3 Management of MDR-TB**

MDR-TB / XDR-TB patients should be managed by physicians with expertise and experience in MDR-TB treatment under the national programme so that they can receive their treatment under DOT for the entire duration (refer to recommendation in 7.6 Management of multidrug-resistant/extensively drug-resistant tuberculosis). This will allow their progress and adherence to be monitored closely and to adjust the treatment regimen accordingly, especially if there are side effects to the medications (refer to 7.5 Monitoring of patients on tuberculosis treatment).<sup>174</sup>

### **8.4 DOT under the national tuberculosis programme, STEP**

The tuberculosis patient is required to take many drugs over several months, making adherence to the full course of treatment a major

challenge. Irregular, interrupted treatment or premature cessation of treatment may result in continued infectiousness and transmission of the disease in the community, the generation of drug resistant strains, and an increased risk of relapse. As tuberculosis is a major public health threat, the responsibility for successful treatment is assigned to the healthcare provider and not the patient. Physicians who treat tuberculosis patients must therefore also have the means to assure treatment adherence.

It is imperative that medical practitioners support the national DOT programme, as DOT is the surest way to ensure that patients comply strictly with their medications. Non-adherence is a major problem in tuberculosis control and DOT should be considered for all patients as it is impossible to predict which patients will adhere or which will default treatment on their own. All patients should be educated about tuberculosis, the dosing of medications, possible side effects and adverse reactions to medications, and the importance of adherence to medications. Inadequate treatment can lead to relapse, continued transmission and the development of drug resistance.

In Singapore, DOT is carried out at the 18 polyclinics nation-wide and at the Tuberculosis Control Unit (TBCU). TBCU healthcare workers also administer outreach DOT to selected patients e.g. the frail or elderly, in their homes.

As a principle, all long-term pass holders who are diagnosed with TB are required to undergo DOT under the care of the TBCU. This is to ensure that they are adherent to their treatment regimen and do not pose a risk to the community while they are living in Singapore.

## 8.5 Surveillance and notification of tuberculosis

**All medical practitioners must report both new or relapsed tuberculosis cases (including suspect tuberculosis) and their treatment outcomes to the Ministry of Health, in conformance with requirements under the Infectious Diseases Act.<sup>175, 176</sup>**

mandated in Singapore. Notification of suspect and confirmed cases of tuberculosis is mandatory under the Infectious Diseases Act (Chapter 137) and must be made via **MD 532 Notification Form (Annex 1)** electronically or by fax within 72 hours of a new diagnosis. Failure to notify a case in a timely manner is an offence under the Infectious Diseases Act.

**Treatment progress report (MD117) (Annex 2)** should be submitted every month for each patient with active tuberculosis (even if he is temporarily not on treatment), until the patient is cured, transferred for management, discharged, permanently lost to follow-up (e.g. left country), or some other end-point is reached. Patients should be followed up on a regular basis to ensure that they are adhering to their treatment regimen and that their tuberculosis condition is resolving. Treatment progress reports enable STEP to closely monitor the progress of all tuberculosis patients regardless of whether they are seen at TBCU or not. As the treatment for tuberculosis is long, treatment surveillance allows STEP to keep track of outcomes of all currently active tuberculosis. In the event that a patient defaults treatment but is still considered a public health risk, appropriate actions will be taken to recall the patient to resume treatment.

A comprehensive tuberculosis surveillance framework provides the necessary information for STEP to prevent and control tuberculosis. Surveillance information allows STEP to monitor trends in tuberculosis disease, including drug-resistance, and to identify possible outbreaks for action. All medical practitioners should therefore notify all tuberculosis cases, whether microbiologically confirmed or otherwise, to MOH promptly to facilitate the implementation of downstream control actions to reduce the transmission in the community and to identify latently infected contacts.

Notification and treatment reporting are critical surveillance tools used by STEP to monitor the tuberculosis situation in Singapore. Delays in notification inadvertently results in lags in activating downstream public health control measures such as contact investigation and screening. Medical practitioners should promptly submit notifications via **MD 532 Notification Form (Annex 1)**, once there is suspicion of tuberculosis in a patient, even before laboratory results are out. Patients suspected of having tuberculosis



should be notified to STEP so that they can be followed up in a timely manner, especially when suspicion has prompted tuberculosis treatment in the first place.

## 8.6 Infection control for tuberculosis in healthcare settings

**D** Healthcare facilities that potentially receive tuberculosis patients should have an infection control plan for tuberculosis, comprising administrative controls, environmental controls and use of personal protective equipment to protect staff and patients from potential tuberculosis transmission.<sup>177</sup>

**Grade D, Level 4**

Transmission of tuberculosis may take place in healthcare settings, particularly where patients and healthcare workers come into contact with undiagnosed (and therefore untreated) infectious tuberculosis or those who have not received adequate or appropriate treatment, or have not been separated from others. While precautions can be taken by healthcare workers working in tuberculosis clinics, the risk of transmission posed by undiagnosed tuberculosis patients in other health care settings cannot be underestimated. Undiagnosed patients may access medical care services in hospitals and clinics for non-tuberculosis related issues, and inadvertently spread tuberculosis to other patients and healthcare workers in those settings.

Healthcare settings such as clinics and hospitals should therefore have a tuberculosis infection control plan as part of their general infection control programme to ensure the following:

- Prompt detection of tuberculosis;
- Airborne precautions for suspected or confirmed tuberculosis patients; and
- Prompt treatment of persons who have been suspected or confirmed tuberculosis.

A tuberculosis infection control programme generally has three levels of hierarchy:

- 1) Administrative controls, which reduce risk of exposure;
- 2) Environmental controls, which prevent spread and reduce concentration of droplet nuclei in the environment; and
- 3) Personal protective equipment.

**D** Persons with tuberculosis symptoms should be promptly identified in healthcare settings and if necessary, separated from other patients.<sup>175</sup>

**Grade D, Level 4**

Administrative controls should be implemented as a first priority as they have been shown to reduce the transmission of tuberculosis in healthcare facilities. Case-finding is the most important strategy in preventing transmission and prompt identification of people with tuberculosis symptoms is important; however, the criteria for triaging patients will depend on local settings and patient population (refer to Chapter 4 Clinical diagnosis of tuberculosis). In general, persons suspected of having tuberculosis must be separated from other patients, and be placed in well-ventilated areas.<sup>178</sup> Case-finding must also be complemented by effective referral to treatment for tuberculosis patients so that the risk of transmission is reduced.

