Tuberculosis case management at the Auckland and Northland region DHBs: the diagnostic, clinical and public health processes in adults

Auckland version

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Auckland/Northland Regional TB Liaison Group (TBLG)
Purpose of this document

This document summarises key points from the *Guidelines for Tuberculosis Control in New Zealand 2010* (available from [http://www.moh.govt.nz/cd/tbcontrol](http://www.moh.govt.nz/cd/tbcontrol)). The aim of the document is to provide an evidence-based, standardised and concise TB case management tool. This document should always be used in conjunction with the full *Guidelines for Tuberculosis Control in New Zealand 2010*. Readers are directed in each section of this document to the relevant section/pages of the *Guidelines for Tuberculosis Control in New Zealand 2010*.

The intended audience for this document is clinical staff working in services at the three Auckland region DHBs and the Northland DHB, who regularly or occasionally may see adult patients with TB.

The document excludes management of TB in children, which is challenging to diagnose and treat. Children 15 years of age and younger who are suspected to have TB or are diagnosed with TB should always be discussed promptly with a Paediatrician (in the Auckland region, discuss with a clinician from the Paediatric Infectious Disease Service at Starship Children’s Hospital).

The document was drafted by a Public Health Medicine registrar and the Medical Officer of Health working in TB control at Auckland Regional Public Health Service, on behalf of members of the Auckland regional TB Liaison Group (TBLG, which has representatives from each of the DHBs who are experienced in treating patients with TB). A draft copy of the document was forwarded for comment to relevant clinical staff at the three Auckland region DHBs, as well as to the Northland Medical Officer of Health who circulated it to public health and clinical staff at the Northland DHB.

Once reviewed, amended and agreed by the TBLG members, the document was signed off by the TBLG. The document will be reviewed every three years by Medical Officers of Health from ARPHS and the Northland DHB, and the TBLG. It will be reviewed earlier if there are significant changes to the *Guidelines for Tuberculosis Control in New Zealand 2010* in the interim.
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1 Clinical features, investigation and diagnosis of active TB
disease in adults

1.1 Clinical features

1.1.1 General symptoms of active TB

Active tuberculosis (TB) disease refers to individuals with evidence of replicating TB organisms, demonstrated by smear or culture, or by granulomatous inflammation on histology, or by other suggestive tests.

Active TB may be asymptomatic particularly in the early stages of disease, but the usual clinical features include malaise, fever, anorexia, weight loss and night sweats.

1.1.2 Pulmonary TB

Pulmonary TB is the most common presentation of active TB worldwide, and may occur along with extrapulmonary TB. Pulmonary TB may be asymptomatic initially, but as the extent and severity of the disease progress, symptoms appear. Along with the general symptoms mentioned above, other clinical features of pulmonary TB may include:

- a dry cough, subsequently becoming productive
- haemoptysis, particularly in cavitatory disease, but may also occur in inactive (past) TB with bronchiectasis
- breathlessness, often a late feature when parenchymal destruction or pleural effusion has occurred.

1.1.3 Extrapulmonary TB

TB can affect any organ system in the body.

The most common form of extrapulmonary TB is TB lymphadenitis, particularly in the cervical or mediastinal regions. However TB adenitis can involve any lymph node group. It is often painless, but acute inflammation and pain can occur.

Isolated pleural TB (without pulmonary involvement) is the next most common form of extrapulmonary TB and may present with chest discomfort or breathlessness. Pleural TB may also complicate pulmonary TB but would not then be classed as extrapulmonary.

Abdominal TB may present in peritoneal, enteric, hepatic and biliary forms, and is often associated with prominent systemic symptoms and weight loss. Symptoms of peritoneal TB, the commonest form of intra-abdominal TB, are often insidious, with abdominal pain and distention as well as systemic symptoms of TB. Ileo-caecal and ano-rectal disease are the most common forms of enteric TB. Hepatic and biliary TB is also insidious and difficult to diagnose and frequently present with systemic symptoms of TB and deranged liver function tests (LFT’s). It is often uncertain whether abnormal liver function tests (LFTs), which are commonly found in association with extensive TB, are due to TB involvement of the liver or due to non-specific hepatotoxicity caused by the major infection.

Genitourinary TB, especially renal TB and female genital TB, is often asymptomatic and diagnosis is often delayed, which may result in renal impairment or infertility. The most common manifestation of renal TB is sterile pyuria, and female genital tract TB is an important cause of infertility.

Central nervous system (CNS) TB causes significant morbidity and mortality, onset is often insidious and diagnosis is often delayed. Non-specific neurological symptoms including
headaches are most common initially, proceeding to symptoms and of meningitis plus progressive deterioration in level of consciousness, with focal signs less common.

Cardiovascular TB is rare, but pericardial TB is its most common form, often presenting with heart failure or pericarditis symptoms and may lead to permanent morbidity from constrictive pericarditis.

TB may also affect bones and joints, the eye, ear, skin or endocrine organs (adrenal, pituitary and thyroid).

Disseminated TB (TB involving multiple body systems) and miliary TB (multiple < 2mm nodules of active TB throughout the body) are caused by blood-borne spread. These are life threatening conditions with high morbidity and mortality. Presenting features usually include systemic symptoms such as weight loss and fevers, but other manifestations are protean.

1.2 Investigation and diagnosis

Investigation for active TB disease primarily relies on

- chest X-ray (CXR) and
- examination of appropriate specimens (according to the possible site(s) of TB disease) for acid-fast bacilli (AFB) smear, mycobacterial culture and histological demonstration of necrotising granulomatous inflammation.

Most immunocompetent patients who have a normal chest x-ray will not have active TB but the diagnosis should still be considered if there is a high clinical suspicion or immune compromise and further investigations including CT imaging, host defence assessment and sputum for TB culture may be required.

Investigations should be carried out so as to maximise the chance of identifying the organism and its drug sensitivity pattern. This is particularly important when drug resistant TB is possible or suspected.

1.2.1 Chest X-ray

Chest X-ray (CXR) is an essential test whenever TB (pulmonary or extrapulmonary) is considered.

A normal CXR does not exclude extrapulmonary TB, therefore appropriate testing should be pursued if the patient has suggestive systemic or site-specific symptoms.

In an immune competent patient, pulmonary TB is an unlikely diagnosis when a CXR is normal or lacks the typical features of TB, and in this situation, invasive tests for TB are unlikely to yield positive results.

If TB remains strongly suspected, a CT scan may be helpful or the patient should be reassessed with a repeat CXR 2-3 weeks later.

Patients with HIV/AIDS or other immunosuppressive illnesses (such as diabetes) may have active pulmonary TB in the presence of a normal CXR or minor/atypical CXR changes. Therefore if TB is suspected in these patients, immediate sputum testing is justified, even if the CXR is normal.

Table 1.1 provides an overview of CXR appearances in active and inactive TB.

Table 1.2 outlines the radiological criteria for pursuing detailed mycobacteriological tests (induced sputum testing and bronchoscopy).
### Table 1.1: Typical chest X-ray features in tuberculosis
Reproduced from *Guidelines for Tuberculosis Control in New Zealand 2010 Table 2.1, section 2.4.2*

<table>
<thead>
<tr>
<th>Anatomical site</th>
<th>Favour active tuberculosis</th>
<th>Favour inactive tuberculosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Consolidation, variable size:</td>
<td>Linear scarring</td>
</tr>
<tr>
<td></td>
<td>• unifocal, commonly</td>
<td>Dense scarring</td>
</tr>
<tr>
<td></td>
<td>• ‘soft’, ‘fluffy’ areas with poorly defined margins</td>
<td>Volume loss</td>
</tr>
<tr>
<td></td>
<td>Cavities</td>
<td>Destroyed lobe or lung</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Calcification</td>
</tr>
<tr>
<td></td>
<td>Nodules:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• focal, non-calcified; or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• miliary pattern</td>
<td></td>
</tr>
<tr>
<td>Mediatinum and hilar</td>
<td>Lymphadenopathy* – hilar and/or paratracheal</td>
<td>Calcified lymph nodes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pericardial calcification</td>
</tr>
<tr>
<td>Pleura</td>
<td>Pleural effusion/empyema</td>
<td>Pleural thickening:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• basal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• apical (irregular, &gt; 1 cm thickness)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pleural calcification</td>
</tr>
</tbody>
</table>

**Notes:**
* Lymphadenopathy is very common in paediatric tuberculosis (TB).
Most of these chest X-ray features are not specific to TB.
High-resolution chest CT (computed tomography) is more sensitive at detecting cavities, lymphadenopathy, the factors contributing to ‘apical fibrosis’, and post-TB complications such as bronchostenosis and bronchiectasis.
Table 1.2: Radiological criteria for detailed mycobacteriological tests*
Reproduced from Guidelines for Tuberculosis Control in New Zealand 2010 Table 2.2, section 2.4.2

<table>
<thead>
<tr>
<th>Chest X-ray shows</th>
<th>Do sputum (three times) (or bronchoscopy and broncho-alveolar lavage)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No abnormality</td>
<td>No (except that in HIV-positive(^1) patients the chest X-ray in tuberculosis may be normal)</td>
</tr>
<tr>
<td>Calculated lymph nodes or pleura, with normal parenchyma</td>
<td>No</td>
</tr>
<tr>
<td>Minor apical pleural thickening only</td>
<td>No</td>
</tr>
<tr>
<td>Single granuloma less than 10 mm</td>
<td>No</td>
</tr>
<tr>
<td>Minor lobar scarring or several tiny less than 3 mm dots of calcification</td>
<td>Yes</td>
</tr>
<tr>
<td>Larger focal areas of scarring</td>
<td>Yes</td>
</tr>
<tr>
<td>Possible patchy consolidation or infiltration</td>
<td>Yes and consider transbronchial lung biopsies</td>
</tr>
<tr>
<td>Definite infiltration or consolidation or cavitation</td>
<td>Yes and consider transbronchial lung biopsies</td>
</tr>
</tbody>
</table>

Notes:
* Induced sputum is the preferred procedure.
† Tests shown are for subjects at risk of tuberculosis who have no sputum or little sputum that is smear- or culture-negative.

1.2.2 Specimens for AFB smear, mycobacterial culture and histology

- If pulmonary TB is suspected, three (preferably early morning) sputum specimens should be sent for TB testing. In general, all three samples are processed for both AFB smear and TB culture. PCR testing is also available.

- Induced sputum testing is better than bronchoscopy for the diagnosis of active pulmonary TB, and is more sensitive than bronchoscopy in smear-negative cases. It is the preferred method of obtaining specimens for smear and culture if the patient cannot produce sputum. Induced sputum testing must be carried out under respiratory isolation conditions i.e. in an Airborne Infection Isolation (AI1) Room.

- Bronchoscopy poses a greater risk of nosocomial transmission of pulmonary TB than induced sputum testing carried out under respiratory isolation conditions. If bronchoscopy is indicated, broncho-alveolar lavage (BAL) should be used to obtain specimens as it produces a better yield than bronchial washings. Where TB is a possible diagnosis, bronchoscopy should be performed under respiratory isolation conditions.

- Gastric aspirates are used mainly in children where pulmonary TB is suspected or needs to be excluded, and spontaneous sputum cannot be produced.

- Tissue specimens obtained by bronchoscopy, fine needle aspiration (FNA) or excision biopsy should be sent separately in saline (for TB culture) as well as in formalin (for histology).

