Guidelines for Tuberculosis Control in New Zealand 2010
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Chapter 1: Epidemiology and Surveillance of Tuberculosis in New Zealand

Summary
For the latest epidemiological information, see the Public Health Surveillance website (http://www.surv.esr.cri.nz).

Epidemiology of tuberculosis
Recent tuberculosis (TB) notification rates in New Zealand have been around 10 per 100,000. Incidence has decreased slightly in recent years to around 7 per 100,000.

Higher rates of disease in New Zealand compared to other developed countries may be attributed to socioeconomic deprivation and immigration from high-incidence countries. Over two-thirds of all TB cases in New Zealand are in foreign-born individuals.

The highest rates of disease are seen in individuals:
- in urban areas, particularly Auckland and South Auckland
- of non-European ethnicity, particularly ‘Other’ and Pacific People.

Type, management and outcome of tuberculosis cases
Two-thirds of TB cases are pulmonary. Of the extra-pulmonary cases, the most common sites of infection are lymph nodes.

Morbidity and mortality from TB have been declining in recent years.
Multi-drug resistance occurs in less than 1% of all TB isolates.

Surveillance of tuberculosis
Surveillance is important for supporting the local management of TB, monitoring disease incidence and identifying risk factors.

A medical practitioner who diagnoses or suspects a case of new or relapsed TB must, under the Tuberculosis Act 1948, notify the case to the local medical officer of health.

It is not a legal requirement for clinicians to notify the local medical officer of health about people receiving treatment for latent TB infection. However, clinicians are asked to report cases to the local medical officer of health, for monitoring purposes, if the cases are of latent TB infection that are, or are recommended to be, under treatment.

Recent changes to surveillance include:
- alterations to the TB case report form
- the production of an annual surveillance report for TB (see the Public Health Surveillance website, http://www.surv.esr.cri.nz)
- DNA fingerprinting of all isolates.

Recent improvements to the system include:
- laboratory notification of positive results to identify un-notified cases
- regular review of surveillance data to inform policy development.
Introduction

This chapter:
- reviews the epidemiology of tuberculosis (TB) in New Zealand using EpiSurv notification data from 2002 to 2007
- describes the system of TB surveillance adopted in New Zealand.

The information in this chapter was obtained from:
- recent reviews of TB epidemiology in New Zealand\textsuperscript{1,2}
- data from the Institute of Environmental Science and Research (ESR).

For the latest epidemiological information, visit the Public Health Surveillance website (http://www.surv.esr.cri.nz).

1.1 Epidemiology of tuberculosis

1.1.1 Trends in incidence

Compulsory notification for all forms of TB was introduced in New Zealand in 1940.\textsuperscript{1} Notifications peaked in 1943 with 2600 cases, a rate of 142 per 100,000 (see Figure 1.1). After this peak in cases around the time of the Second World War there was a steady decline in disease incidence.

Figure 1.1: Tuberculosis notification rates, 1943–2009
Between 1995 and 2004, the incidence of TB increased in New Zealand (see Figure 1.2), and a similar trend was observed in other developed countries. Occurrence of human immunodeficiency virus (HIV) infection and acquired immune deficiency syndrome (AIDS), emergence of multi-drug-resistant organisms, and increased immigration from high incidence countries, have been implicated as causes for the TB increase. The findings of a New Zealand study in 2006 indicated that HIV is making only a small contribution to TB incidence in New Zealand, unlike some other countries, and that migration from high TB-incidence countries was the predominant source of TB in New Zealand. Since 1997, there is some evidence that incidence is decreasing, resulting in a low of 290 TB disease notifications in 2007 — the lowest figure since records began.

Figure 1.2: Trend in tuberculosis incidence, 1980–2009

The current average annual rate of TB in New Zealand of around 7–10 per 100,000 is lower than that reported from the United Kingdom (15 per 100,000), but is higher than that reported from the United States (4 per 100,000), Canada (5 per 100,000) and Australia (6 per 100,000).