**D** A ventilation system (natural, mechanical or mixed mode) should be employed for health care facilities to ensure sufficient air exchange and control airflow direction to reduce the risk of tuberculosis exposure.<sup>178</sup>

**Grade D, Level 4**

**D** Where necessary, healthcare workers should use particulate respirators when caring for patients suspected or known to have infectious tuberculosis, especially drug-resistant tuberculosis patients and in situations where high-risk procedures are being performed.<sup>178</sup>

**Grade D, Level 4**

## 8.7 Infection prevention in the home and the community

Once treatment is started, infectiousness decreases rapidly. Therefore, the most important element of infection control is to ensure that the tuberculosis patient is taking the medications regularly as prescribed. This is best achieved by DOT. The patient should also practise cough etiquette at all times (i.e. covering his or her nose and mouth when coughing or sneezing), and the home environment should be well-ventilated. As the patient would have been infectious and his or her household members exposed for some time before treatment commencement, it is not necessary for the patient to avoid contact with these persons. The exception would be household members who are immunocompromised or less than 5 years old who should not be further exposed to the patient until he or she has received at least two weeks of appropriate treatment. After two weeks of effective treatment, no special efforts need to be undertaken to avoid contact with others.

**D** Physicians should advise patients with suspected or confirmed tuberculosis to practise cough etiquette and respiratory hygiene (especially surgical mask use).<sup>178</sup>

**Grade D, Level 4**

## 9.1 STEP contact investigations

Although the highest priority in tuberculosis control is the early detection and successful treatment of active tuberculosis cases, effective tuberculosis control requires attention to also be directed to the pool of persons with Latent Tuberculosis Infection from which active cases emerge. The Singapore Tuberculosis Elimination Programme (STEP) has, since 1998, included targeted Latent Tuberculosis Infection testing and treatment in its contact investigation activities as a key tuberculosis control strategy.

Recently infected contacts are a high priority group for preventive therapy as the risk of developing active tuberculosis is greatest in the first two years after infection. The Tuberculosis Control Unit (TBCU) performs contact investigations in households, workplaces, schools and congregate settings such as prisons, nursing homes, dialysis centres and the mental institution. It is a high yield, cost-effective strategy for the detection of active tuberculosis cases and persons with recently acquired Latent Tuberculosis Infection.<sup>179-181</sup>

It is important that screening be targeted only at close contacts who, if found to have Latent Tuberculosis Infection, will benefit from preventive therapy. The intention to test should be the intention to treat should the result be positive. Casual contacts (who are at low or no risk of acquiring Latent Tuberculosis Infection) may clamour for testing because of anxiety, stigma or lack of understanding about tuberculosis. These persons should not be included in the investigations as they are more likely to throw up false positive results, and this may result in needless exposure to the toxicity risk of isoniazid preventive treatment. Accurate identification of close contacts involves detailed assessment including multiple interviews and site visits by experienced personnel.

Factors which determine the risk of tuberculosis transmission include:

- (1) The infectiousness of the tuberculosis case:
  - Pulmonary tuberculosis cases especially with bacteriologically positive sputum.

- Laryngeal tuberculosis cases (all other extrapulmonary tuberculosis cases are not considered infectious).
  - Duration and severity of cough
- (2) The characteristics of the environment:
- A small room
  - An enclosed space
  - A poorly ventilated space
- (3) The duration of the time spent sharing ventilation between the tuberculosis case and the contact.

Tuberculosis notification is required by law in Singapore. Contact investigations are initiated by the National Tuberculosis Programme.

From the notification, bacteriologically sputum positive pulmonary cases and laryngeal tuberculosis cases are flagged. These are identified as Index cases i.e. the cases which would initiate the contact investigations. Letters are automatically generated to recall these Index cases to the TBCU for the Index interview.

At the Index interview performed by the nurses at the Tuberculosis Control Unit, the close contacts of the Index are identified.

These identified contacts are evaluated by screening for symptoms of active tuberculosis, clinical assessment and tuberculin skin test/IGRA (refer to 9.2 Testing for Latent Tuberculosis Infection). Chest x-rays and sputum tests are performed where indicated.

If they are determined to have active tuberculosis disease, they will be started on tuberculosis treatment.

If they are assessed to have Latent Tuberculosis Infection, preventive treatment with isoniazid is advised to reduce the risk of developing tuberculosis disease.

**Contact investigations should be centralised at the national tuberculosis programme.**

**B** Contact investigations are carried out by the National Tuberculosis Programme. Persons with recent close exposure to infectious tuberculosis cases (i.e. bacteriologically positive cases of pulmonary tuberculosis, especially if acid-fast bacilli smear is positive) should be evaluated for active tuberculosis and Latent Tuberculosis Infection.

**Grade B, Level 2++**

## 9.2 Testing for Latent Tuberculosis Infection

There is currently no gold standard diagnostic test for Latent Tuberculosis Infection. The state of Latent Tuberculosis Infection is inferred from a positive tuberculin skin test (TST) or interferon- $\gamma$  release assay (IGRA) in the absence of clinical and radiological evidence of active tuberculosis.

The TST and IGRAs reflect immunosensitisation to *M. tuberculosis* antigens. These tests do not distinguish between persistent *M. tuberculosis* infection (i.e. presence of viable bacilli) and immunological memory of an infection which has been eradicated by chemotherapy or by a protective host response. These tests also do not discriminate between infection acquired from remote or recent exposure, and between active and latent tuberculosis. Testing should be targeted towards individuals with risk factors for progression to active disease (e.g. recent close exposure to an infectious tuberculosis case, immunocompromised state and other medical conditions) who would benefit from Latent Tuberculosis Infection treatment). The test result may be negative during the window period for test conversion (i.e. within the first 8-12 weeks after infection), therefore the need for repeat testing post-window period. It should be noted that persons at extremes of age or who are severely immunocompromised may have a higher likelihood of false negative results. Persons at low risk for progression to active disease (and for whom the risk of isoniazid hepatotoxicity outweighs any potential benefit of treatment) should not be tested.<sup>182</sup>

## KEY RECOMMENDATION

**D** Testing for Latent Tuberculosis Infection should be targeted at high-risk groups and should only be performed if there is an intention to treat for Latent Tuberculosis Infection if detected.