- Imaging such as CT, ultrasound or endobronchial/endoscopic ultrasound may help to guide FNA. Several FNA specimens should be sent for AFB smears and TB culture (and TB PCR if necessary). It is often not possible to obtain an adequate amount of tissue from an FNA and this limits the yield from culture and the ability to have drug susceptibility results to guide treatment. If adequate tissue cannot be obtained by FNA, excision biopsy should be considered and undertaken before starting treatment.

\(^1\) This should also apply to patients with significant immunocompromise due to causes other than HIV.
• Routine urine microscopy for the presence of sterile pyuria should be performed when TB is suspected. The culturing of early morning urine (EMU) specimens for TB is expensive and the yield is very low. If sterile pyuria is demonstrated on microscopy, always eliminate any obvious cause first (e.g. menstruation or on a treatment course for bacterial urinary tract infection); then repeat MSU; if sterile pyuria is still demonstrated and TB is suspected, then send three EMU specimens for TB testing.

• Blood culture for mycobacteria is an important test in patients with advanced HIV infection or other severe immune compromise and in whom TB is suspected.

• According to the possible site(s) of TB disease, other specimens may need to be obtained, for example lymph node FNA or excision biopsy; pleural, pericardial or peritoneal fluid and/or biopsy specimens; lumbar puncture (preceded by CT scan if available).

1.2.3 Other routine tests

Other routine tests recommended in patients suspected/diagnosed with TB include

• HIV test – should be offered to every patient suspected of having or diagnosed with TB, as each disease affects the course of the other

• Routine haematology and biochemistry – including FBC, creatinine, ALT (full LFT if ALT elevated), glucose (preferably fasting)

• Hepatitis B surface antigen as a minimum and hepatitis C serology

• Pregnancy test for women of childbearing age.

1.2.4 Tuberculin skin tests and interferon-gamma release assays

The Mantoux test is the form of tuberculin skin test (TST) used in New Zealand. TSTs and interferon-gamma release assays (IGRAs) are primarily tests for TB exposure and latent TB infection (LTBI). They are required only for assistance in the diagnosis of active TB when culture or histology is negative or inconclusive. They are not routinely used in the diagnosis of active TB.

A positive TST or IGRA result cannot distinguish between active TB disease and LTBI, and a TST or IGRA may be falsely negative in a person with active TB disease.

TST and IGRAs should not be repeated if previously documented to be positive or if there is a previous history of TB treatment.
2 Treatment of active TB disease in adults

2.1 Management principles

2.1.1 General principles

- Treatment regimens require 3 or more multiple drugs to which organisms are susceptible.
- Adherence to anti-TB treatment is paramount, and all possible measures within the limits of available resources should be made to ensure that patients do not miss doses or interrupt treatment. Directly Observed Therapy (DOT) is recommended in most situations to enhance adherence.
- Ethambutol should be part of the initial regimen for all adult TB patients and in most patients is continued for the entire intensive treatment phase.
- Single agents should not be added to an existing treatment regimen, particularly if the regimen is failing. The addition of two or more drugs is required if treatment failure is suspected.
- Ciprofloxacin is no longer recommended to treat either drug-susceptible or drug-resistant TB. Moxifloxacin is the fluoroquinolone that is currently used.
- All patients with multi-drug resistant TB (MDR-TB) or extensively drug-resistant TB (XDR-TB) require directly observed therapy (DOT).
- TB is a notifiable disease. A notification must be made to the Medical Officer of Health (MOH) whenever TB treatment is commenced for active or inactive TB.

2.1.2 Phases of treatment

Treatment of active TB usually includes two phases:

- the intensive phase of treatment – the bactericidal phase (when more drugs are used)
- the continuation phase – the sterilisation phase (when fewer drugs are used).

The standard treatment regimen for a fully sensitive TB isolate usually consists of four drugs during the intensive phase and two drugs during the continuation phase.

2.1.3 Abbreviations of treatment regimens

In a treatment regimen such as ‘2HREZ/4HR’, the number and letters before the backslash refer to the initial phase and those after it refer to the continuation phase. In this example, the treatment regimen is two months of daily isoniazid, rifampicin, ethambutol and pyrazinamide during the intensive phase followed by four months of daily isoniazid and rifampicin in the continuation phase. The absence of a subscript number means the drug is taken daily.

In a treatment regimen such as ‘H3R3’, the subscript numbers indicate the number of doses per week in an intermittent regimen. For example, H3R3 means a treatment regimen of three doses per week of isoniazid and three doses per week of rifampicin.

2.1.4 Dosing frequency, TB drug dosage recommendations

Whenever possible and practicable, daily dosing throughout the course of TB treatment is optimal for any TB patient. One alternative is daily dosing in the intensive phase, followed by intermittent dosing in the continuation phase. Another acceptable alternative, but only in HIV-negative patients with less severe/low burden TB disease, is intermittent dosing throughout the course of TB treatment.
Daily dosing can be self administered, or by directly observed therapy (DOT) if indicated. Intermittent regimens must always be given by three times per week (thrice weekly) DOT.

Daily dosing should ideally be given to all smear-positive pulmonary TB patients, as well as to patients with HIV-associated TB, at least during the intensive phase of treatment. A daily dosing schedule should be used for patients with miliary/disseminated TB, central nervous system TB and bone and joint TB. Daily dosing should also be for all patients with any drug resistance.

Dosage recommendations for TB drugs for adults are in Appendix 5.1.

Refer to section 4 and the Appendices for further details about adherence, dosing and DOT.

2.1.5 Pyridoxine

Pyridoxine is recommended in adult patients taking isoniazid and/or cycloserine.

- In patients taking isoniazid: it is advisable to give pyridoxine 10-25mg/day. Higher doses may interfere with isoniazid activity. Pyridoxine is essential for people at risk of peripheral neuropathy from other causes such as diabetes, chronic renal failure, malnourishment, alcoholism, HIV infection and pregnancy.
- In patients taking cycloserine: the pyridoxine dose should be 50mg for every 250mg of cycloserine prescribed.

2.1.6 Duration of treatment

The minimum recommended treatment periods for fully sensitive TB are shown below:

- **6 months**: pulmonary TB, most extrapulmonary TB (exceptions requiring longer treatment are listed below)
- **9-12 months**: bone or joint TB
- **12 months**: miliary TB, meningeal TB
- **12 months or longer**: intracerebral TB

Extending the duration of treatment is recommended for patients with:

- extensive TB disease, disseminated TB
- severe TB disease, including cavitatory pulmonary TB
- slow clinical or radiological improvement
- immunosuppressive conditions
- recurrent/relapsed TB (i.e. who are being retreated).

A longer minimum duration of 18-24 months is recommended for MDR-TB and XDR-TB.

2.2 Treatment regimens

2.2.1 Fully susceptible TB (pulmonary/extrapulmonary)

Adults should be treated with a standard six month regimen (2HREZ/4HR) consisting of:

- an intensive phase of isoniazid, rifampicin, ethambutol, and pyrazinamide for two months followed by
- a continuation phase of isoniazid and rifampicin for four months.

No other agents can be substituted in the intensive or continuation phase of treatment, as this would decrease the efficacy of the regimen and a longer duration of therapy would be required.
Ethambutol should be added to the initial regimen for the treatment of all TB patients until such time as drug susceptibility tests establish that it is not necessary. However in patients with a significant disease burden, even if the isolate is fully sensitive, consideration should be given to continuing ethambutol for the entire intensive phase of treatment (the first two months) or until smear conversion has occurred.

An injectable agent or moxifloxacin may be used instead of ethambutol when ethambutol is contraindicated in a patient who has been confirmed as having fully susceptible disease.

2.2.2 Mono- and poly-drug resistant TB

The duration of treatment must be re-evaluated when drug resistance is encountered. If drug resistance is suspected, multiple additional agents are required in the initial regimen. A daily dosing schedule should be used for all patients with confirmed or suspected drug-resistant TB. Daily DOT should be used in all of multiple drug resistance and may be necessary in cases of isoniazid resistance. Appendix 5.4 lists the drug regimens recommended for mono- and poly-drug resistance (but does not include regimens for MDR-TB or XDR-TB).

2.2.3 Multi-drug resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB)

MDR-TB is defined as TB that is resistant to rifampicin and isoniazid. Resistance to other drugs may or may not be present.

Resistance to rifampicin and isoniazid eliminates the two most important TB drugs from the treatment regimen.

XDR-TB is defined as MDR-TB that is also resistant to one or more of the fluoroquinolones and injectable agents.

Key recommendations for the treatment of MDR-TB include:

- prompt diagnosis and initiation of appropriate therapy
- treatment with a minimum of four or more drugs to which the patient has not been previously exposed and to which the isolate is susceptible
- the use of drug susceptibility testing (DST) to guide therapy
- ciprofloxacin should not be used as an anti-tuberculosis agent
- continuing treatment for at least 18 months past culture conversion
- immediate and adequate treatment of adverse effects
- mandatory daily DOT.

WHO classifies five different groups of drugs available for use for the treatment of MDR-TB. These groups provide a systematic method for allocating drugs to an MDR-TB treatment regimen. Treatment regimens should be designed with a consistent approach based on the hierarchy of the five groups of anti-tuberculosis drugs. See table 2.1 below. For further information about MDR-TB and XDR-TB, refer to Guidelines for Tuberculosis Control in New Zealand 2010, sections 3.5.4 and 3.5.5.
### Table 2.1: WHO classification of anti-TB drugs

<table>
<thead>
<tr>
<th>Group</th>
<th>Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1 – first line agents (oral)</td>
<td>Isoniazid, rifampicin, ethambutol, pyrazinamide</td>
</tr>
<tr>
<td>Group 2 – injectable agents</td>
<td>Streptomycin, amikacin, kanamycin, capreomycin</td>
</tr>
<tr>
<td>Group 3 – Fluoroquinolone group</td>
<td>Moxifloxacin, ofloxacin, levofloxacin, gatifloxacin</td>
</tr>
<tr>
<td>Group 4 – Other, second line agents (bacteriostatic)</td>
<td>Ethionamide, protonamide, cyloserine, PAS</td>
</tr>
<tr>
<td>Group 5 – Agents of uncertain efficacy (not routinely recommended)</td>
<td>Clofazamine, amoxicillin-clavulanate, clarithromycin, linezolid</td>
</tr>
</tbody>
</table>


All cases of MDR-TB must be treated by/in consultation with a tertiary centre experienced in the care of such patients. In the Auckland region, consult the ADHB Respiratory Service and/or ADHB ID service for advice and support.

### 2.3 Initiating treatment for TB: inpatient or outpatient

Extrapulmonary TB is non-infectious to others, and therefore only requires inpatient care for commencement of TB treatment if the patient is unwell.

However, pulmonary TB is potentially infectious to others, depending on the patient’s smear status. Smear-positive pulmonary TB patients pose the greatest risk of transmitting TB to others, with 4+ smear-positive patients being the most infectious and 1+ smear-positive patients the least infectious. Although smear-negative pulmonary TB patients pose a much lower infectious risk to others, they can pose a small risk, and their close contacts require follow up.

It is essential that exemplary infection control practices are maintained in all smear-positive pulmonary TB cases admitted to hospital, and this is particularly important in patients with drug-resistant TB.

If admitted to hospital, all smear-positive pulmonary TB patients should be placed in a negative pressure room and treated under respiratory isolation conditions. See section 2.4 on infection control.