Although the validity of international comparisons is limited by variations in case detection and reporting practices, higher rates in New Zealand have raised concerns about the effectiveness of current prevention and control activities. Sociodemographic factors such as poverty, overcrowding and migration from countries of high incidence have been identified as contributing to the disease’s resurgence in New Zealand. In late 2004 TB screening was introduced for international students staying more than six months in New Zealand and in late 2005 new migrant health screening requirements (including for TB) were implemented in New Zealand.
1.1.2 Outbreaks

An estimated 10% of all notified TB cases occur as part of recognised TB outbreaks. Accurate reporting of outbreak-related cases of TB is limited by incomplete recording of outbreak numbers on EpiSurv. Large outbreaks, involving 12–61, cases have occurred in a school, church group and prison.\textsuperscript{7–9}

1.1.3 Incidence by District Health Board

In New Zealand, several District Health Boards (DHBs) report consistently high rates of TB. In 2008, Auckland (12.3 per 100,000), Counties-Manukau (12.0 per 100,000) and Hutt Valley (12.0 per 100,000) had the highest rates.\textsuperscript{10} This is consistent with overseas findings that disease tends to persist in urban areas,\textsuperscript{11} and is consistent with the geographic distribution of ethnic groups most affected by the disease.

Several studies have examined the epidemiology of TB in the Auckland\textsuperscript{12–14} and Wellington regions.\textsuperscript{15,16} The clustering of cases in areas of socioeconomic deprivation and the importance of immigration from countries with a high incidence of TB have been noted in both areas.

1.1.4 Incidence by age

The majority of TB cases occur in adults, with the highest rates per 100,000 in those aged 20–29 years followed by those aged 70 and over (see Table 1.1). Children aged under 15 years account for 7–14% of all cases, but this proportion varies significantly by ethnicity (25% of cases in Pacific peoples, 14% in Māori, 5% in Europeans and 4% in ‘Others’). Although the incidence of TB in children remains low, it has not fallen in recent years.\textsuperscript{17}

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>2005</th>
<th>2006</th>
<th>2007</th>
<th>2008</th>
<th>2009</th>
<th>Total 2005–09</th>
<th>% cases Census population 2006</th>
<th>Average rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>12</td>
<td>0.8%</td>
<td>55,015</td>
</tr>
<tr>
<td>1 to 4</td>
<td>9</td>
<td>10</td>
<td>9</td>
<td>3</td>
<td>9</td>
<td>40</td>
<td>2.6%</td>
<td>220,061</td>
</tr>
<tr>
<td>5 to 9</td>
<td>6</td>
<td>4</td>
<td>7</td>
<td>6</td>
<td>6</td>
<td>29</td>
<td>1.9%</td>
<td>286,491</td>
</tr>
<tr>
<td>10 to 14</td>
<td>9</td>
<td>19</td>
<td>4</td>
<td>6</td>
<td>3</td>
<td>41</td>
<td>2.6%</td>
<td>306,009</td>
</tr>
<tr>
<td>15 to 19</td>
<td>17</td>
<td>20</td>
<td>20</td>
<td>15</td>
<td>15</td>
<td>87</td>
<td>5.6%</td>
<td>300,198</td>
</tr>
<tr>
<td>20 to 29</td>
<td>85</td>
<td>88</td>
<td>53</td>
<td>59</td>
<td>64</td>
<td>349</td>
<td>22.3%</td>
<td>513,417</td>
</tr>
<tr>
<td>30 to 39</td>
<td>62</td>
<td>58</td>
<td>51</td>
<td>58</td>
<td>53</td>
<td>282</td>
<td>18.0%</td>
<td>578,121</td>
</tr>
<tr>
<td>40 to 49</td>
<td>51</td>
<td>48</td>
<td>33</td>
<td>29</td>
<td>48</td>
<td>209</td>
<td>13.4%</td>
<td>607,116</td>
</tr>
<tr>
<td>50 to 59</td>
<td>30</td>
<td>33</td>
<td>29</td>
<td>35</td>
<td>39</td>
<td>166</td>
<td>10.6%</td>
<td>486,303</td>
</tr>
<tr>
<td>60 to 69</td>
<td>28</td>
<td>26</td>
<td>34</td>
<td>39</td>
<td>30</td>
<td>157</td>
<td>10.0%</td>
<td>328,170</td>
</tr>
<tr>
<td>70+</td>
<td>34</td>
<td>45</td>
<td>39</td>
<td>42</td>
<td>30</td>
<td>190</td>
<td>12.1%</td>
<td>347,046</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
<td>2</td>
<td>0.1%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td>333</td>
<td>354</td>
<td>284</td>
<td>293</td>
<td>300</td>
<td>1564</td>
<td>100.0%</td>
<td>4,027,947</td>
</tr>
</tbody>
</table>

Source: EpiSurv - Institute of Environmental Science and Research.
1.1.5 Incidence by ethnicity

The TB rate among Māori is five times that among Europeans while in Pacific peoples it is 10 times higher than in Europeans and in Asian ethnic groups the rate is 25 times greater than in Europeans (see Table 1.2). Ethnic disparities have increased in recent times, although differences in TB incidence by ethnic group are confounded by place of birth.