**Grade D, Level 4**

**GPP** Low risk groups (i.e. casual contacts) should not be screened as they are more likely to throw up false positive test results for Latent Tuberculosis Infection.

**GPP**

### Tuberculin skin test (TST)

For a valid TST, 0.1 ml of tuberculin-purified protein derivative is injected intradermally into the flexor surface of the forearm. The diameter of induration (not erythema) is measured in millimetres at 48-72 hours.<sup>48, 183</sup>

The TST measures the skin reaction which results from cell-mediated, delayed type hypersensitivity to purified protein derivative, a crude mixture of > 200 mycobacterial antigens including the bacillus Calmette-Guerin (BCG) *M. bovis* substrain. False positive reactions therefore may occur in BCG-vaccinated persons and in those immunosensitised to non-tuberculous mycobacteria (NTM). A systematic review of 24 studies evaluating the effect of BCG on TST, and of 12 studies evaluating the effect of NTM on TST concluded that BCG had a definite influence on TST. This appeared to wane with increasing interval between BCG vaccination and TST testing: the impact of BCG on TST appeared to be minimal and short lasting if given in infancy but was more long-lasting if given after 1 year of age, likely reflecting a more durable immunologic response to BCG if given after 1 year. NTM was not considered to be a clinically important cause of false-positive TST, except in populations with high prevalence of NTM sensitisation and low tuberculosis prevalence.<sup>184</sup> Besides its low specificity in BCG-vaccinated individuals, other drawbacks of the TST include

its wide inter and intra reader variability and potential biases in the measurement of induration, and the need for a return visit 48-72 hours post-PPD injection for its reading.<sup>48</sup> Administering and reading of the TST also require training and expertise.

A large cohort study in Singapore schoolchildren found, using receiver operating characteristic (ROC) analysis, the optimum TST cut-off reading of  $\geq 10$  mm to predict progression to active tuberculosis in those 12 years of age who received one BCG (at birth).<sup>185</sup> In contrast, the optimum TST cut-off reading to predict progression to active tuberculosis was  $\geq 15$  mm in those 16 years of age who had received two BCG vaccinations (at birth and at 12 years of age). The School Health Service BCG re-vaccination policy was discontinued in 2001; hence persons born in Singapore after 1989 would have received only one BCG vaccination (at birth). Thus, for the Singapore population, the specificity of the TST for BCG-vaccinated individuals is improved by using higher cut-offs for diagnosing latent tuberculosis.

### **Interferon- $\gamma$ release assays (IGRAs)**

The commercially available IGRAs are the QuantiFERON-TB Gold In-tube (QFT-GIT) (Cellestis, Carnegie, VIC, Australia) and the T-SPOT.TB (Oxford Immunotec, Abingdon, UK). These in-vitro tests require special blood collection tubes. The QFT-GIT is a whole blood ELISA assay, while the T-SPOT utilises the ELISPOT platform. Both assays measure interferon- $\gamma$  released by viable patient white blood cells in response to incubation with *M. tuberculosis* complex (MTC)-specific antigens ESAT-6 and CFP-10 (and also TB 7.7 in the QFT-GIT).<sup>186</sup> These antigens are absent in the BCG vaccine and most NTM, thus avoiding false positive results.

An indeterminate result (where there is failure of the negative or positive control) or borderline result may be reported for the IGRAs. Because of technical factors, test variability<sup>187</sup> and biological (within-subject) variability,<sup>188</sup> fluctuation in qualitative IGRA results may occur in serially-tested subjects, especially when the quantitative values are in the borderline range.

Since the availability of the commercial IGRAs in 2005, there have been numerous publications on the use of these assays in adults and adolescents. In low tuberculosis incidence countries,



the IGRAs have been shown to be significantly more specific than the TST in recipients of the BCG vaccine.<sup>189</sup> A systematic review and meta-analysis on the performance of the IGRAs in HIV-infected individuals found the T-SPOT.*TB* to be less affected by immunosuppression than QFT-GIT and the TST; however the differences among the three tests were small or inconclusive.<sup>190</sup> A systematic review concluded that the QFT-GIT was more strongly associated with risk factors for Latent Tuberculosis Infection than the TST in persons with end-stage renal disease.<sup>191</sup> Although the evidence base on IGRAs in persons with immune-mediated inflammatory diseases thus far does not indicate superiority of the IGRAs over the TST, expert opinion favours the use of the IGRAs for Latent Tuberculosis Infection screening before instituting anti-TNF therapy in this risk group.<sup>192, 193</sup> There is currently a lack of published data on the performance of the IGRAs in children < 5 years of age.

### **Utility of IGRA and TST in predicting development of active disease**

The risk for progression of Latent Tuberculosis Infection to active disease is highest in the first two years after infection (~5%), after which the risk decreases to ~5% over the rest of the person's lifetime. The inability of the IGRAs and the TST to discriminate recently acquired Latent Tuberculosis Infection from that acquired in the remote past may account for the low positive predictive values (PPVs) of these tests reported by two meta-analyses.<sup>194, 195</sup> The more recent meta-analysis found a pooled PPV for all studies using commercial IGRAs to be 2.7% versus 1.5% for the TST. The PPV increased to 6.8% for IGRA and 2.4% for TST when only high-risk groups were considered. The pooled negative predictive value (NPV) was 99.7% for IGRA and 99.4% for TST.<sup>195</sup> It should be remembered that the PPVs of these tests are dependent on the prevalence of tuberculosis in the community and on the risk group tested.

**A** Either the tuberculin skin test or the interferon-gamma release assay may be used for the diagnosis of Latent Tuberculosis Infection in adults and children 5 years or older.

**Grade A, Level 1+**

**A** The interferon-gamma release assay is the preferred test for adolescents and adults who have received Bacillus Calmette-Guerin (BCG) vaccination, while the tuberculin skin test is the preferred test for the diagnosis of latent tuberculosis in children <5 years of age.