Smear-negative, culture-positive pulmonary TB patients who are well can be commenced on treatment as outpatients in the community. However as smear-negative pulmonary TB does pose some infectious risk to others, a public health risk assessment should be done prior to commencement of treatment in these cases. It is also recommended that the patient should not have contact with previously unexposed or casually exposed people, especially children, until they have completed the first two weeks of their TB treatment.

### 2.4 Infection control

Isolation of patients with infectious TB is an important public health intervention. This may occur either in hospital or in the community.

Infectious patients should be admitted to hospital and isolated if they are:

- sufficiently unwell to require admission to hospital and/or
- unable or unwilling to comply with community infection control precautions.

In addition to Standard Precautions, inpatients with infectious pulmonary TB should be cared for using Airborne Precautions, which are designed to reduce the risk of airborne transmission...
of infectious agents. The patient should be placed in an AII room. All individuals entering the room must wear respiratory protection (N95 respirator) when entering the room. These should be fit tested.

For infectious patients who are not acutely ill, and where the home situation is suitable, home isolation and initiation of treatment in the community may be preferable. A Public Health Nurse (PHN) experienced in TB control should visit the home of the isolated patient as soon as possible and carry out a public health risk assessment with the patient and their family. If the risk is considered to be low then a home isolation agreement should be signed by the patient and the PHN (and the clinician, if appropriate).

Isolation requirements are that:

- the patient should stay at home
- the family must minimise the duration and number of visits by previously unexposed or casually exposed people (this is especially important if visitors are children – all visiting by children from outside of the family should not occur until the patient is smear-negative)
- where possible the patient should minimise contact with children less than five years of age
- previously unexposed people should not come to live with the family until sputum converts to negative
- the patient must wear a surgical mask when previously unexposed or casually exposed people (including visiting PHNs) visit the house. Visitors and PHNs need to wear a correctly fitted N95 mask
- the patient must cover their mouth when sneezing or coughing
- the patient needs to adhere to the schedule of medication and side-effect monitoring.

Isolation must continue until at least the following criteria have been met (for further information, see the decision table to aid discharge from isolation in Appendix 5.10):

- the patient has had a minimum of two weeks effective chemotherapy and
- the patient has stopped coughing and
- the patient is known to be infected with a fully susceptible strain of TB and
- the patient is responding well to treatment.

### 2.5 Corticosteroid treatment in the management of TB

Corticosteroids should only be given when adequate anti-tuberculosis treatment is also being given. Oral corticosteroids are no longer routinely recommended for TB pleural effusion, or for TB ascites.

Corticosteroid treatment is recommended in the following circumstances:

- TB meningitis
- TB pericarditis
- Life threatening illness due to advanced TB (e.g. sick patients with disseminated tuberculosis, with or without miliary pattern on CXR, and suspected hypoadrenalism)
- Urinary tract TB causing/at risk of causing stenosis (pelvi-ureteric junction, or ureterovesical junction).
2.6 Special situations associated with TB treatment

2.6.1 HIV-associated TB

The treatment of HIV-associated TB is complex and requires expertise in HIV and TB. HIV-associated TB requires appropriate and adequate treatment of TB. In the Auckland region, all cases of TB in patients with HIV infection should be managed by the infectious diseases department at Auckland City Hospital.

Duration:
- Six-month regimens are considered appropriate only for patients with fully sensitive TB who have limited disease.
- Treatment should be extended to a minimum of nine months for most patients especially in patients with more extensive disease, including cavitary disease or where there is a slow response to treatment.
- A six- to nine-month regimen is recommended for fully sensitive extrapulmonary TB unless there is central nervous system disease or bone and joint TB, which may require 12 months of treatment.

Dosing regimen:
- All patients with HIV-associated TB should receive daily therapy for the intensive phase (first eight weeks) of treatment. For the continuation phase, the optimal dosing frequency is also daily. If daily continuation phase treatment is not possible during the continuation phase, three times weekly dosing may be used in selected cases.
- Adverse events are common in TB patients with HIV infection. If available and subject to Public Health resources, directly observed therapy (DOT) is recommended for HIV-infected patients with TB disease. Anti-retroviral therapy (ART) should be started as soon as possible within the first eight weeks of starting TB treatment.

Treatment regimen in HIV-infected patients:
- There are significant drug-drug interactions between the rifamycin drugs (rifampicin and rifabutin) and antiretrovirals including both the protease inhibitors (PIs) and the non-nucleoside reverse transcriptase inhibitors (NNRTIs). See Appendix 5.2.1 for further detail on dosages for these drugs.
- In patients with HIV there may be up to a 70% reduction in serum TB drug concentrations compared with control subjects.
- In patients with advanced HIV and CD4+ counts below 100, there is an increased risk of acquired rifamycin resistance if these drugs are given intermittently and therefore intermittent dosing regimens should not be used.
- MDR-TB is a serious threat to patients with HIV infection and outcomes may be improved by ART and immune recovery.
- Preventive treatment for LTBI should be given to HIV infected patients with a Mantoux >5mm or a positive IGRA, previously documented positive Mantoux and no prior LTBI treatment, minor CXR abnormalities consistent with old TB, or documented recent exposure to a smear-positive TB case.

For further information, refer to Guidelines for Tuberculosis Control in New Zealand 2010, Chapter 6.
2.6.2 Renal impairment and dialysis

Isoniazid, rifampicin, pyrazinamide, ethionamide and proionomide are eliminated almost entirely by non-renal routes (i.e. by metabolism or biliary secretion). When prescribing TB drugs in a person with significant renal impairment, monitoring of blood levels may be required.

In patients on peritoneal dialysis, it is acceptable to give the normal dose of rifampicin and isoniazid. Ethambutol should be avoided unless absolutely necessary.

Isoniazid, rifampicin and ethambutol are not significantly removed by haemodialysis. Isoniazid and rifampicin can be given in their usual daily doses to patients on haemodialysis. Conventional doses are safe and effective. Ethambutol should be avoided unless absolutely necessary.

See Appendix 5.2.2 for doses of TB drugs in renal impairment. For further information, refer to Guidelines for Tuberculosis Control in New Zealand 2010, section 3.11.1.

2.6.3 Hepatic dysfunction

Hepatic dysfunction before TB treatment is started may be due to TB. If this is the cause of the hepatic dysfunction, improvement should occur within the first few weeks of treatment.

Other drugs taken at the time TB is diagnosed or during TB treatment may also cause abnormal liver function.

Patients with HIV infection or hepatitis B or C infection may have abnormal liver function when starting treatment and are also more likely to develop hepatotoxicity.

In hepatic failure, there is decreased total body clearance of isoniazid and rifampicin, resulting in drug accumulation and higher serum levels. The elimination half-life may increase 30–100% in hepatic failure. Significant accumulation of pyrazinamide can occur in icteric patients. Although 50% of fluoroquinolone clearance occurs in the liver, their serum concentrations are not substantially altered in hepatic disease.

If a person with active TB has major hepatic dysfunction, consultation with a TB clinical expert and a hepatologist is strongly recommended. In patients with major hepatic dysfunction, TB treatment should start with an effective, non-hepatotoxic regimen such as amikacin, ethambutol and moxifloxacin. If these do not cause side effects in the first three to four days, the potentially hepatotoxic agents (rifampicin, isoniazid and pyrazinamide) may be added one at a time. Rifampicin would be the next agent of choice to add. Therapeutic drug monitoring may be helpful.

Ascites presents a problem with many anti-tuberculosis drugs, because those that distribute freely into water will display a larger volume of distribution and therefore a longer elimination half-life. Therapeutic drug monitoring is recommended for people with persistent ascites.

For further information, refer to Guidelines for Tuberculosis Control in New Zealand 2010, section 3.11.2.

2.6.4 Diabetes

Recent literature reviews have shown that people with diabetes have at least a two-fold higher risk of developing active TB compared to those without diabetes. Having a high index of suspicion and screening for active TB amongst diabetes patients, particularly those with poor glycaemic control, increases detection of new TB cases. In addition, people with newly diagnosed TB should be screened for undiagnosed diabetes (preferably using fasting glucose), especially in population groups in whom diabetes is prevalent.

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2 Ottmani, SE et al. Consultation meeting on tuberculosis and diabetes mellitus: meeting summary and recommendations. Int J Tuberc Lung Dis 14(12):1513-1517

Auckland/Northland DHBs TB case management document – Auckland version

July 2011
Diabetes also impacts on TB treatment outcomes, with an increased risk of fatality and of recurrent TB. There may be an association between diabetes and MDR-TB, but this requires further investigation. There are also knowledge gaps on the interaction between diabetes and TB medications and the required length of treatment. Patients with diabetes do not require specific dosage alterations of anti-TB medications, however as diabetes is associated with renal disease (diabetic nephropathy) and hepatic disease (fatty liver disease) renal and hepatic function should be closely scrutinised prior to treatment initiation.

2.6.5 Obesity

Antimicrobial dosing in obese patients is complex and poorly understood. Obesity leads to physiological changes with effects on antimicrobial pharmacokinetics; these factors may be interactive. Important considerations include:

- increased body mass (including lean body mass and adipose mass)
- increased cardiac output and blood volume
- increased renal clearance (equations to estimate creatinine clearance do not accurately predict the higher creatinine clearance observed in obesity)
- hepatic metabolic changes
- changes in serum protein levels.

Maximum doses of the standard TB medicines are shown in Appendix 5.1.

In short obese adults, standard maximum doses may be excessive. Here the ideal body weight (IBW) should be obtained, and the dose of the first-line agents should be based on this.

The calculation of IBW (or lean body weight) for:

- women is 45 kg + 0.9 kg per cm of height above 150 cm
- men is 50 kg + 0.9 kg per cm of height above 150 cm.

For further information, refer to Guidelines for Tuberculosis Control in New Zealand 2010, section 3.11.4.

2.6.6 Pregnancy and lactation

The risk of untreated TB to a pregnant woman is far greater than the risk of toxic effects to the fetus from the drugs used in its treatment. Active TB in a pregnant woman always requires prompt and effective treatment.

Isoniazid, rifampicin and ethambutol have been well studied and are considered safe in pregnancy. Pyrazinamide is also considered safe and is used routinely in pregnancy, though there are differences in the British and CDC guidelines for its use. There is limited data on the safety of second-line agents during pregnancy. These drugs should only be used in specific instances after consultation with a TB specialist.

If there are strong indications of active TB disease but bacteriological confirmation is lacking, treatment may often be deferred until after the first trimester.

In pregnant women with no symptoms, negative bacteriology, a lack of radiological change but evidence of past TB infection, initiation of preventive therapy for LTBI may be delayed until after the birth unless the infection has been recently acquired or the woman has other medical conditions such as HIV infection that places her at higher risk of developing TB disease.

All pregnant women on isoniazid should receive pyridoxine to prevent neurotoxicity in the foetus.
Treatment with first line agents for TB is not a contraindication for breast-feeding as the small concentrations of these drugs in breast milk do not produce toxic effects in the newborn.

For further information, refer to Guidelines for Tuberculosis Control in New Zealand 2010, section 3.11.3.

2.7 Monitoring, drug side effects, managing drug reactions, drug interactions

For further information, refer to Guidelines for Tuberculosis Control in New Zealand 2010, sections 3.7, 3.8, 3.9 and 3.10.