Table 1.2: Age-specific tuberculosis notifications by ethnicity, 2005–09

<table>
<thead>
<tr>
<th>Ethnicity prioritised</th>
<th>Total notifications</th>
<th>Annual rate per 100,000</th>
<th>Relative rate cf European</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asian</td>
<td>756</td>
<td>44.4</td>
<td>25.7</td>
</tr>
<tr>
<td>European</td>
<td>197</td>
<td>1.7</td>
<td>1.0</td>
</tr>
<tr>
<td>Maori</td>
<td>254</td>
<td>9.0</td>
<td>5.2</td>
</tr>
<tr>
<td>Other</td>
<td>97</td>
<td>4.4</td>
<td>2.5</td>
</tr>
<tr>
<td>Pacific peoples</td>
<td>207</td>
<td>18.3</td>
<td>10.6</td>
</tr>
<tr>
<td>Unknown</td>
<td>44</td>
<td>5.2</td>
<td>3.0</td>
</tr>
<tr>
<td>Total</td>
<td>1,555</td>
<td>7.7</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Source: EpiSurv - Institute of Environmental Science and Research.

1.1.6 Incidence by place of birth

Immigration has been an important factor contributing to the TB incidence in New Zealand (see Table 1.3 and Chapter 10).

Table 1.3: Tuberculosis in people born in and outside New Zealand, 2005–09

<table>
<thead>
<tr>
<th>Year</th>
<th>Number born outside New Zealand</th>
<th>Number born in New Zealand</th>
<th>Number for whom place of birth unknown</th>
<th>Total</th>
<th>Percent born outside New Zealand</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>240</td>
<td>77</td>
<td>13</td>
<td>330</td>
<td>72.7%</td>
</tr>
<tr>
<td>2006</td>
<td>230</td>
<td>104</td>
<td>16</td>
<td>350</td>
<td>65.7%</td>
</tr>
<tr>
<td>2007</td>
<td>187</td>
<td>84</td>
<td>11</td>
<td>282</td>
<td>66.3%</td>
</tr>
<tr>
<td>2008</td>
<td>213</td>
<td>79</td>
<td>1</td>
<td>293</td>
<td>72.7%</td>
</tr>
<tr>
<td>2009</td>
<td>220</td>
<td>78</td>
<td>2</td>
<td>300</td>
<td>73.3%</td>
</tr>
<tr>
<td>Total</td>
<td>1090</td>
<td>422</td>
<td>43</td>
<td>1555</td>
<td>70.1%</td>
</tr>
</tbody>
</table>

Source: EpiSurv - Institute of Environmental Science and Research.

1.1.7 Social vulnerability as a risk factor for tuberculosis

TB has been described as a ‘barometer of social justice and equity’. Although TB affects people in all countries, it mostly affects the poorest and most vulnerable communities. The effect of poverty on rates of TB appears to be independent of ethnicity. In Auckland, notification rates among New Zealand-born individuals are 60 times higher in the least affluent parts of the region (NZDep 10) than in the most affluent (NZDep 1).
1.1.8 Other risk factors
The following are the known risk factors for contacting TB.

- Contact with a known case of TB – the most common risk factor for disease (see Chapter 7).

- Institutional contact – listed institutions include refugee camps and immigration centres, prisons, rest homes, and mental health facilities (see Chapters 9 and 12).

- Occupational contact – as a risk factor this is poorly documented. A study of Auckland medical students, residents and registrars found a risk of TB infection among medical staff.20

- Exposure to cattle, deer, possums and certain animal products – this is a risk factor for the development of Mycobacterium bovis infection (bovine TB). Around 3% of TB cases are M. bovis. Low rates are attributable to herd testing and the widespread pasteurisation of milk.

- Association with the HIV/AIDS epidemic – TB in certain high-incidence countries is increasing because of the disease’s association with the HIV/AIDS epidemic. However, in New Zealand TB is uncommon in patients with HIV infection (around 1% of TB cases have HIV co-infection). See Chapter 6.