**Grade A, Level 1+**

**C** In significantly immunocompromised individuals, especially those with HIV/AIDS, the T-SPOT.TB may be preferable to the tuberculin skin test and the QuantiFERON-TB Gold In-Tube (QFT-GIT) for the diagnosis of Latent Tuberculosis Infection.

**Grade C, Level 2+**

### Utility of IGRA in assessing

Studies so far have consistently shown that the majority of IGRA-positive individuals who received prophylaxis do not convert to a negative result after treatment.<sup>196-200</sup> The significance of a positive or negative post-treatment result is as yet unknown. Repeat testing of persons who have received prophylaxis does not provide useful or interpretable information and should not be done.

**C** The interferon-gamma release assay (IGRA) should not be used to monitor response to preventive therapy.

**Grade C, Level 2+**

## 10 Tuberculosis in children - specific considerations

### 10.1 Clinical diagnosis of tuberculosis in children

Taking a careful patient history remains the most important aspect of diagnosing tuberculosis. Unfortunately all the classic symptoms traditionally associated with pulmonary tuberculosis (cough, dyspnoea, chest pain, haemoptysis, anorexia, weight loss, fatigue, fever, night sweats) may not occur in previously healthy children, and occasionally some children can have tuberculosis without any symptoms (diagnosed through epidemiologic contact with positive immunologic testing and pre-defined CXR changes) as was seen in a community-based survey in a high burden setting.<sup>201</sup> This often leads to a heavy reliance on investigations, which can be performed and interpreted erroneously. However, the presence of an exposure history (especially to household cases of adult tuberculosis) and a TST of  $\geq 15\text{mm}$  were strongly associated with the diagnosis of childhood tuberculosis. Fever was not significant in the above study. Children with persistent, unremitting cough for 2 weeks, plus objective weight loss, together with fatigue, should be evaluated for tuberculosis disease. The strength of this recommendation is greater when there is a known exposure to infectious tuberculosis, or when cough persists beyond 3-4 weeks.<sup>202</sup>

**C** Children with persistent, unremitting cough for 2 weeks, plus objective weight loss, together with fatigue, should be evaluated for tuberculosis.

**Grade C, Level 2+**

### 10.2 Chest radiographic screening in children<sup>69-74</sup>

The chest radiograph (CXR) is an extremely useful component of any evaluation for childhood tuberculosis in resource-adequate situations, and is an important adjunct in diagnosis especially since children often have paucibacillary tuberculosis.

It is well recognised that, depending on the quality of the radiograph and the experience of the person viewing the radiograph, the interpretation of CXR is not always straightforward; furthermore, significant inter-observer variation exists when interpreting paediatric CXR, and the CXR can be “normal” in more than 50% of children with smear or culture confirmed pulmonary tuberculosis.<sup>71</sup> In addition, very few studies have been published on the diagnostic accuracy of CXR in childhood tuberculosis.

Swingler et al<sup>74</sup> prospectively evaluated 100 children with suspected tuberculosis and performed antero-posterior and lateral chest radiography as well as computerised tomography (CT) in parallel to detect mediastinal lymphadenopathy (a hallmark of paediatric tuberculosis) and other radiologic features consistent with tuberculosis, using 1 cm as a cut-off for the definition of enlarged lymphadenopathy on CT, with 2 groups of observers (paediatricians with special interest in tuberculosis, and doctors working in local primary care tuberculosis clinics). The addition of a lateral CXR increased both sensitivity and specificity only marginally (1.8% and 2.5% respectively).

**C** All children being evaluated for latent or active tuberculosis (pulmonary or otherwise) should have a frontal chest radiograph. Where tuberculosis is strongly suspected, a lateral radiograph should be performed even if the frontal view is normal.

**Grade C, Level 2+**

Hesseling et al<sup>203</sup> conducted a systematic review of studies that reported on the use of diagnostic approaches or scoring systems to diagnose tuberculosis. The sensitivity and specificity of all the approaches or score charts were at best moderate (often sacrificing specificity for sensitivity resulting in false positives), and were very poor in children with HIV infection. An updated review by Pearce et al<sup>204</sup> including 21 additional studies and guidelines produced similar results.

**B** Currently available scoring systems for predicting tuberculosis in children lack sensitivity and/ or specificity, and are not recommended to be used for diagnosis.

**Grade B, Level 2++**

### 10.3 Immunologic diagnosis of tuberculosis in children (tuberculin skin test and interferon-gamma release assays)

Farhat et al<sup>184</sup> conducted a systematic review of 24 studies evaluating the effect of BCG on tuberculin skin test (TST), and of 12 studies evaluating the effect of non-tuberculous mycobacteria (NTM) on TST. The authors concluded that BCG had a definite influence on TST, which appeared to wane with increasing interval between BCG vaccination and TST testing. However, while the impact of BCG on TST appeared to be minimal and short lasting if given in infancy, it was more long-lasting if given after 1 year of age, likely reflecting a more durable immunologic response to BCG if given after 1 year. NTM was not considered to be a clinically important cause of false-positive TST, except in populations with high prevalence of NTM sensitisation and low tuberculosis prevalence. Two local studies support the above observation.<sup>185, 205</sup>

TST is an extremely sensitive test with a robust negative predictive value, with high specificity when the cut-off size is increased (and with appropriate clinical symptoms), and at such low cost, remains a very important screening and diagnostic tool in children. When it is thought to be false positive, other methods (e.g. IGRA) may be considered to further evaluate the child for tuberculosis.

Interferon-gamma release assay (IGRA) are sometimes used in children when TST is uninformative. Below the age of 4 years, the T-spot is the preferred IGRA. Bergamini et al<sup>206</sup> showed that the rates of indeterminate results were significantly higher in children <4 years of age than in children ≥4 years of age for QFT-GIT (21.5% vs. 0.4% [p < .001]), whereas there was no statistically significant difference between the two age groups for T-SPOT.TB (1.7% vs 2.0% [p = .895]).

Children less than 5 years of age have an increased risk for infection and rapid progression to severe disease. There are a limited number of studies on IGRA use in this age group. Although BCG at birth may have an effect on the TST reading, it remains a useful test in evaluating children with symptom or sign suggestive of tuberculosis.

**B** In children younger than 5 years old suspected of having tuberculosis infection or disease, the tuberculin skin test (TST) is the preferred mode of initial immunological assessment.