2.7.1 Monitoring infectivity

Patients with pulmonary TB who are sputum smear-positive before treatment should have repeat sputum tests at least monthly to confirm sterilisation. The majority (85%) are expected to be smear and culture-negative after completing 2 months of treatment. If the specimen at the end of the third month is both smear and culture-positive, repeat drug susceptibility testing (DST) should be performed. Repeat DST should be considered earlier, at two months, in patients where there is concern about the potential of acquired drug resistance.

2.7.2 Radiological monitoring

Chest X-ray (CXR) monitoring during treatment is required for all patients with CXR abnormalities consistent with TB. The intervals between films will depend on the clinical circumstances. If there is no CXR improvement after 3 months of treatment the following scenarios need to be considered:

- the diagnosis of TB may be wrong
- the TB may have produced scarring before treatment, so radiological improvement may not occur
- a mixed pathology may be present with TB co-existing with another condition. CT imaging should occur if there is a possibility that the abnormalities are due to a lung cancer.
- primary drug resistance may have been present from the outset.
- the patient may not have followed their medication regimen and secondary drug resistance must be considered.

Chest CT scanning is useful for monitoring extensive mediastinal lymph node TB. A comparison of an early CT with another done just before planned completion of treatment may lead to the treatment cessation date being revised. Longer treatment is indicated if lymph nodes continue to have a necrotic appearance or have not diminished greatly in size during treatment.

The need for serial imaging in patients with TB at extrapulmonary sites will depend on:

- the site of involvement (for example, abdominal ultrasound for intra-abdominal disease; cerebral CT or MRI for intra-cerebral TB)
- the severity of involvement at the site(s) of disease.

2.7.3 Monitoring for drug toxicity

Prior to commencing a TB treatment regimen the following tests should be undertaken:

- Baseline full blood count, creatinine, LFTs (alanine amino-transferase (ALT) as a minimum), hepatitis B surface antigen, and hepatitis C and HIV serology should be completed in all adults who are to be treated for TB disease or latent TB infection (LTBI).
• For patients with an elevated ALT, a full panel of LFTs should be completed and the case should be discussed with a clinical TB expert.

All patients should be advised to avoid drinking alcohol while taking TB drugs.

**Hepatotoxicity**

Hepatotoxicity is a major issue with TB treatment.

*During TB treatment regular clinical monitoring of liver function should occur* as severe hepatic dysfunction can be asymptomatic. After baseline testing (recommendations are for minimum testing frequency – more frequent testing is obviously needed if results are abnormal):

• adults being treated for LTBI should have ALT monitoring at one month and then every two months

• adults being treated for TB disease who have no risk factors for hepatotoxicity, should have ALT monitoring at one month, two months, and then every two months thereafter at a minimum. Many clinicians test more regularly – for example testing at 2 weeks, 4 weeks and 6 weeks.

• adults being treated for TB disease who have risk factors for hepatotoxicity, should have complete liver function tests every month.

**Action for abnormal results:**

• If a patient’s ALT is more than three times the normal level, advice should be sought from a clinical TB expert promptly.

• *Any patient with jaundice should be referred to a liver unit or gastroenterologist and all hepatotoxic drugs should be stopped immediately.*

• Any patient whose TB treatment is stopped because of abnormal liver function should be notified to the Centre for Adverse Reactions Monitoring (CARM).

**Ocular toxicity**

Ocular toxicity is the most important side effect of ethambutol.

All patients starting ethambutol should have a baseline visual acuity test and a red–green colour vision assessment. Patients with abnormalities should be referred to an ophthalmologist.

All patients on ethambutol should be asked to report new visual symptoms and visual acuity effects. Monthly testing of visual acuity and colour discrimination is recommended for patients receiving ethambutol for longer than two months and for any patient with renal impairment.

Ophthalmological review should occur if there are any abnormalities. Ethambutol should be avoided unless absolutely necessary in people unable to report changes in vision and in people with moderate or severe renal insufficiency.

**Renal toxicity**

Nephrotoxicity is most commonly an issue with the aminoglycosides, of which amikacin is the usual drug of choice.

**Monitoring of patients on amikacin**

• Trough levels: Serum amikacin trough levels should be measured regularly, with samples taken just before giving a dose. The trough level should be less than 1mcg/mL if toxicity is to be minimised. If the estimated creatinine clearance is less than 50ml/min or serum creatinine is increasing, then trough levels should be monitored frequently. Serum peak levels may need to be assessed in some patients to confirm adequate dosing.
• Creatinine clearance: In patients with normal renal function requiring long-term amikacin dosing, fortnightly creatinine clearance monitoring is recommended to monitor plasma creatinine concentration.

Ototoxicity
Ototoxicity is most commonly an issue with the aminoglycosides, of which amikacin is the usual drug of choice.

• Ototoxicity and vestibular function: With long-term amikacin dosing, audiometry testing should be completed fortnightly to monitor ototoxicity and vestibular dysfunction. Electronystagmography may be considered if vestibular symptoms develop.

Hypothyroidism
Patients on PAS and ethionamide may develop hypothyroidism. All patients on these medications should have thyroid function tests at baseline and then every three months.

Weight and nutrition
Many patients with TB are poorly nourished. Weight and nutrition status are important markers of disease status. The patient’s weight should be monitored throughout the course of treatment and nutrition should be optimised.

Monitoring by a nurse
All patients who are self administering anti-tuberculosis treatment should be reviewed by a Public Health Nurse (PHN) nurse every month (at a minimum). At the start of treatment, patients must be educated about TB and potential drug side effects and should be instructed to watch for common drug reactions. Regular monitoring should include a pill count to check adherence, and enquiry about drug side effects and symptoms suggestive of possible relapse.

Medical appointments
A medical review may be completed every two to three months provided there are no risk factors for poor compliance, the patient can be relied on to report symptoms, and a monthly review by a PHN is being carried out. However some patients may need monthly (or even more frequent) review.

2.7.4 Indications for therapeutic drug monitoring
Most patients with uncomplicated TB usually respond to standard treatment, however there are several situations in which the monitoring of serum drug concentrations might be helpful. Rifampicin and isoniazid therapeutic drug monitoring should be considered in the following circumstances:

• The disease does not show the expected improvement.
• Non-adherence or malabsorption is suspected.
• Malabsorption is particularly likely in patients with HIV infection, cystic fibrosis or diabetes mellitus. Sub-therapeutic drug concentrations carry a significant risk of drug resistance developing
• The patient has ascites.
• The patient experiences drug side effects, especially if the offending drug needs to be re-introduced.
• There are patients with isolates that are multidrug resistant or have acquired drug resistance.
• Risk factors for drug toxicity are present.
• The patient is obese.

2.7.5 Paradoxical reactions to TB treatment

A paradoxical reaction to TB treatment is defined as a ‘worsening of disease at a pre-existing site, or the development of new tuberculosis lesions following initiation of appropriate treatment’. These reactions generally occur about one to three months after the start of treatment, but can occur even after treatment is complete. Paradoxical reactions occur more frequently in HIV-infected people who are receiving TB treatment and then start taking anti-retroviral agents.

The differential diagnosis of apparent paradoxical reactions includes:

• incorrect or inadequate treatment, with worsening of the TB through non-adherence with drug treatment, malabsorption of TB drugs, the presence of primary drug resistance or the development of secondary drug resistance

• drug reaction

• other concurrent infection or malignancy.

The diagnosis of paradoxical reactions may be difficult, depending on the site of involvement and the presence of immune-suppression. Investigations should be carried out to detect other possible causes including tissue sampling and repeating TB cultures.

2.7.6 Symptomatic management of common drug side effects

Common adverse side effects of TB drugs are listed in Appendix 5.6.

Dermatological side effects such as itching and rash are common and can occur with any TB drug. Symptomatic measures to treat itching and mild rashes include recommending non-perfumed soap or soap substitutes, use of skin moisturisers to avoid/treat dry itchy skin, antihistamines such as loratidine and 1% hydrocortisone cream or ointment if necessary.

Nausea is a common side effect. If ongoing treatment for nausea is needed, it may be preferable to use prochlorperazine (as theoretically, agents such as metoclopramide, which stimulate gastric emptying, may have an effect on TB drug levels).

The most commonly hepatotoxic TB drugs are isoniazid, rifampicin and pyrazinamide. See section 2.7.3 for further information.

2.7.7 Management of drug reactions: temporary regimens and drug challenges

Important points

• The maximum period for a patient with active TB to be off all drugs is four weeks.

• The maximum period for a patient to be on a partial regimen is 10 days.

• A typical temporary regimen is amikacin (or streptomycin), ethambutol and moxifloxacin (ethionamide or protonamide could also be used in a temporary regimen).

If it is necessary to stop anti-tuberculosis treatment (particularly to give a steroid to counteract treatment side effects), consider whether a new, temporary regimen would be helpful. This regimen should continue until full doses of all drugs in the definitive regimen have been started. A person who is acutely ill with TB or is infectious should be put on a temporary regimen immediately. For a non-infectious, well person, four weeks without treatment is an arbitrary maximum period to be off anti-tuberculous treatment. The development of infectiousness or the spread of disease to other sites is unlikely in this time.
Progressive but non-effective partial regimens

The period for which a progressive but non-effective partial regimen may be given without inducing drug resistance is not certain, but is in the order of days. In a person who is well despite TB, the period should not exceed 10 days. If the person is ill with TB, an alternative regimen should be started as soon as the original regimen is modified.

Repeated periods of partial treatment or no treatment should be avoided. A second episode without treatment or partial treatment is an indication for a temporary regimen that should be continued for several weeks, until the difficulties have been fully resolved.

The development of resistance to moxifloxacin can appear relatively quickly and has been observed to occur in patients with TB who have been exposed to moxifloxacin monotherapy for as short a period as 10 days.

Agents in the temporary regimen

Agents in the temporary regimen could include amikacin (or streptomycin), moxifloxacin, ethambutol, and ethionamide (or prothionamide).

Management of drug challenges

When troublesome side effects occur, stop current treatment and allow the reaction to resolve. Then identify the agent or agents causing the reaction, by re-introducing the drugs sequentially.

Give the patient a few days on each dose of each agent; the more severe the reaction, the more caution is required. It may be necessary to start with small incremental doses and build up to the full dose over several days. It may be necessary to cover the patient with a temporary regimen to prevent resistance emerging during the challenge period.

If the patient experiences no side effects, repeat the process with the next drug. With less-severe reactions, it may be possible to introduce full doses.

Drug challenge doses for mild-to-moderate reactions are shown in Appendix 5.7.

Clinicians unfamiliar with conducting drug challenges should discuss the case with a clinical TB expert.

For further information, refer to Guidelines for Tuberculosis Control in New Zealand 2010, section 3.9.

2.7.8 Interactions with anti-TB drugs

A table of clinically important interactions with anti-TB drugs is included in Appendix 5.8.

For further information, refer to Guidelines for Tuberculosis Control in New Zealand 2010, section 3.10.
3 Diagnosis and treatment of latent TB infection (LTBI) in adults

For further information, refer to the Guidelines for Tuberculosis Control in New Zealand 2010, Chapter 8: Diagnosis and treatment of latent tuberculosis infection.

The diagnosis of latent TB infection (LTBI) depends on finding evidence of TB infection in an asymptomatic person in the absence of radiological or other signs of active or inactive TB disease.