1.2 Type, management and outcome of notified tuberculosis cases

1.2.1 Laboratory confirmation
The proportion of laboratory-confirmed cases increased from 44% in 1988 to 82% in 2009.

1.2.2 Site of infection
Of the notified cases for which the site of infection is recorded, 67% are pulmonary. The remaining cases are a combination of pulmonary and extra-pulmonary (5%) and extra-pulmonary alone (28%). A breakdown of extra-pulmonary cases by site of infection is in Table 1.4.
Table 1.4: Extra-pulmonary tuberculosis cases, by site, 2002–07

<table>
<thead>
<tr>
<th>Site of extra-pulmonary tuberculosis</th>
<th>Number</th>
<th>Proportion of extra-pulmonary cases* (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Node (excluding abdominal)</td>
<td>404</td>
<td>27.7</td>
</tr>
<tr>
<td>Intra-abdominal (excluding renal)</td>
<td>96</td>
<td>6.6</td>
</tr>
<tr>
<td>Pleural</td>
<td>151</td>
<td>10.4</td>
</tr>
<tr>
<td>Renal/urinary tract</td>
<td>30</td>
<td>2.1</td>
</tr>
<tr>
<td>Tuberculous meningitis</td>
<td>24</td>
<td>1.6</td>
</tr>
<tr>
<td>Miliary tuberculosis</td>
<td>17</td>
<td>1.2</td>
</tr>
<tr>
<td>Bone/joint</td>
<td>113</td>
<td>7.8</td>
</tr>
<tr>
<td>Other†</td>
<td>92</td>
<td>6.3</td>
</tr>
<tr>
<td>Not stated or unknown</td>
<td>584</td>
<td>40.1</td>
</tr>
<tr>
<td>Total</td>
<td>1511</td>
<td></td>
</tr>
</tbody>
</table>

Notes:
* Some patients had disease at more than one site, so the percentages total more than 100.
† Other includes TB of the skin.
Source: Institute of Environmental Science and Research.

1.2.3 Morbidity and mortality

Although the incidence of disease has decreased slightly over recent years, the proportion of all cases hospitalised or dying (the case fatality rate) as a result of TB changed only slightly between 2002 and 2008 (Table 1.5).

Table 1.5: Morbidity and mortality of tuberculosis cases, 1997–2009

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of notifications</th>
<th>Annual notification rate</th>
<th>Number of hospitalisations</th>
<th>Number of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>323</td>
<td>8.5</td>
<td>229</td>
<td>15</td>
</tr>
<tr>
<td>1998</td>
<td>365</td>
<td>9.6</td>
<td>252</td>
<td>8</td>
</tr>
<tr>
<td>1999</td>
<td>446</td>
<td>11.6</td>
<td>267</td>
<td>14</td>
</tr>
<tr>
<td>2000</td>
<td>354</td>
<td>9.2</td>
<td>204</td>
<td>8</td>
</tr>
<tr>
<td>2001</td>
<td>369</td>
<td>9.5</td>
<td>208</td>
<td>2</td>
</tr>
<tr>
<td>2002</td>
<td>381</td>
<td>9.6</td>
<td>200</td>
<td>6</td>
</tr>
<tr>
<td>2003</td>
<td>423</td>
<td>10.5</td>
<td>236</td>
<td>6</td>
</tr>
<tr>
<td>2004</td>
<td>375</td>
<td>9.2</td>
<td>222</td>
<td>6</td>
</tr>
<tr>
<td>2005</td>
<td>330</td>
<td>8.0</td>
<td>187</td>
<td>4</td>
</tr>
<tr>
<td>2006</td>
<td>350</td>
<td>8.4</td>
<td>188</td>
<td>5</td>
</tr>
<tr>
<td>2007</td>
<td>283</td>
<td>6.7</td>
<td>152</td>
<td>3</td>
</tr>
<tr>
<td>2008</td>
<td>296</td>
<td>6.9</td>
<td>171</td>
<td>4</td>
</tr>
<tr>
<td>2009</td>
<td>306</td>
<td>7.1</td>
<td>182</td>
<td>3</td>
</tr>
</tbody>
</table>

Source: Institute of Environmental Science and Research.

Nearly two-thirds (65%) of TB hospitalisations are in adults. Hospitalisation and mortality rates are highest for adults aged 70 years and over.
1.2.4 Antibiotic resistance

Despite the high proportion of imported cases of TB in New Zealand, multi-drug–resistant TB is not a major problem in New Zealand (see Table 1.6). Multi-drug resistance is resistance to at least the antibiotics isoniazid and rifampicin.