**Grade B, Level 2++**

**C** When the interferon-gamma release assay (IGRA) testing is performed in children <4 years old, the T-SPOT.TB is preferred over the QFT-G IT due to a lower incidence of indeterminate results.

**Grade C, Level 2+**

**B** Because of its excellent specificity, children with a positive interferon-gamma release assay (IGRA) are considered to have tuberculosis infection or disease, and should be offered treatment.

**Grade B, Level 2++**

**D** For children with a clinical suspicion of tuberculosis disease with a negative tuberculin skin test (TST), the interferon-gamma release assay (IGRA) may be performed to increase sensitivity. However, treatment for tuberculosis should be considered when other factors are strongly supportive of tuberculosis (epidemiologic, radiologic, histologic, microbiologic), and neither a negative TST nor IGRA should delay treatment.<sup>69</sup>

**Grade D, Level 4**

## 11 Cost-effectiveness issues

A cost-effectiveness analysis in the 1990s showed that short-course drug treatment for new smear-positive tuberculosis cases is one of the most cost-effective healthcare interventions available.<sup>207</sup> This finding is supported by an updated analysis in 2005 covering sub-Saharan Africa and South East Asia. This study additionally showed that treatment of smear-negative and extra-pulmonary cases in DOTS programmes and treatment of multidrug-resistant cases in DOTS-Plus programmes is also highly cost effective.<sup>208</sup>

## 12 Clinical quality improvement

The following clinical parameters, based on recommendations in these guidelines are proposed:

1. Percentage of patients with unexplained cough of more than 3 weeks, with tuberculosis diagnosis ruled out.
2. Percentage of tuberculosis patients who have a relevant clinical specimen(s) sent for mycobacterial cultures.
3. Percentage of patients who are assigned to DOT out of all index tuberculosis cases in a given year.
4. Percentage of tuberculosis patients who achieve 1-year treatment completion rate.
5. Cure rate\* at one year for smear/culture positive pulmonary tuberculosis.
6. Percentage of delays in notification of suspect or confirmed tuberculosis cases (MD532), i.e. submitted more than 72 hours after diagnosis.
7. Percentage of delays in submission of treatment progress form (MD117), i.e. submitted more than two weeks after the declared follow-up appointment date.

\***Cure rate** (for treatment cohort for smear/culture + pulmonary tuberculosis only) is defined as:

No. of cured cases (initially smear or culture positive patients who have completed treatment and who had at least 2 negative sputum smear and/or culture during the continuation phase, one of which was at the end of treatment)

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Total no. of cases with smear and or culture positive started on treatment



**D** Recommendations for sputum collection are as follows:

### 1. General

- a) Specimens should be collected before starting patients on anti-tuberculosis drug therapy.
- b) Sputum specimens should be collected in a well-ventilated area and precautions should be taken to ensure that health care workers and others are not exposed to infectious aerosols and materials. Contaminated materials should be disposed of in accordance with standard biosafety procedures.
- c) Specimens should be obtained under the direct supervision of a healthcare worker.

### 2. Procedure for sputum collection

- a. Sputum must be collected in sterile, screw-capped, leak-proof, disposable, plastic containers. Containers must be free from paraffin and other waxes or oils. The container should be clear so the specimen can be visualised without opening the container.
- b. Sputum collection visualised should be labelled with the patient's name, NRIC number, nature of specimen, date and time of collection. The label should be on the side of the container instead of the lid.
- c. Patients should be instructed to:
  - i. Collect the specimen in the morning before any oral intake.
  - ii. Rinse his or her mouth with water before starting to collect the specimen to remove contamination such as food particles and bacteria. Patients with postnasal discharge should clear these passages before beginning sputum collection.
  - iii. Cough from as deep inside the chest as possible as it is important to collect sputum and not saliva.
    1. Instruct patient to take a deep breath, hold his/her breath for a few seconds, and then exhale slowly.
    2. Do this twice.


3. The third time, inhale deeply, hold his/her breath, and then forcefully exhale through the mouth.
  4. The fourth time, inhale deeply and cough. Instruct patient to carefully direct the sputum into the container to minimise contamination of the outside of the container for safe handling.
  5. Patient is to repeat the process until at least 5 ml of specimen has been obtained.
- d. The healthcare worker supervising the sputum collection may rap gently and firmly on the applicant's back to help induce coughing and sputum production.
  - e. The supervising healthcare worker should inspect the specimen to ensure that it contains sputum and not saliva. Sputum is frequently thick and mucoid, but may consist of dull white or light green fluid with fine chunks of dead tissue that show up like solid flakes. Blood may or may not be present. In contrast, saliva appears thin and nearly clear; and should not be accepted.
  - f. The specimen container should be capped tightly to avoid leakage. Wipe off the outside of the container with a clean tissue before placing into a biohazard-labelled plastic specimen bag. Each specimen should be accompanied by a request with relevant patient and clinical data.
  - g. The healthcare worker and patient should practise hand hygiene after specimen collection to prevent transmission of microorganisms.
  - h. The specimen should be delivered to the laboratory as soon as possible after collection to minimise overgrowth of commensal bacteria or deterioration of the mycobacteria.