LTBI is ‘latent’ because live, dormant, non-reproducing Mycobacterium tuberculosis organisms are sequestered in the tissues, although they are not clinically apparent.

People with LTBI are non-infectious to others.

Treatment of LTBI in an individual at high risk of developing active TB disease is effective at reducing that person’s future risk of developing TB disease.

If untreated, adults with LTBI have a 5–15% chance of developing active TB disease at some point in their lives. This risk is greater in certain subgroups including recently infected people, children under five and the immunosuppressed.

3.1 Diagnosis of LTBI

3.1.1 Who should be tested, risk factors

The purpose of testing for LTBI is primarily to identify people who are at high risk for developing active TB disease, and who would therefore benefit by treatment of LTBI.

The following groups of people should be tested for LTBI:

- People likely to have been infected recently: primarily contacts of a patient with recent diagnosis of active infectious TB disease and refugees aged under 16 years.

- People who have an increased risk of developing active TB disease if they have LTBI, due to impaired immunity: people with HIV infection, chronic renal failure, solid organ transplantation, anti-tumour necrosis factor (TNF) treatment, those intending to undertake immunosuppressive therapy such as organ transplantation and various other chronic conditions and treatments.

- Health care workers because they are at increased risk of exposure to people with active infectious TB disease.

Refer to Guidelines for Tuberculosis Control in New Zealand 2010, Section 8.1.2 for further information regarding risk factors for infection (Table 8.1) and risk factors for developing disease following infection (Table 8.2).

3.1.2 Tests for LTBI

There is no gold standard test for the diagnosis of LTBI. Tuberculin skin tests (TSTs) such as the Mantoux test have been used for many years. In a person previously infected with Mycobacterium tuberculosis a hypersensitivity reaction occurs at the site of injection.

Interferon-gamma release assays (IGRAs) have been developed more recently as an alternative to Mantoux tests for the diagnosis of LTBI. IGRAs work on the principle that if a person is infected with Mycobacterium tuberculosis, T-lymphocytes circulating in their blood will produce interferon-gamma if re-exposed to TB antigens in vitro.

While the Mantoux test has been used for many years, IGRAs are much newer tests and evidence and experience in their use is still accumulating.

In general, either test can be used to diagnose LTBI. However in certain circumstances one test may be preferable to the other, or both tests can be done.
When screening adults for LTBI, use:

- Mantoux test or
- IGRA or
- Mantoux test followed by IGRA if Mantoux positive.

An IGRA is particularly recommended:

- in BCG-vaccinated people
- in immunocompromised people
- when it is considered a high risk that the person will not return for the reading of their Mantoux test
- when it is impractical for the person to make repeat visits for sequential testing.

### 3.1.3 Interpretation of results

If an IGRA or a Mantoux test is positive, the person should be investigated further for LTBI.

If an IGRA or a Mantoux test is negative, and the person is asymptomatic, not immunocompromised, and has not had recent exposure to an infectious TB case, they usually do not have LTBI. Note that if there has been recent exposure to an infectious TB case then contact investigation should be carried out by the Public Health Unit.

If an IGRA is indeterminate, consider repeating it.

In an immuno-compromised person, if IGRA and Mantoux tests results are discordant (i.e. one test is positive and the other is negative), or the tests are negative, but the person’s likelihood of having acquired LTBI is high (e.g. clear history of TB exposure or has resided long-term in an area of high TB endemicity), the clinician should still consider treating the person for LTBI.

In general, either test can be used to diagnose LTBI. However in certain circumstances one test may be preferable to the other or both tests can be done.

Further detail on the interpretation of these tests and their use in different clinical situations can be found in the New Zealand Guidelines Chapter 8.

### 3.1.4 Chest X-ray

The diagnosis of LTBI depends on finding evidence of TB infection (positive Mantoux or IGRA) in an asymptomatic person in the absence of radiological or other signs of active or inactive TB disease. Therefore a CXR is essential as part of the diagnosis of LTBI, prior to starting LTBI treatment. In LTBI the CXR is normal or shows trivial and stable evidence of past TB (e.g. a small scar or patch of calcium).

People with radiological evidence of active or inactive TB disease should not be treated for LTBI unless active disease has been excluded, and require prompt further investigations to confirm or exclude active or inactive TB disease (see section 1.2).

### 3.2 Treatment of LTBI in adults

#### 3.2.1 Decision to treat

The decision to treat must be a joint one by the patient and the treating doctor (as well as the Public Health Nurse, if the patient is a contact of a TB case).

Factors that need to be considered are the person’s likelihood of actually having LTBI (taking into account prior BCG vaccination), their likelihood of progression to active TB disease, the risks of an adverse reaction to treatment and their likelihood of adherence to treatment and monitoring.
If the risks of infection and/or disease outweigh the risk of adverse reactions, and an appropriate TB drug is available for treatment (based on the sensitivity of index case’s isolate, if known), the patient should be offered treatment.

In an immune-suppressed person who has been exposed recently to an infectious case and had a Mantoux or IGRA conversion, the risks of infection and progression to disease are high and a 9 month or even 12 month course of isoniazid is appropriate (by DOT if possible/practicable).

3.2.2 Contraindications and precautions

There is currently no good evidence for treatment of LTBI in people who are close contacts of an MDR-TB case.

Caution is needed, and the risks versus benefits of LTBI treatment need to be assessed carefully, when deciding whether or not to treat a person to whom one or more of the following apply: pregnancy, acute or chronic liver disease, individual taking concurrent medications that can cause hepatotoxicity, high alcohol intake/alcohol abuse, individual unlikely to adhere to treatment or monitoring (clinical and/or laboratory), or an individual with peripheral neuropathy or risk factors for its development (e.g. diabetes, chronic renal failure, alcohol abuse or malnutrition).

3.2.3 Recommended regimens for LTBI treatment

The recommended treatment regimens for LTBI are listed in Appendix 5.5.

3.2.4 LTBI case management

LTBI cases are not legally required to be notified. However, clinicians are requested to report every case under treatment to the MOH for surveillance purposes (see section 4.2).

Careful follow up of people on LTBI treatment is essential.

Auckland Regional Public Health Service (ARPHS) does not generally have the capacity to offer follow up for high risk patients diagnosed with LTBI in the Auckland region, unless they are contacts of active TB disease cases i.e. were identified as having LTBI as part of contact follow up – in which case ARPHS does supervise their LTBI treatment.

Therefore clinicians prescribing LTBI treatment for those high risk patients who are not contacts of current TB cases are responsible for their follow up, including patient education, baseline and follow up laboratory testing, and ongoing monitoring of adherence to treatment and side effects of treatment.

In the Auckland region, all treatment of LTBI in patients with HIV infection should be managed by the infectious diseases department at Auckland City Hospital.

For further information regarding follow up and practical considerations in treating LTBI, refer to the Guideline for Tuberculosis Control in New Zealand 2010, Chapter 8, particularly sections 8.2.3, 8.2.4 and 8.2.5. Regarding monitoring for toxicity and side effects, sections 2.7.3 and 2.7.6 of this document may also be useful.
4 Public Health

4.1 Aspects of TB control
The goals of the Auckland Regional Public Health Service (ARPHS) TB Control Programme (TBCP) are to:

- Prevent the transmission of TB within the Auckland region through early detection and complete treatment of TB disease, complete and timely contact follow up, treatment of latent TB infection (LTBI), and provision of BCG vaccination to eligible children according to the Ministry of Health’s BCG eligibility criteria.
- Prevent TB disease recurrence through complete treatment of TB disease.
- Prevent development of MDR-TB through complete treatment of TB disease.
- Monitor TB disease trends in the Auckland region through surveillance.
- Raise public awareness about TB and reduce stigma relating to TB in the Auckland region through education and health promotion.

4.2 How to notify cases to the Medical Officer of Health
A medical practitioner who diagnoses or suspects a case of new or relapsed active TB disease has a legal responsibility under the Tuberculosis Act 1948 notify the case to the Medical Officer of Health (MOH).

For patients in the Auckland region, notification should be made to the TB Support Officer at Auckland Regional Public Health Service (ARPHS) by telephone or fax:

- Phone: 09 623 4600
- Fax: 09 630 7431

Direct laboratory notifications of TB have taken place since 2008, but prompt clinical notification is still required and is essential to obtain the necessary information.

ARPHS will liaise with the diagnosing clinician.

ARPHS requests notifying clinicians to do the following:

- Complete/supply the necessary information on the TB case report form (by phone or fax). The case report form can be downloaded from the ESR Public Health Surveillance website.
- Fax a copy of the prescription (for TB drugs and pyridoxine only, i.e. not including the patient’s other routine drugs) to ARPHS. Post the original script to the pharmacy. A list of pharmacy names, addresses and contacts are included in the index. The ARPHS PHN allocated to the patient will arrange for the TB drugs to be dispensed, blister packed if necessary, etc. (Allow a minimum of 24 hours for TB drugs to be dispensed).
- Inform the TB Support Officer or the PHN (if known) of the expected date and time of discharge (if hospitalised), allowing sufficient time for TB drugs to be obtained.
- Avoid discharge from hospital on Fridays (as patients may need intensive input in the first few days/first week, and this puts pressure on weekend staffing).

Clinicians are asked not to give the prescription directly to the patient (because only a few pharmacies stock the TB drugs, and because patients may start taking their TB medicines before the PHN has had a chance to educate them comprehensively about adherence, side effects, etc).

There is no co-payment for TB drugs i.e. TB drugs are free of charge to all patients, regardless of their eligibility for publicly funded health care services (as per the New Zealand
Pharmaceutical Schedule: ‘Infections – Agents for Systemic Use, Antituberculotics and Antileprotics’).

If a presumptive case (notified on suspicion) is subsequently shown not to meet the case definition, the clinician must notify the Medical Officer of Health of this, so that the record can be de-notified (that is, reclassified as ‘not a case’) in EpiSurv, the national surveillance database. Reactivated (recurrent) cases must also be notified to the MOH using the TB case report form. Additionally, the clinician must re-notify cases if treatment is started but the patient then becomes infectious again (as a result of treatment failure or non-adherence).

LTBI cases are not legally required to be notified. However, clinicians are requested to report every case under treatment to the MOH for surveillance purposes. The clinician should obtain the patient’s consent to this.

Contacts are identified as part of the investigation of cases by Public Health, and contact investigation and follow up is the responsibility of ARPHS.

4.3 Public Health roles in TB control

4.3.1 Adherence and its supervision

Tuberculosis (TB) control requires a high level of adherence to the treatment regimen. Adherence is defined as reliable consumption of anti-TB medication according to a pre-determined plan which increases the chance of curing a person’s TB.

Adherence is particularly important in the treatment of TB for the following reasons:

- To increase the likelihood of cure for individual patients
- To prevent the spread of TB to others in the community
- To prevent the development of MDR-TB.

Healthcare staff must support patients and enable them to adhere to the full course of treatment.

The optimal level of supervision is influenced by patient factors, clinical factors such as drug resistance and the presence of side effects, and social factors. The level of supervision of TB cases may change during the course of treatment. See Appendix 5.9 for risk factors for poor adherence and appropriate levels of supervision.

4.3.2 Contact tracing

All contact tracing should be supervised by the MOH in the district where the index case is notified – ARPHS does all the TB contact tracing in the Auckland region. General practitioners and other clinical staff should not undertake contact tracing activity for TB.