Table 1.6: Resistance patterns among culture-positive cases of TB notified in 2003–08

<table>
<thead>
<tr>
<th>Resistance</th>
<th>Number (%) of isolates</th>
<th>Resistance pattern (^a)</th>
<th>Number (%) of isolates with each pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully susceptible</td>
<td>1359 (84.5)</td>
<td>H</td>
<td>71 (4.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>S</td>
<td>66 (4.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Z</td>
<td>49 (3.1)(^b)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>R</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Resistant to one agent</td>
<td>190 (11.8)</td>
<td>HS</td>
<td>36 (2.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HZ</td>
<td>3 (0.2)(^c)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HR</td>
<td>2 (0.1)(^d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HE</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ZS</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Resistant to two agents</td>
<td>43 (2.7)</td>
<td>HRE</td>
<td>2 (0.1)(^d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HRZ</td>
<td>2 (0.1)(^d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HES</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HZS</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Resistant to three agents</td>
<td>8 (0.5)</td>
<td>HRES</td>
<td>3 (0.2)(^d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HREZ</td>
<td>1 (0.1)(^d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HEZS</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>Resistant to four agents</td>
<td>5 (0.3)</td>
<td>HREZS</td>
<td>3 (0.2)(^d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Resistant to five agents</td>
<td>3 (0.2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes:

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

b Includes 31 of the 34 *Mycobacterium bovis* isolates.

c Includes the remaining 3 *M. bovis* isolates.

d Multi-drug–resistant isolates (that is, resistant to at least isoniazid and rifampicin).

Source: Institute of Environmental Science and Research.

1.3 Surveillance of tuberculosis

1.3.1 Objectives

Notification of cases of TB forms the basis of the surveillance and public health follow-up of cases and contacts. The early identification of TB cases is central to the effective management and control of this disease.

The specific objectives of surveillance are to:

- support the local management of identified cases, contacts and screening programmes
- monitor the incidence and distribution of disease and infection, at both local and national levels
- identify risk factors to support interventions aimed at preventing TB
1.3.2 Definitions of terms used in surveillance

The accurate classification of cases is essential for high-quality surveillance. ESR has produced a manual for public health surveillance in New Zealand, which explains how to complete the TB case report form. For current case definitions and terms, see the ESR website (http://www.surv.esr.cri.nz).

1.3.3 Notification and data collection

**Tuberculosis disease: new cases**

A medical practitioner who diagnoses or suspects a case of new or relapsed TB must, under the Tuberculosis Act 1948, notify the case to the local medical officer of health. Notification should be made by telephone or fax. The public health service will liaise with the diagnosing clinician. The clinician must complete the TB case report form. The public health service then enters details of the suspected case into the national TB computerised surveillance database (EpiSurv).

The details entered into EpiSurv are only provisional, since laboratory results and some other surveillance data are not usually available until some time after the initial diagnosis has been made. Once further results are obtained, the database is updated. When a presumptive case is subsequently shown not to meet the case definition, the clinician must notify the medical officer of health, so the record can be de-notified (that is, reclassified as ‘not a case’ in EpiSurv).

**Tuberculosis disease: relapse or reactivation**

Reactivated cases must be notified or re-notified to the medical officer of health. The TB case report form allows reactivated cases to be clearly distinguished from new cases of disease. Clinicians should record information about previous diagnoses and treatment on the relevant sections of the form. Importantly, the clinician must re-notify cases if treatment is started or the patient is rendered non-infectious and then becomes infectious again (as a result of treatment failure or non-adherence).

**Tuberculosis: treatment of latent tuberculosis infection and tuberculosis infection – old disease on preventive treatment**

Latent TB infection and TB infection cases are not legally required to be notified. However, clinicians are requested to report every case under treatment, or that is recommended to be under treatment, to the local medical officer of health for surveillance and control purposes (for example, adherence monitoring). The patient should consent to this.

TB surveillance is overviewed in Appendix 1.1 at the end of this chapter.
Contacts

Contacts are identified as part of the investigation of cases by public health service staff. Details should be recorded on the summary of contact information form (see Chapter 7).

Where contacts are subsequently identified as cases of TB disease or are commenced on treatment for TB infection, public health service staff should complete a case report form and the data should be entered onto the EpiSurv database.
Appendix 1.1: Tuberculosis surveillance information flows

CLINICAL/DIAGNOSTIC LEVEL

Specimens

Diagnosis and management by clinician

Lab results and reminder to notify

Laboratory investigation

LOCAL PUBLIC HEALTH LEVEL

Suspected cases referred

Consultation regarding case management

Case management (disease and infection)

Screening programmes

Suspected cases detected in the community

Contact investigation

Case notifications

Identified contacts

TB disease and infection database

Anonymised case and contact data

NATIONAL PUBLIC HEALTH LEVEL

Provision of isolation and sensitivity data on cases

National TB database (ESR:Health)

Analysis of national data

Ministry of Health

Reporting

KEY: TB control activity  TB database  information flows
References


Chapter 2: Clinical Features, Investigation and Assessment of Active Tuberculosis Disease

Summary
This chapter gives a summary of the definitions of different states of TB infection, and an overview of the clinical features of active TB disease. The investigation of TB disease is also described. For a more comprehensive account, a list of further reading is supplied at the end of this chapter.