**Grade D, Level 4**

# Annex 1 MD 532 Notification of Tuberculosis

## MD 532 NOTIFICATION OF TUBERCULOSIS

http://www.moh.gov.sg/content/dam/moh\_web/Forms/MD532\_19%20Dec%20 8.pdf


 <p><b>NOTIFICATION OF TUBERCULOSIS (MD 532)</b></p> <p>1. Notification date (dd/mm/yy)</p> <p>_____</p>		<p>This notification form <b>must</b> be completed and faxed not later than 72 hours from the time of diagnosis, to:</p> <p><b>The Director, TB Control Unit c/o STEP REGISTRY 142 Moulmein Road Singapore 308087 Tel: 6258-4369 Fax: 6252-4051</b></p>																											
<b>PERSONAL PARTICULARS</b>																													
<p>2. Name (as in NRIC/Passport/other document)</p> <p>3. NRIC/ Passport/ Foreign Identification No.</p> <p>4. Gender <input type="checkbox"/> Male <input type="checkbox"/> Female</p> <p>5. Ethnic group</p> <p><input type="checkbox"/> Chinese <input type="checkbox"/> Indian <input type="checkbox"/> Caucasian</p> <p><input type="checkbox"/> Malay <input type="checkbox"/> Eurasian <input type="checkbox"/> Others (please specify) _____</p> <p>6. Date of birth (dd/mm/yy) / (if unknown please specify age)</p> <p>_____</p>		<p>7. Marital Status</p> <p><input type="checkbox"/> Single <input type="checkbox"/> Widowed</p> <p><input type="checkbox"/> Married <input type="checkbox"/> Divorced</p> <p><input type="checkbox"/> Separated <input type="checkbox"/> Unknown</p> <p>8. Occupation</p>																											
<p>9. Residence</p> <p>Name (If place of residence is long-term care facility)</p> <p>House / Blk no.    Unit no.    Contact no.</p> <p>_____ # _____ (H) _____ (Pg/HP)</p> <p>Street name _____ Postal code _____</p>		<p>10. Housing type</p> <p><input type="checkbox"/> HDB 1&amp;2 rm</p> <p><input type="checkbox"/> HDB 3 rm</p> <p><input type="checkbox"/> HDB 4 rm</p> <p><input type="checkbox"/> HDB 5 rm &amp; above</p> <p><input type="checkbox"/> HUDC</p> <p><input type="checkbox"/> Private condominium/apartment</p> <p><input type="checkbox"/> Landed property</p> <p><input type="checkbox"/> Others (specify) _____</p>																											
<p>11. Workplace/School (if applicable)</p> <p>Name</p> <p>House / Blk no.    Unit no.    Contact no.    Ext.</p> <p>_____ # _____ _____ _____</p> <p>Street name _____ Postal code _____</p>		<p>12a. Residential status (tick all that apply)</p> <table border="0"> <tr> <td><input type="checkbox"/> Singapore citizen (pink NRIC)</td> <td>Holder #</td> <td>Applicant #</td> </tr> <tr> <td><input type="checkbox"/> Permanent resident (blue NRIC)</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/> Work permit</td> </tr> <tr> <td><input type="checkbox"/> Short-term social visitor</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/> Employment pass</td> </tr> <tr> <td><input type="checkbox"/> Illegal immigrant</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/> Student pass</td> </tr> <tr> <td><input type="checkbox"/> Others (please specify) _____</td> <td><input type="checkbox"/></td> <td><input type="checkbox"/> Dependant pass</td> </tr> <tr> <td></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/> Long-term social visit pass</td> </tr> <tr> <td></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/> Professional visit pass</td> </tr> <tr> <td></td> <td><input type="checkbox"/></td> <td><input type="checkbox"/> Special pass</td> </tr> </table> <p>12b. If PR applicant, tick here <input type="checkbox"/> #Please indicate pass no. _____</p>		<input type="checkbox"/> Singapore citizen (pink NRIC)	Holder #	Applicant #	<input type="checkbox"/> Permanent resident (blue NRIC)	<input type="checkbox"/>	<input type="checkbox"/> Work permit	<input type="checkbox"/> Short-term social visitor	<input type="checkbox"/>	<input type="checkbox"/> Employment pass	<input type="checkbox"/> Illegal immigrant	<input type="checkbox"/>	<input type="checkbox"/> Student pass	<input type="checkbox"/> Others (please specify) _____	<input type="checkbox"/>	<input type="checkbox"/> Dependant pass		<input type="checkbox"/>	<input type="checkbox"/> Long-term social visit pass		<input type="checkbox"/>	<input type="checkbox"/> Professional visit pass		<input type="checkbox"/>	<input type="checkbox"/> Special pass	<p>13. Country of citizenship    14. Country of birth</p> <p>15. When first arrived in Singapore (if not born in Singapore)</p> <p>16. Type of long-term care facility (if applicable)</p> <p><input type="checkbox"/> Home for the aged/aged sick</p> <p><input type="checkbox"/> Psychiatric hospital</p> <p><input type="checkbox"/> Prison or other correctional facility</p> <p><input type="checkbox"/> Others (please specify) _____</p>	
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<p>17a. Patient category*</p> <p><input type="checkbox"/> New case</p> <p><input type="checkbox"/> Relapse (state year previously treated) _____</p> <p><input type="checkbox"/> Reinstatement</p> <p><input type="checkbox"/> Uncertain</p>		<p>18. Case diagnosed through</p> <p><input type="checkbox"/> Symptoms of disease    <input type="checkbox"/> Incidental finding</p> <p><input type="checkbox"/> Screening of contacts    <input type="checkbox"/> Mobile CXR</p> <p><input type="checkbox"/> Pass application/renewal    <input type="checkbox"/> Others# _____</p>																											
<p>17b. If transferred from overseas, tick here <input type="checkbox"/></p>		<p>19a. Status at diagnosis</p> <p><input type="checkbox"/> Alive    <input type="checkbox"/> Dead</p> <p>19b. If patient died, please indicate date (dd/mm/yy)</p> <p>_____</p>																											
<p>* DEFINITIONS</p> <p><b>Patient category</b></p> <p><b>New:</b> Patient who never previously received treatment for more than 1 month.</p> <p><b>Relapse:</b> Patient who previously completed treatment or was treated and declared cured prior to developing active TB again.</p> <p><b>Reinstatement:</b> Patient who previously had not completed treatment and now returns after one year of last being on medication.</p> <p><b>Treatment delivery mode</b></p> <p><b>DOT:</b> Directly Observed Treatment, i.e. a health care worker watches as the patient swallows each dose of TB medication.</p> <p><b>Polyclinic DOT:</b> DOT carried out by the nurses at the government polyclinics.</p> <p><b>Institutionalised DOT:</b> DOT carried out by health care workers at hospitals, nursing or community homes or correctional facilities.</p> <p><b>Outreach DOT:</b> DOT carried out by health care workers at the patient's home.</p> <p><b>Other DOT:</b> e.g. DOT carried out by a health care workers at general practitioner clinic, school, army camp.</p> <p><b>SAT:</b> Self Administered Treatment</p>																													