The aim of the investigation and follow up of contacts is to minimise morbidity and transmission of tuberculosis by:

- Education of contacts about TB disease and LTBI.
- Identification of infected contacts (who may themselves require treatment of active TB disease, or will be followed up for LTBI).
- Identification of uninfected contacts who may require BCG vaccination (children under five years of age)
- Identification of a source case (especially where the notified TB case is a child).
4.4 Difficult situations – legal duties and powers of the MOH

The pieces of legislation currently relevant to TB control in New Zealand are the Tuberculosis Act 1948 (TB Act) and the Tuberculosis Regulations 1951 (TB Regulations).

Under the TB Act the MOH has a legal duty to ensure that appropriate examinations are carried out in people suspected of suffering from TB, contact tracing is carried out, people who are found to have TB disease obtain medical treatment and action is taken to prevent the spread of TB.

It is important that the statutory powers available to the MOH are used with appropriate regard to their legal context, and that due process is followed.

Frequently used sections of the TB Act include sections 7, 9 and 10:

- **Section 7**: Duties and powers of Medical Officers of Health.
- **Section 9**: Power, in certain cases, to require medical examination and investigations.
- **Section 10**: Power, in certain cases, to give directions for the precautions necessary to prevent the spread of infection.
- **Section 16**: Provision for isolation, in certain cases, of persons likely to spread infection (used only rarely, as a last resort, for an infectious non-compliant TB patient, when the MOH may apply to a District Court Judge for a detention order).

Note that the TB Act and the TB Regulations will be revoked if the Public Health Act comes into force. It is anticipated that similar powers will be available to the MOH under any future legislation.

The Eligibility Direction 2011 came into effect on 16 April 2011. The purpose of the Eligibility Direction is to guide DHBs regarding patients’ eligibility (and ineligibility) for publicly funded health care services. Infectious diseases case and contact management is specifically covered in section B23 of the Eligibility Direction 2011 ‘to the extent appropriate in the circumstances to address risks to other persons’. In other words, TB cases (including diagnosis, treatment and follow up) and contacts are eligible for publicly funded services and should not be required to pay for services relating to TB case/contact follow up.

Clinicians must contact the MOH in the following situations, so that the MOH can take appropriate action and issue the relevant order under the TB Act 1948:

- If a person suspected of having TB refuses to undergo investigations – MOH will issue a section 9 order requiring the person to attend clinic and undergo investigations.
- If a person known to have TB refuses to attend/DNAs clinic for follow up – MOH will issue a section 9 order requiring the person to attend clinic and undergo investigations.
- If a person known to have infectious TB refuses to take precautions to prevent spread of infection to others – MOH will issue a section 10 order requiring the person to take specified precautions to prevent spread of TB to others. As a last resort, the MOH can apply for an order to isolate an infectious non-compliant patient under section 16 of the TB Act.
## 5 Appendices

### 5.1 Dosage recommendations for anti-tuberculosis agents for adults

Reproduced from *Guidelines for Tuberculosis Control in New Zealand 2010, Table 3.1, section 3.2.1*

<table>
<thead>
<tr>
<th>Medication</th>
<th>Daily dose</th>
<th>Thrice-weekly dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Isoniazid#</td>
<td>5 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Maximum dose/kg</td>
<td>300 mg</td>
<td>900 mg</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>5 mg</td>
<td></td>
</tr>
<tr>
<td>Maximum dose/kg</td>
<td>300 mg*</td>
<td></td>
</tr>
<tr>
<td>Rifampicin\§</td>
<td>10 mg</td>
<td>10 mg</td>
</tr>
<tr>
<td>Maximum dose/kg</td>
<td>600 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>25 mg</td>
<td>35 mg</td>
</tr>
<tr>
<td>Maximum dose/kg</td>
<td>2 g</td>
<td>3 g</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>15 mg</td>
<td>30 mg (25–35)</td>
</tr>
<tr>
<td>Maximum dose/day</td>
<td>2.5 g</td>
<td></td>
</tr>
<tr>
<td><strong>Second-line agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protionamide and ethionamide|</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum dose/kg</td>
<td>15–20 mg</td>
<td></td>
</tr>
<tr>
<td>Maximum dose</td>
<td>1 g</td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>400 mg</td>
<td></td>
</tr>
<tr>
<td>Streptomycin</td>
<td>15-20 mg</td>
<td></td>
</tr>
<tr>
<td>Maximum dose/kg</td>
<td>1 g</td>
<td></td>
</tr>
<tr>
<td>Maximum, intramuscular, intravenous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amikacin</td>
<td>15-20 mg</td>
<td></td>
</tr>
<tr>
<td>Maximum, intramuscular, intravenous</td>
<td>1 g</td>
<td></td>
</tr>
<tr>
<td>Kanamycin</td>
<td>15-20 mg</td>
<td></td>
</tr>
<tr>
<td>Maximum, intramuscular, intravenous</td>
<td>1 g</td>
<td></td>
</tr>
<tr>
<td>Capreomycin</td>
<td>15-20 mg</td>
<td></td>
</tr>
<tr>
<td>Maximum dose</td>
<td>1 g</td>
<td></td>
</tr>
<tr>
<td>Cycloserine</td>
<td>15-20 mg</td>
<td></td>
</tr>
<tr>
<td>Maximum dose/kg</td>
<td>750 mg-1 g</td>
<td></td>
</tr>
<tr>
<td>P-aminosalicylic acid (4 g sachets)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amount/kg</td>
<td>150 mg</td>
<td></td>
</tr>
<tr>
<td>Maximum dose</td>
<td>8–12 g</td>
<td></td>
</tr>
</tbody>
</table>

* Sometimes doses up to 450 mg are used.
\§ An intravenous form of rifampicin is available.
\|| Protionamide and ethionamide are given in divided doses.
\# Patients >50kg should be prescribed Rifinah 300 x2 tablets daily (rifampicin 600mg daily and isoniazid 300mg daily); adult patients <50kg are usually prescribed Rifinah 150 x3 tablets daily (rifampicin 450mg and isoniazid 300mg daily).

Sources: refer to Table 3.1 in *Guidelines for Tuberculosis Control in New Zealand 2010*
5.2 Special situations

5.2.1 HIV-associated TB

Recommendations for using non-nucleoside reverse transcriptase inhibitor (NNRTI) anti-retrovirals with rifampicin, and protease inhibitor (PI) and NNRTI anti-retrovirals with rifabutin

Reproduced from Guidelines for Tuberculosis Control in New Zealand 2010, Table 6.2, section 6.4.2

<table>
<thead>
<tr>
<th>Anti-retroviral drug</th>
<th>Recommended change in dose of anti-retroviral drug</th>
<th>Recommended change in dose of rifamycin</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recommendations with rifampicin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NNRTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>600 mg daily (consider 800 mg daily if weight over 60 kg)</td>
<td>None</td>
<td>May use 600 mg daily if higher dose not tolerated</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>200 mg twice a day</td>
<td>None</td>
<td>Use when no other option available</td>
</tr>
<tr>
<td><strong>Recommendations with rifabutin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protease inhibitor*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ritonavir</td>
<td>None</td>
<td>150 mg every other day or thrice weekly</td>
<td>Rifabutin AUC increased 430%</td>
</tr>
<tr>
<td>Atazanavir</td>
<td>None</td>
<td>150 mg every other day or thrice weekly</td>
<td>Rifabutin AUC increased 250%</td>
</tr>
<tr>
<td>Lopinavir–ritonavir</td>
<td>None</td>
<td>150 mg every other day or thrice weekly</td>
<td>Rifabutin AUC increased 303%</td>
</tr>
<tr>
<td><strong>NNRTI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Efavirenz</td>
<td>None</td>
<td>450–600 mg daily or 600 mg thrice weekly</td>
<td>Rifabutin AUC decreased 38%</td>
</tr>
<tr>
<td>Nevirapine</td>
<td>None</td>
<td>300 mg daily or 300 mg thrice weekly</td>
<td>Rifabutin and nevirapine AUC not significantly changed</td>
</tr>
</tbody>
</table>

Notes: The table applies to combination anti-retroviral therapy regimens that consist of a 2NRTI 'backbone' plus one of the above. No relevant data pertain to PI–NNRTI combinations. AUC = area under the curve (a measure of drug concentration).

* Rifabutin 150 mg three times weekly in combination with LPV/r has resulted in inadequate rifabutin levels and has led to acquired rifamycin resistance in patients with HIV-associated TB. Therapeutic drug monitoring for rifabutin is recommended.

Source: Adapted from Centers for Disease Control and Prevention (2007).
### 5.2.2 Renal impairment and treatment of TB

Doses of major anti-tuberculosis agents and renal impairment

Reproduced from *Guidelines for Tuberculosis Control in New Zealand 2010, Table 3.9, section 3.11.1*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Chronic renal failure</th>
<th>Peritoneal dialysis</th>
<th>Haemodialysis*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Normal dose</td>
<td>Normal dose</td>
<td>Normal dose</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Normal dose</td>
<td>Normal dose</td>
<td>Normal dose</td>
</tr>
<tr>
<td>Ethambutol#</td>
<td>Avoid unless absolutely necessary</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GFR 20–50: Dose as in normal renal function</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GFR 10–20: 15mg/kg every 24–36 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>GFR &lt; 10 ml/min: 15 mg/kg every 48 hours or 5–7.5 mg/kg daily</td>
<td>Avoid unless absolutely necessary</td>
<td>Avoid unless absolutely necessary</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>GFR &lt; 10 ml/min: 15–25 mg/kg daily (use 50–100% of dose)</td>
<td>25 mg/kg daily</td>
<td>25–30 mg/kg three times a week, after dialysis</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>Avoid if possible; or single dose and monitor serum levels</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GFR = glomerular filtration rate (mL/min).
* TB medicines are given after haemodialysis.
# Ethambutol should be avoided in renal impairment unless absolutely necessary.

5.3 Treatment regimens for drug-susceptible TB disease

Refer to *Guidelines for Tuberculosis Control in New Zealand 2010*, sections 3.3 and 3.4

- Standard 6 month regimen: 2HREZ/4HR
- When pyrazinamide is not tolerated (or if pyrazinamide resistant) 9 months: 2HRE/7HR
- Bone or joint TB: 9-12 months of treatment
- Miliary/disseminated TB: 12 months of treatment or longer
- Meningeal or intra-cerebral TB: 12 months of treatment or longer (see table below)

### Treatment of tuberculous meningitis and intra-cranial tuberculosis in adults

Reproduced from *Guidelines for Tuberculosis Control in New Zealand 2010*, Table 3.3, section 3.4

<table>
<thead>
<tr>
<th>Drug penetration across the blood/brain barrier:</th>
<th>Rifampicin (R)</th>
<th>Isoniazid (H)</th>
<th>Pyrazinamide (Z)</th>
<th>Ethambutol (E)</th>
<th>Streptomycin (S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infamed meninges</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>Non-infamed meninges</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>–</td>
<td>+/-</td>
</tr>
<tr>
<td>Drug efficacy in central nervous system tuberculosis (TB)</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>–</td>
<td>+/-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Daily drug doses (for adults)*</th>
<th>Rifampicin 10 mg/kg</th>
<th>Isoniazid 5 mg/kg</th>
<th>Pyrazinamide 25–35 mg/kg</th>
<th>Ethambutol 20 mg/kg intramuscular (maximum 1 g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No dose increase needed for central nervous system tuberculosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Oral steroid</th>
<th>Should be given to all patients</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Duration of TB medicines</th>
<th>12 months for adults</th>
</tr>
</thead>
</table>

*For information about doses for children, see Chapter 5 of the *Guidelines for Tuberculosis Control in New Zealand 2010*. 