The most important aspect of making a diagnosis of active TB disease is to maintain a high clinical suspicion, especially in patients recently exposed to TB and with previous prolonged residence in a high incidence TB country, especially if they have recently arrived in New Zealand. The demographics of TB in New Zealand must be borne in mind, and are described fully in Chapter 1.

Active TB disease may be asymptomatic, but common systemic symptoms include fever, night sweats, weight loss, anorexia and malaise.

Pulmonary TB is the most common form of active TB, and is often present in those with extrapulmonary TB. Common symptoms include cough (initially non-productive) and haemoptysis. Chest pain may accompany pleural involvement and breathlessness may occur late when disease becomes extensive. Clinical signs are often few. Characteristically, upper lobe or apical lower lobe changes occur on chest X-ray, although overall chest X-ray changes are not specific and may not predict disease activity. Rapid diagnosis of pulmonary TB is essential as such patients are often infectious to others.

The most common form of extrapulmonary TB is lymphadenopathy, most commonly presenting in the cervical or mediastinal regions. Nodes may enlarge even during or after completion of successful treatment. Pleural TB is the next most common form and may present with chest pain or breathlessness, and without obvious pulmonary TB. Abdominal TB is often associated with prominent systemic symptoms and weight loss. Peritoneal or ileo-caecal disease are most common. Liver function tests may be abnormal due to presumed hepatic granulomatous inflammation.

Central nervous system (CNS) TB causes significant morbidity and mortality, and diagnosis is often delayed. Meningitis or focal signs and reduced conscious level may occur. Pericardial TB may also lead to permanent morbidity from constrictive pericarditis. Genitourinary TB is often silent and may thus cause renal impairment, bladder damage, or infertility. TB may also affect the larynx, eye, or endocrine organs. Finally, disseminated or miliary (blood borne) TB is a life threatening condition with the potential for serious morbidity and mortality.

Investigation for TB still relies on chest X-ray and examination of appropriate specimens for AFB smear, mycobacterial culture and the histological hallmark of necrotising granulomatous inflammation. Specimens may be obtained via sputum induction, bronchoscopy, fine needle aspiration and biopsy. Imaging such as CT, ultrasound or endobronchial/endoscopic ultrasound may help to guide needle aspiration. Despite newer laboratory techniques, TB culture still takes time so PCR techniques may provide additional more rapid information. Tuberculin skin testing and interferon gamma release assays may provide supportive evidence for a diagnosis of active TB in appropriate clinical settings.
Introduction

Primary pulmonary TB infection is usually asymptomatic. The only sign that infection has occurred is the conversion of the tuberculin skin test (TST) or interferon gamma release assay (IGRA) to positive (see Chapter 8). Occasionally, erythema nodosum (a characteristic skin rash) may occur during TST conversion, as may mediastinal lymphadenopathy as part of the primary TB complex. Development of subsequent TB disease only occurs in approximately 10% of otherwise healthy individuals, and the risk is highest early, in the first two years after primary infection.

‘Latent TB infection’ (LTBI) is the term used to describe a TST or IGRA positive individual who is asymptomatic with no signs of TB disease, and from whom TB organisms cannot be cultured. It is usually thought that such individuals harbour dormant or inactive TB organisms, although this is controversial. Such persons have normal or only trivial changes on chest X-ray, such as a small scar or patch of calcification.

The phrase ‘Inactive TB’ is sometimes used to refer to individuals with LTBI who have more extensive chest X-ray abnormalities, but who are found not to have evidence of active TB. Dependent on the extent of changes, such individuals are usually treated with a regimen as for active disease (see Chapter 3), as it is assumed they have a heavier burden of ‘dormant’ tubercle bacilli.

‘Active TB disease’ refers to individuals with evidence of replicating TB organisms, demonstrated either by smear and culture, or by histological evidence of characteristic granulomatous inflammation, or by other suggestive tests. Active TB may be asymptomatic particularly in the early stages of disease, but the usual clinical features are described in this chapter.