PTO

<b>NRIC/ Passport/ Foreign Identification No.</b> <b>20. Concurrent medical conditions</b> (Tick all that apply) <input type="checkbox"/> Diabetes mellitus <input type="checkbox"/> Steroid therapy <input type="checkbox"/> End stage renal failure <input type="checkbox"/> Impaired immunity other than HIV <input type="checkbox"/> Cancer <input type="checkbox"/> Others (please specify) <input type="checkbox"/> HIV test done: Yes/No _____ If Yes, result of latest test: <b>Reactive/Non-reactive</b> <b>Date of test</b> _____		<b>21. No. of BCG scars</b> <input type="checkbox"/> 0 <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> Unknown	<b>23. CXR Date:</b> _____ <input type="checkbox"/> Normal <input type="checkbox"/> Scar (old TB) <input type="checkbox"/> Active TB (with cavitation) <input type="checkbox"/> Active TB (without cavitation) <input type="checkbox"/> Millitary TB <input type="checkbox"/> Not done <input type="checkbox"/> Others (Specify) _____																																
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<b>26a. Date started (dd/mm/yy)</b> _____		<b>27a. State reason</b> <input type="checkbox"/> Patient referred to other treatment centre (complete item 27b,c,d) <input type="checkbox"/> Patient recalled for treatment (complete item 27d) <input type="checkbox"/> Not suitable for treatment due to medical contraindication (please specify) _____ <input type="checkbox"/> Others (please specify) _____																																	
<b>26b. Treatment centre</b> <input type="checkbox"/> TBCU <input type="checkbox"/> SATA <input type="checkbox"/> TTSH <input type="checkbox"/> Polyclinic <input type="checkbox"/> NUH <input type="checkbox"/> General practitioner (please specify) <input type="checkbox"/> SGH <input type="checkbox"/> CGH <input type="checkbox"/> Private hospital/specialist (please specify) <input type="checkbox"/> AH		<b>27b. Name of hospital/centre/clinic referred to</b> _____																																	
<b>26c. Intended duration</b> <input type="checkbox"/> 6 months <input type="checkbox"/> 18-24 months <input type="checkbox"/> Others   _____ months <input type="checkbox"/> 9 months <input type="checkbox"/> Unknown		<b>27c. Name of physician referred to</b> _____																																	
<b>26d. Intended regimen (e.g. 2HRZ/4H<sub>r</sub>)</b> _____ Tick if Fixed Dose Combination used <input type="checkbox"/>		<b>27d. Appointment date (dd/mm/yy)</b> _____																																	
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<b>28. Name and Signature of Notifying Doctor:</b>		<b>30. Name of clinic/hospital/institution:</b> <b>Department / Ward (if applicable) :</b>																																	
<b>29. MCR NO:</b>		<b>31. Address of clinic/hospital/institution:</b> (Tel) _____ (Fax) _____ Postal code _____																																	

# Annex 2 MD 117 Treatment Progress Report

[http://www.moh.gov.sg/content/dam/moh\\_web/Forms/Treatment%20progress%20MD117.pdf](http://www.moh.gov.sg/content/dam/moh_web/Forms/Treatment%20progress%20MD117.pdf)

 Ministry of Health Singapore	<b>TREATMENT PROGRESS REPORT (MD 117)</b>	This notification form <b>must</b> be completed promptly for all cases of active Tuberculosis. Completed form is to be <b>posted</b> or <b>faxed</b> to: <b>The Director, TB Control Unit</b> c/o STEP REGISTRY 142 Moulinet Road Singapore 308087 Tel: 6258-4369 Fax: 6252-4051
1. Date (dd/mm/yy) : <input style="width: 100px;" type="text"/>		
<b>A. Patient Particulars</b>		
2. Name	4. Name and Signature of Attending Doctor:	
3. NRIC/Passport/FIN no.	5. MCR No.	
<b>B. Treatment Centre</b>		
6. Current treatment centre <span style="float: right;">Name &amp; Address of Treatment Centre (* please specify)</span>		
<input type="checkbox"/> TBCU <input type="checkbox"/> TTSH <input type="checkbox"/> CGH <input type="checkbox"/> AH <input type="checkbox"/> SGH <input type="checkbox"/> NUH <input type="checkbox"/> SATA <input type="checkbox"/> Others #		
Department / Ward		Telephone      Fax
<b>C. Treatment Progress</b>		
If patient data not available, please state reason and give details of arrangements for follow-up of TB treatment (e.g. if admitted to hospital for cause other than TB)		
7. Is patient compliant*?      If No, please indicate action(s) taken :		
<input type="checkbox"/> Yes <input type="checkbox"/> Reinforced compliance <input type="checkbox"/> Changed from SAT to DOT <input type="checkbox"/> Others _____ <input type="checkbox"/> No <input type="checkbox"/> Changed regimen <input type="checkbox"/> Transferred to TBCU      (please specify)		
8. Latest smear results :      Not done / Negative / + / ++ / +++ / ++++ / Contaminated ( <b>circle one</b> )		
Lab No: _____		Date (dd/mm/yy): _____
<b>Management Decision</b>		<b>13. Transfer Centre - Follow Up</b>
9.a Continue previous regimen <input type="checkbox"/> 9.b Start or change regimen <input type="checkbox"/>		If patient is transferred to another treatment centre for TB treatment, please indicate:
_____ Drugs prescribed at this visit (Please state drugs)		a. Appointment date (dd/mm/yy) <input style="width: 100px;" type="text"/>
10. Treatment delivery mode (each visit) *		b. Treatment centre/hospital:
<input type="checkbox"/> Polyclinic DOT <input type="checkbox"/> SAT <input type="checkbox"/> Outreach DOT <input type="checkbox"/> Institutionalised DOT		<input type="checkbox"/> TBCU <input type="checkbox"/> TTSH <input type="checkbox"/> CGH <input type="checkbox"/> AH <input type="checkbox"/> SGH <input type="checkbox"/> NUH <input type="checkbox"/> SATA <input type="checkbox"/> Others #
11. Temporarily cease treatment (if applicable):		(* please specify) c. Name and Address
Reason: <input type="checkbox"/> Drug reaction <input type="checkbox"/> Refusal of treatment <input type="checkbox"/> Others (Specify) _____		_____ Telephone      Fax
12. Duration to next TCU :		<b>14. Final Outcome</b>
<input style="width: 30px;" type="text"/> <input style="width: 30px;" type="text"/> weeks		Date of final outcome _____
		<input type="checkbox"/> Completed treatment* Cured * ? <input type="checkbox"/> Yes <input type="checkbox"/> No
		Final regimen used (e.g. 2HRZ/4H <sub>r</sub> ) _____
		<input type="checkbox"/> Drug reaction, decided no further action <input type="checkbox"/> Left country <input type="checkbox"/> Diagnosis revised (not TB, specify diagnosis) _____ <input type="checkbox"/> Lost to follow-up after refusing treatment <input type="checkbox"/> Lost to follow-up after starting treatment (Defaulted) <input type="checkbox"/> Died of
		<input type="checkbox"/> TB <input type="checkbox"/> Other Cause (specify): _____
		<input type="checkbox"/> Others (specify) _____

\* See reverse for definitions.