---

**Table**: Drug penetration across the blood/brain barrier and drug efficacy in central nervous system tuberculosis (TB)

- **++**: High penetration
- **+**: Moderate penetration
- **+/-**: Slight penetration
- **-**: Low penetration
5.4 Treatment regimens for drug-resistant TB disease

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

Reproduced from Guidelines for Tuberculosis Control in New Zealand 2010, Table 3.4, section 3.5.3

<table>
<thead>
<tr>
<th>Pattern of drug resistance</th>
<th>Suggested regimen</th>
<th>Minimum duration of treatment (months)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>H (+/- S)</td>
<td>R, Z and E</td>
<td>6–9*</td>
<td>A fluoroquinolone may strengthen the regimen for patients with extensive disease</td>
</tr>
<tr>
<td>H and Z</td>
<td>R, E and moxifloxacin</td>
<td>9–12*</td>
<td>A longer duration of treatment should be used for patients with extensive disease</td>
</tr>
<tr>
<td>H and E</td>
<td>R, Z and moxifloxacin</td>
<td>9–12*</td>
<td>A longer duration of treatment should be used for patients with extensive disease</td>
</tr>
<tr>
<td>R</td>
<td>H, E, moxifloxacin plus at least two months of Z</td>
<td>12–18*</td>
<td>An injectable agent may strengthen the regimen for patients with extensive disease</td>
</tr>
<tr>
<td>R and E (+/- S)</td>
<td>H, Z, moxifloxacin plus an injectable agent for at least the first 2–3 months</td>
<td>18</td>
<td>A longer course (six months) of the injectable agent may strengthen the regimen for patients with extensive disease</td>
</tr>
<tr>
<td>R and Z (+/- S)</td>
<td>H, E, moxifloxacin plus an injectable agent for at least the first 2–3 months</td>
<td>18</td>
<td>A longer course (six months) of the injectable agent may strengthen the regimen for patients with extensive disease</td>
</tr>
<tr>
<td>H, E, Z (+/- S)</td>
<td>R, moxifloxacin plus an oral second-line agent, plus an injectable agent for the first 2–3 months</td>
<td>18</td>
<td>A longer course (six months) of the injectable agent may strengthen the regimen for patients with extensive disease</td>
</tr>
</tbody>
</table>

* In most cases of drug-resistant TB, the longer time period is the preferred minimum duration of treatment.

Note: This table does not cover treatment of MDR-TB and XDR-TB – for further information about MDR-TB and XDR-TB, refer to Guidelines for Tuberculosis Control in New Zealand 2010, sections 3.5.4 and 3.5.5.
### 5.5 Recommended drug regimens for treatment of LTBI

Reproduced from *Guidelines for Tuberculosis Control in New Zealand 2010, Table 8.4, section 8.2.4*

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Drug</th>
<th>Administration</th>
<th>Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard regimen for adherent clients</td>
<td>H</td>
<td>Self, daily</td>
<td>6</td>
</tr>
<tr>
<td>Standard regimen for non-adherent clients</td>
<td>H</td>
<td>DOT, thrice weekly</td>
<td>6</td>
</tr>
<tr>
<td>Client HIV-positive (see Chapter 6)</td>
<td>H</td>
<td>Self, daily</td>
<td>9</td>
</tr>
<tr>
<td>Adherent clients with multiple risk factors (see Table 8.2)</td>
<td>H</td>
<td>Self, daily</td>
<td>9–12</td>
</tr>
<tr>
<td>Non-adherent clients with multiple risk factors (see Table 8.2)</td>
<td>H</td>
<td>DOT, thrice weekly</td>
<td>9–12</td>
</tr>
<tr>
<td>Short course regimen for adherent clients</td>
<td>RH</td>
<td>Self, daily</td>
<td>3</td>
</tr>
<tr>
<td>Short course regimen for non-adherent clients</td>
<td>RH</td>
<td>DOT, thrice weekly</td>
<td>4</td>
</tr>
<tr>
<td>Source case H-resistant or client cannot tolerate H or short course regimen preferred</td>
<td>R</td>
<td>Self, daily</td>
<td>4</td>
</tr>
<tr>
<td>Source case multi-drug-resistant* (see important note below)</td>
<td>Individually tailored (eg, ZE, or Z + quinolone)</td>
<td>Self, daily</td>
<td>6 (if immuno-competent) or alternatively no treatment 12 (if immuno-suppressed)</td>
</tr>
</tbody>
</table>

*Consultation and co-case management with a hospital specialist experienced in the treatment of MDR-TB/contacts of MDR-TB is essential. Most contacts of MDR-TB cases should not be treated but should be monitored closely for at least two years. Efficacy of these regimens is unproven. One prospective cohort study found individually tailored regimens to be effective in preventing active TB in children.

Notes: DOT = directly observed therapy; E = ethambutol; H = isoniazid; R = rifampicin; Z = pyrazinamide.

*A DR-TB/contacts of MDR-TB is essential. Most contacts of MDR-TB cases should not be treated but should be monitored closely for at least two years. Efficacy of these regimens is unproven. One prospective cohort study found individually tailored regimens to be effective in preventing active TB in children.
### 5.6 Adverse effects of tuberculosis drugs

Reproduced from *Guidelines for Tuberculosis Control in New Zealand 2010, Table 3.6, section 3.8*

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides (amikacin, capreomycin, kanamycin, streptomycin)</td>
<td>Ototoxicity (lowest incidence with streptomycin); renal damage, skin rashes, fevers, circum-oral paraesthesiae, neuromuscular blockade</td>
</tr>
<tr>
<td>Para-amino-salicylic acid</td>
<td>Gastrointestinal effects, hepatitis, fever, rash and hypothyroidism</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Dose-related central nervous system effects (drowsiness, vertigo, disorientation, confusion, coma and psychosis)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Optic neuropathy (dose-related); peripheral neuropathy, arthralgia or rash are rare</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>Gastrointestinal effects, liver toxicity; rarely hypothyroidism, hypotension, hypoglycaemia, alopecia, convulsions and neuropathy</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Gastrointestinal disturbances, dizziness, anxiety, depression, confusion and convulsions; rarely, achilles tendon rupture, arthropathy and photosensitivity. For use in children, consult a paediatric tuberculosis expert.</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Isoniazid hepatotoxicity: Hypersensitivity reactions are unusual. Peripheral neuropathy, optic neuritis, fever, hepatitis, ataxia, euphoria, convulsions, tinnitus, insomnina, hyperglycaemia, gynaecomastia, dry mouth, epigastric discomfort, urinary retention, anaemia, arthralgias. Contraindicated in manic states and porphyria. Idiosyncratic reactions may include a (usually reversible) lupus-like syndrome (fever, arthritis, pleuritis, pericarditis, positive rheumatoid factors, etc), and, very rarely, a rheumatoid arthritis-like syndrome, and agranulocytosis. Very rare hypersensitivity reactions include eosinophilia, angiitis, toxic psychosis, and meningo-encephalitis. Toxic doses decrease the synthesis of the inhibitory neurotransmitter gamma aminobutyric acid. Central nervous system depression or stimulation may result.</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Gastrointestinal side effects, hyperuricaemia, hepatotoxicity, fever, anorexia, nausea and vomiting; precipitation of gout (see section 3.11.2); arthralgias, urticaria, sideroblastic anaemia. Of the TB drugs, pyrazinamide is the most common cause of a rash.</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Rash, gastrointestinal disturbance, neutropaenia; uveitis, particularly in combination with macrolide antibiotics</td>
</tr>
</tbody>
</table>
Rifampicin
Gastrointestinal disturbance, cholestatic hepatic dysfunction, transient elevation of hepatic enzymes.
Danger with intermittent therapy: flu-like syndrome, shock, acute renal failure, death.
Acute haemolytic anaemia.
Rare reports of rifampicin-induced light chain proteinuria and renal failure, attributed to dehydration associated with fluid restriction for syndrome of inappropriate antidiuretic hormone.

Thiocetazone
Nausea, vomiting, diarrhoea, bone marrow depression, vertigo, ataxia, tinnitus, occasional liver toxicity, cutaneous hypersensitivity.

5.7 Drug challenge doses for mild-to-moderate reactions
Reproduced from Guidelines for Tuberculosis Control in New Zealand 2010, Table 3.7, section 3.9.2

<table>
<thead>
<tr>
<th>Drug</th>
<th>Day 1 dose</th>
<th>Day 2 dose</th>
<th>Days 3 and 4 doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>50 mg</td>
<td>100 mg</td>
<td>300 mg</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>75 mg</td>
<td>150 mg</td>
<td>450–600 mg</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>250 mg</td>
<td>500 mg</td>
<td>Full dose</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>100 mg</td>
<td>400 mg</td>
<td>Full dose</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>100 mg</td>
<td>500 mg</td>
<td>Full dose</td>
</tr>
</tbody>
</table>

## 5.8 Clinically important interactions with tuberculosis drugs

Reproduced from *Guidelines for Tuberculosis Control in New Zealand 2010*, Table 3.8, section 3.10