2.1 General symptoms

The demographics of TB in New Zealand are presented in Chapter 1, and should be borne in mind when assessing patients with possible TB in New Zealand.

It is very important to maintain a high index of suspicion to make a diagnosis of TB. TB disease should always be considered in individuals with a history of contact with TB, or with previous prolonged residence in high-TB incidence countries, especially in those recently arrived in New Zealand.

TB may be asymptomatic until the condition is advanced. However, common systemic symptoms include malaise, fever, anorexia, weight loss and night sweats.

2.2 Pulmonary tuberculosis

Pulmonary TB is the most common presentation of TB both worldwide and in New Zealand.
2.2.1 Symptoms

Active pulmonary TB may be asymptomatic initially, but as the extent and severity of the disease progress, symptoms appear. Cough is usually dry initially but may subsequently become productive. Haemoptysis may also occur, particularly in cavitary disease, but may also occur in inactive (past) TB with bronchiectasis. Breathlessness is a late feature when parenchymal destruction or pleural effusion has occurred. Pleuritic chest pain may also occur in pleural TB.

Characteristically, TB causes few clinical signs on chest examination despite extensive radiological abnormality. Abnormal chest signs are usually the result of lung fibrosis, cavities or pleural disease.

A multivariate analysis described symptoms associated with culture positive TB in patients presenting with respiratory disease: the presence of TB risk factors and symptoms (odds ratio (OR) 7.9); a high temperature (OR 2.8); and upper lobe changes on chest X-ray (OR 14.6). The following were negatively correlated with active TB: shortness of breath (OR 0.2) and crackles on clinical examination (OR 0.29).

Endobronchial TB is uncommon, but it is important because it may result in tracheal or bronchial stenosis, which may be misdiagnosed as asthma or lung cancer. The incidence of involvement of the bronchial tree in pulmonary TB is unknown.

2.2.2 Chest X-ray appearances

Opacities are often seen apico-posteriorly in the upper and, albeit to a lesser extent, the apical segment of the lower lobes. As the disease progresses, there is more extensive consolidation and cavities develop, which then usually implies that the condition is infectious. Cavity formation is uncommon in primary TB. It is often seen in ‘reactivation’ TB where a heightened immune host response is more likely to occur. Vascular involvement is common in areas of active TB, and endarteritis obliterans may result in necrosis and cavity formation. Rupture of a vascular aneurysm (so-called Rasmussen’s aneurysm) in the wall of a cavity may result in life-threatening haemoptysis.

A ‘miliary pattern’ describes the chest X-ray appearance of tiny, evenly distributed nodules. This pattern represents haematogenously disseminated TB.

Atypical or diminished chest X-ray appearances are seen in conditions associated with varying degrees of immunosuppression such as diabetes and HIV/AIDS.

Section 2.4.2 discusses the chest X-ray changes of TB in more detail. Pleural and mediastinal nodal disease are classified as extrapulmonary TB (see below).
2.3 Extrapulmonary tuberculosis

2.3.1 Lymph node TB
In adults, TB is the most common mycobacterial cause of adenopathy in the neck and supraclavicular regions. In countries with low TB prevalence, mycobacteria other than tuberculosis are a more common cause of mycobacterial adenopathy in children. Women are more predisposed to develop TB adenitis than men (a ratio of 2:1), and TB occurs more commonly in non-Caucasians.

TB adenitis can involve any lymph node group. Mediastinal TB adenitis is commonly associated with extensive or severe local pulmonary TB. TB adenitis is often painless, but acute inflammation and pain can occur. Characteristically, nodes lack redness and warmth and are firm and discrete initially, but may become fluctuant as necrosis develops.

The progress of tuberculous adenitis can be unpredictable during treatment. Involved nodes may regress and disappear, or expand, develop into a lymph node abscess, and spontaneously perforate. The node perforation may cause a discharge onto the skin or, in the case of mediastinal nodes, into the mediastinum or one of its structures, a bronchus or the pleural space. Sometimes lymph nodes increase in size during treatment or even after completion of TB treatment. This is sometimes referred to as a paradoxical upgrading reaction.

2.3.2 Pleural TB
Tuberculous pleuritis is the second most common form of extra-pulmonary TB. In two-thirds of cases, the onset of tuberculous pleuritis is acute. Tuberculous pleuritis occurs more commonly in adults than in children with TB.