## **\*DEFINITIONS**

### ***Compliant to Treatment***

Patient who has consumed at least 80% of prescribed medications in the judgement of the attending physician.

### ***Completed Treatment***

Patient who has been compliant with at least 80% of medications for the total length of treatment, in the judgement of the attending physician.

### ***Cured***

Sputum smear or culture positive patient who has completed treatment, and who had at least 2 negative sputum smears and/or cultures during the continuation phase, one of which was at the end of treatment.

### ***Treatment delivery mode:***

**DOT:** Directly Observed Treatment, ie. a health care worker watches as the patient swallows each dose of TB medication.

**Polyclinic DOT:** DOT carried out by the nurses at the government polyclinics.

**Institutionalised DOT:** DOT carried out by health care workers at hospitals, nursing or community homes or correctional facilities.

**Outreach DOT:** DOT carried out by STEP designated health care workers at the patient's home or workplace.

**SAT:** Self Administered Treatment

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## Self-assessment (MCQs)

After reading the Clinical Practice Guidelines, you can claim one CME point under Category 3A (Self-Study) of the SMC Online CME System. Alternatively, you can claim one CME point under Category 3B (Distance Learning - Verifiable Self Assessment) if you answer at least 60% of the following MCQs correctly. You can submit your answers through the SMJ website at this link: <http://sma.org.sg/publications/index.aspx?ID=26> (the link will only be available once the March 2016 issue of the SMJ becomes available). The answers will be published in the SMJ May 2016 issue and at the MOH webpage for these guidelines after the period for submitting the answers is over.

*Instruction: Choose True or False.*

- |  | True                     | False                    |
|--|--------------------------|--------------------------|
| 1. Pertaining to Latent Tuberculosis Infection:  |                          |                          |
| A) A person with Latent Tuberculosis Infection can transmit the tuberculosis bacillus to others.   | <input type="checkbox"/> | <input type="checkbox"/> |
| B) The highest risk period for progression of Latent Tuberculosis Infection to active disease is the first two years after infection.  | <input type="checkbox"/> | <input type="checkbox"/> |
| C) HIV infection carries the same risk as diabetes of progression of Latent Tuberculosis Infection to active tuberculosis.   | <input type="checkbox"/> | <input type="checkbox"/> |
| D) Both the tuberculin skin test (TST) and interferon gamma release assay (IGRA) do not distinguish recently acquired Latent Tuberculosis Infection from that acquired in the remote past. | <input type="checkbox"/> | <input type="checkbox"/> |
| 2. Pertaining to active tuberculosis:  |                          |                          |
| A) Tuberculosis affects the lungs in ~50% of cases.  | <input type="checkbox"/> | <input type="checkbox"/> |
| B) The person with pulmonary tuberculosis may present with an abnormal chest x-ray in the absence of any symptoms.   | <input type="checkbox"/> | <input type="checkbox"/> |
| C) Persons with diabetes have a three-fold higher risk of tuberculosis than non-diabetics.   | <input type="checkbox"/> | <input type="checkbox"/> |
| D) Close contacts of persons with lymph node tuberculosis should be screened.  | <input type="checkbox"/> | <input type="checkbox"/> |

	<b>True</b>	<b>False</b>
3. Pertaining to evaluation of patients for active tuberculosis:		
A) Patients undergoing evaluation for tuberculosis in extrapulmonary sites (e.g. tuberculosis lymph node, tuberculous meningitis) should have samples sent for Xpert/RIF as well as for tuberculosis culture and drug susceptibility testing.	<input type="checkbox"/>	<input type="checkbox"/>
B) There is no need to perform sputum sampling for AFB smear and tuberculosis culture and drug susceptibility testing in persons with typical chest radiograph features of tuberculosis.	<input type="checkbox"/>	<input type="checkbox"/>
C) The elderly person with tuberculosis may present with non-specific signs and symptoms.	<input type="checkbox"/>	<input type="checkbox"/>
D) Extrapulmonary tuberculosis is more common in young children.	<input type="checkbox"/>	<input type="checkbox"/>
4. Pertaining to tuberculosis in Singapore:		
A) Non-residents comprised approximately half the total number of tuberculosis cases in Singapore in 2013.	<input type="checkbox"/>	<input type="checkbox"/>
B) The Chinese have the highest tuberculosis incidence rate among the three main ethnic groups in Singapore.	<input type="checkbox"/>	<input type="checkbox"/>
C) BCG vaccination is given at birth to protect against tuberculosis in adulthood.	<input type="checkbox"/>	<input type="checkbox"/>
D) A key intervention of the Singapore Tuberculosis Elimination Programme is the surveillance of treatment progress and outcome of all tuberculosis cases in Singapore.	<input type="checkbox"/>	<input type="checkbox"/>
5. Pertaining to tuberculosis risk factors:		
A) Cigarette smoking is associated with an increased risk for tuberculosis.	<input type="checkbox"/>	<input type="checkbox"/>
B) Persons with end-stage renal failure are not at higher risk for tuberculosis.	<input type="checkbox"/>	<input type="checkbox"/>
C) Use of TNF-alpha blockers increases the risk of progression of latent to active tuberculosis.	<input type="checkbox"/>	<input type="checkbox"/>
D) HIV infection is the most important known risk factor for tuberculosis.	<input type="checkbox"/>	<input type="checkbox"/>

## Workgroup members

The members of the workgroup, who were appointed in their personal professional capacity, are:

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