<table>
<thead>
<tr>
<th>Tuberculosis drug</th>
<th>Interacting agent</th>
<th>Effect</th>
<th>Advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Antacids, containing aluminium</td>
<td>Reduced absorption of isoniazid</td>
<td>As for fluoroquinolones + antacids</td>
</tr>
<tr>
<td></td>
<td>Anti-epileptics:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• carbemazepine</td>
<td>Inhibition of carbemazepine hepatic metabolism has been described</td>
<td>Monitor carbemazepine blood levels</td>
</tr>
<tr>
<td></td>
<td>• phenytoin</td>
<td>Inhibition of phenytoin hepatic metabolism; phenytoin toxicity may develop over days to weeks</td>
<td>Monitor phenytoin levels and symptoms</td>
</tr>
<tr>
<td></td>
<td>Antipsychotics</td>
<td>Possible increased plasma haloperidol</td>
<td>Adjust dose if needed</td>
</tr>
<tr>
<td></td>
<td>Anxiolytics and hypnotics</td>
<td>Possible delayed metabolic clearance of diazepam and triazolam, causing prolongation of their effects</td>
<td>Monitor effects; decrease dose if necessary</td>
</tr>
<tr>
<td></td>
<td>Anti-fungals</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ketoconazole</td>
<td>Possible decreased antifungal blood level</td>
<td>No problem using Fluconazole</td>
</tr>
<tr>
<td></td>
<td>Cyclosporin</td>
<td>Marked rise in cyclosporin levels</td>
<td>Monitor cyclosporin blood levels</td>
</tr>
<tr>
<td></td>
<td>Disulfiram</td>
<td>Central nervous system toxic effects of Disulfiram among 30% of people on both</td>
<td>Reduce dose or discontinue Disulfiram</td>
</tr>
<tr>
<td></td>
<td>Enfluorane</td>
<td>Enhanced defluorination of this anaesthetic agent may lead to accumulation of nephrotoxic fluoride (more likely in isoniazid rapid acetylators)</td>
<td>Avoid concurrent use of these two agents</td>
</tr>
<tr>
<td></td>
<td>Histamine-rich food: cheese, sauerkraut, yeast extract, tuna</td>
<td>Flushing, chills, headache, wheeziness, palpitations, diarrhoea, vomiting, burning</td>
<td>Advise on diet; give antihistamine, if necessary</td>
</tr>
<tr>
<td></td>
<td>Tyramine-rich foods</td>
<td>Red wine, cheese, yeast extract (due to slight monoamine oxidase effect of isoniazid)</td>
<td>Advise on diet</td>
</tr>
<tr>
<td>Tuberculosis drug</td>
<td>Interacting agent</td>
<td>Effect</td>
<td>Advice</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Rifampicin and rifabutin</td>
<td>Reduced levels of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiarrythmics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• dispyramide</td>
<td></td>
<td></td>
<td>Monitor response</td>
</tr>
<tr>
<td>• mexilitine</td>
<td></td>
<td></td>
<td>Avoid use</td>
</tr>
<tr>
<td>• propafenone</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• quinidine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antifungals</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• itraconazole</td>
<td></td>
<td></td>
<td>Monitor serum level; may increase antifungal dose</td>
</tr>
<tr>
<td>• fluconazole</td>
<td>Raised rifabutin level</td>
<td>As for clarithromycin</td>
<td></td>
</tr>
<tr>
<td>• ketaconazole</td>
<td>Reduced absorption, halving the rifampicin level</td>
<td>Give at least 12 hours apart; check rifampicin level</td>
<td></td>
</tr>
<tr>
<td>Anti-retrovirals (see Chapter 8)</td>
<td>Significant interactions occur between the rifamycin drugs and the protease inhibitors and the non-nucleoside reverse transcriptase inhibitors</td>
<td>See Chapter 6 for details</td>
<td></td>
</tr>
<tr>
<td>Clarithromycin (and possibly other macrolides)</td>
<td>Raised rifabutin levels; risk of uveitis</td>
<td>Keep rifabutin dose at or below 300 mg/day; acute uveitis: stop rifabutin; ophthalmology review.</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Profound reduction in steroid levels</td>
<td>Increase steroid dose two- to three-fold; reduce when rifamycin is discontinued</td>
<td></td>
</tr>
<tr>
<td>• gluco- and mineralo-corticoids</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diazepam, nitrazepam</td>
<td></td>
<td></td>
<td>Monitor serum level; may need to increase dose.</td>
</tr>
<tr>
<td>Digitalis preparations</td>
<td>Likely with renal impairment</td>
<td>Monitor levels; dose may need to be doubled.</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressive agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• cyclosporin</td>
<td>Levels reduced about 50%; significance uncertain</td>
<td>May need three- to five-fold increase in cyclosporin dose</td>
<td></td>
</tr>
<tr>
<td>• tacrolimus</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-aminosalicylic acid</td>
<td>Possible increase in serum rifampicin</td>
<td>Ensure these two agents are taken eight hours apart.</td>
<td></td>
</tr>
<tr>
<td>Phenytoin concurrent isoniazid</td>
<td>Markedly reduced anti-epileptic effect, especially in fast acetylators</td>
<td></td>
<td>Isoniazid counteracts lowering of serum phenybin by rifampicin</td>
</tr>
<tr>
<td>Tuberculosis drug</td>
<td>Interacting agent</td>
<td>Effect</td>
<td>Advice</td>
</tr>
<tr>
<td>-------------------</td>
<td>-------------------</td>
<td>--------</td>
<td>--------</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• tolbutamide</td>
<td></td>
<td></td>
<td>Monitor diabetic control.</td>
</tr>
<tr>
<td>• possibly others (eg, glibenclamide)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Warfarin (see also section 3.10.1)</td>
<td>Markedly reduced anticoagulation</td>
<td>Warfarin dose may need to be doubled or tripled at the start, and be similarly reduced when the rifamycin is stopped (see also section 3.10.1).</td>
<td></td>
</tr>
<tr>
<td>Ethambutol</td>
<td>No interactions of note</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Allopurinol (see also section 3.10.2)</td>
<td>Acute gout</td>
<td>Avoid allopurinol; try colchicine instead. May need to abandon use of pyrazinamide.</td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td>Antacids, containing aluminium, calcium and magnesium</td>
<td>Reduced absorption of fluoroquinolones</td>
<td>Avoid antacids; or give fluoroquinolone two hours before or four hours after antacid</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Occasional, unpredictable prolonged prothrombin time</td>
<td>Monitor anticoagulation carefully, if starting or stopping fluoroquinolones.</td>
<td></td>
</tr>
<tr>
<td>Iron and zinc</td>
<td>As for fluoroquinolones + antacids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sucralfate</td>
<td>As for fluoroquinolones + antacids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethionamide and protonamide</td>
<td>Increased risk of hepatotoxicity with rifampicin, isoniazid and pyrazinamide</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### 5.9 Risk factors for poor adherence

**Recommended level of supervision**

Reproduced from *Guidelines for Tuberculosis Control in New Zealand 2010, Table 4.1, section 4.2.2*

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Level of supervision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent regimens (thrice-weekly doses)</td>
<td>Directly observed therapy</td>
</tr>
<tr>
<td>Resistance to rifampicin or multi-drug resistance (resistance to isoniazid</td>
<td></td>
</tr>
<tr>
<td>and rifampicin) and other cases of multiple drug resistance</td>
<td></td>
</tr>
<tr>
<td>All relapses and re-activations</td>
<td></td>
</tr>
<tr>
<td>Inability or unwillingness to self-medicate (e.g., substance abuse, denial</td>
<td></td>
</tr>
<tr>
<td>of diagnosis, homelessness, intellectual limitations)</td>
<td></td>
</tr>
<tr>
<td>Consistent failure to comply with ward or outpatient clinic requests</td>
<td></td>
</tr>
<tr>
<td>Poor adherence during close supervision</td>
<td></td>
</tr>
<tr>
<td>Extensive disease and high infectiousness</td>
<td></td>
</tr>
<tr>
<td>Weak or absent social support</td>
<td>Close supervision: consider directly</td>
</tr>
<tr>
<td>Psychiatric illness</td>
<td>observed therapy</td>
</tr>
<tr>
<td>Troublesome drug side effects</td>
<td></td>
</tr>
<tr>
<td>Complex treatment regimen</td>
<td></td>
</tr>
<tr>
<td>Record of previous non-adherence with regard to treatment for other</td>
<td></td>
</tr>
<tr>
<td>diseases</td>
<td></td>
</tr>
<tr>
<td>None of the above risk factors</td>
<td>Self-administered treatment</td>
</tr>
<tr>
<td>None of the above risk factors</td>
<td></td>
</tr>
</tbody>
</table>

Auckland/Northland DHBs TB case management document – Auckland version
July 2011
5.10 Decision table to aid discharge from isolation
From the ADHB Respiratory Service’s TB Orientation and Resource Kit (used with permission)

Spontaneous sputum smear-positive and drug resistant TB not identified or suspected:

Discharge can be considered using the following recommendation based on TTD-TB (time to detect TB) criteria for susceptible isolates using the following table.

<table>
<thead>
<tr>
<th>Initial Smear Grade</th>
<th>Duration of isolation for mild disease - Provided clinical improvement has occurred (e.g. “no” cough at discharge)</th>
<th>Duration of isolation for: Extensive cavitation / Frequent/ severe cough/ Little clinical improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>If not coughing, isolation may not be required – discuss with a consultant</td>
<td>Until clinical improvement and after 14 days of treatment</td>
</tr>
<tr>
<td>1</td>
<td>Until clinical improvement and after 14 days</td>
<td>Until clinical improvement and after 14 days</td>
</tr>
<tr>
<td>2</td>
<td>Until clinical improvement and after 14 days</td>
<td>Until clinical improvement and after 14 days</td>
</tr>
<tr>
<td>3</td>
<td>14 days</td>
<td>28 days may be required</td>
</tr>
<tr>
<td>4</td>
<td>25 days may be required</td>
<td>42 days may be required</td>
</tr>
</tbody>
</table>

- Discuss discharge plan with consultant and document in the TB Pathway (document date discussed and the number of days before discharge).
- Patients 1+ or 2+ AFB can be discharged after 7 days if there has been clinical improvement and the patient is not coughing however should remain in isolation at home for further 7 days.
- If patient has extensive disease review clinical response and assess if discharge at 42 days is appropriate.
- Ensure proposed length of treatment is discussed with a Consultant and documented in the TB pathway.

Organism resistant to one or more TB drugs or drug resistance suspected:

Patients with smear-positive spontaneous sputum and resistance to one or more drugs first require retesting of sputum after 2 weeks of TB treatment.

Results:

If 4+ AFB seen (>9 AFB seen per high power field) retest in two weeks
If 3+ AFB seen (1-9 AFB seen per high power field) retest in one week
If 2+ AFB seen (1-9 seen per 10 high power fields) or less send second sputum if less than 3+ AFB or less send third specimen.

- Discharge can be considered when the following have been achieved:
  - three negative sputum’s obtained or sputum is 2+ on two consecutive specimens.
  - Two weeks of treatment completed
  - Clinical improvement
5.11 Pharmacy contact details

South

Hunts Pharmacy,
359 Massey Rd, Mangere
Ph 275-9027   Fx 523-6769

Life Pharmacy,
Manukau Shopping Centre
PO Box 76005, Manukau City
Ph 262-1884   Fx 262-1660

Central

Walls & Roche, Royal Oak Pharmacy,
792 Manukau Road, Royal Oak
Ph 625-7488   Fx 625-7691

Auckland City Hospital Retail Pharmacy
Level 5 Support Building, Auckland City Hospital, Park Rd, Grafton,
Ph 307 8997 (Internal extension 25897) Fx 307 8998

Greenlane Clinical Centre Pharmacy
214 Greenlane West Rd, Greenlane,
Ph 623 4693 (Internal Extension 26789) Fx 630 9801

North

North Harbour Pharmacy,
1/326 Sunset Rd, Mairangi Bay
Ph 479-8006   Fx 479-1083

West

Ratanui Pharmacy
77 Lincoln Rd, Henderson
Ph 837-5234   Fx 836-2943
6 Abbreviations

AFB
Acid-fast bacilli

AII
Airborne infection isolation

BAL
Broncho-alveolar lavage

CARM
Centre for Adverse Reactions Monitoring

CNS
Central nervous system

CXR
Chest X-ray

DOT
Directly Observed Therapy

DST
Drug susceptibility testing

E
Ethambutol

EMU
Early morning urine

FBC
Full blood count

FNA
Fine needle aspiration

H
Isoniazid

IBW
Ideal body weight

IGRA
Interferon-gamma release assay

LFTs
Liver function tests

MDR-TB
Multi-drug resistant TB (resistant to isoniazid and rifampicin)

MOH
Medical Officer of Health

Moxi
Moxifloxacin

MSU
Midstream urine

PHN
Public Health Nurse

Px
Pyridoxine

R
Rifampicin

Rb
Rifabutin

RH
Rifinah

S
Streptomycin

TB
Tuberculosis

TBLG
TB Liaison Group

TST
Tuberculin skin test

U & E
Urea & electrolytes

XDR-TB
Extensively drug-resistant TB (MDR-TB that is, in addition, also resistant to any fluoroquinolone and at least one of three injectable agents)

Z
Pyrazinamide