A lymphocytic, exudative effusion is characteristic of tuberculous pleuritis, but initially neutrophils may predominate. TB requires exclusion in any lymphocyte-predominant exudative pleural effusion. A tuberculous empyema with the presence of frank pus on pleural aspiration may develop later in the course of pleural TB. This is uncommon, and a tuberculous empyema necessitatis (rupturing through the chest wall or into the lung) is now rare in Western countries.

2.3.3 Skeletal TB
Skeletal TB occurs in older people in developed countries, but is more common in younger people in other countries. Any bone or joint may be affected, but TB of the spinal vertebrae (Pott’s disease) is the most common. The collapse of bone may produce pain and kyphotic deformity, and the infection may spread locally (eg, para-vertebral abscess formation) and then track through tissue planes to emerge as a lump or sinus at a more distant site.

Skeletal TB is often an insidious, late complication of lympho-haematogenous spread from unrecognised primary pulmonary disease. Delay in the diagnosis is common because of the often mild, chronic, non-specific nature of the symptoms.
2.3.4 Abdominal tuberculosis

Abdominal TB may present in peritoneal, enteric, hepatic and biliary forms. Systemic symptoms of weight loss, malaise and fever are prominent in this form of TB.

Peritoneal TB is the most common form of intra-abdominal TB. Peritoneal TB may follow the rupture of a small caseous peritoneal focus that has developed after haematogenous spread during primary infection. Peritoneal TB may also develop after the rupture of a larger focus within an abdominal viscus or lymph node. Symptoms of peritoneal TB are often insidious, with abdominal pain and systemic symptoms of TB. Occasionally, peritoneal TB presents as an acute abdomen. Ascites and omental thickening are common. Pleural effusion and pulmonary TB are commonly present. Tuberculous peritonitis is an occasional complication of peritoneal dialysis.

Enteric TB may involve any part of the gastro-intestinal tract, but is most common in the ileo-caecal and ano-rectal regions. Abnormal liver function tests are commonly found in association with extensive TB, and usually settle within two weeks of the treatment starting. It is often uncertain whether this is due to tuberculous involvement of the liver – hepatic TB – or non-specific hepatotoxicity caused by the major infection. Hepatomegaly and upper abdominal pain and tenderness can occur. Biliary involvement may present with obstruction of the biliary tract by lymph node enlargement at the porta hepatitis.

2.3.5 Genitourinary TB

Genito-urinary involvement in TB usually presents many years after haematogenous dissemination at the time of primary tuberculosis.

Renal TB is often silent, and systemic symptoms are uncommon. A finding of sterile pyuria should lead to sending of three early morning urine samples for TB culture. Renal tract involvement is more easily detected by intravenous urogram (or CT IVU) than by ultrasound. Later symptoms may include haematuria, dysuria or loin pain. If untreated, renal TB may lead to unilateral renal destruction, due to direct involvement of the kidney or indirectly from ureteric stenoses. TB cystitis is uncommon, but may cause dysuria and frequency. Bladder wall inflammation and then fibrosis may lead to permanent loss of bladder capacity.

Male genital TB may present as a cold abscess in the testicle or prostate, but epididymitis with local thickening is more common.

Female genital TB is often asymptomatic but menorrhagia may be reported. Female genital TB may involve the distal salpinges, ovary or endometrium, and is a cause of infertility, particularly in women in developing countries.

2.3.6 Neurological TB

TB can involve any part of the nervous system. TB meningitis in children is most common in children aged between six months and five years. TB meningitis tends to occur in adults who are elderly or partially immunosuppressed.
The onset of TB meningitis is often insidious and follows three stages of progression:

- **Stage 1**: low-grade fever, irritability and personality change.
- **Stage 2**: in association with raised intra-cranial pressure, meningitis, seizures and cranial nerve palsies (third, sixth and seventh).
- **Stage 3**: high fever, stupor and coma commonly followed by brain stem herniation and death. Even with chemotherapy, the mortality rate is high in this stage of the disease.

A review of 104 cases of TB meningitis at Auckland Hospital has recently been published. This review demonstrated that 36% of cases had a poor neurological outcome, and 12% were left with moderate disability. The diagnosis of TB meningitis and subsequent institution of treatment was sometimes delayed: the most common reasons were:

1. presentation with mild symptoms wrongly attributed to a systemic infection
2. incorrectly attributing CSF abnormalities to non-tuberculous bacterial meningitis
3. failure to diagnose extraneural tuberculosis associated with meningitis.

Unfortunately, delayed diagnosis leads to increased morbidity. Maori, Pacific and Asian patients were over-represented in the series compared to their proportion in the general population, emphasising that a high index of suspicion in high risk cases is very important. The most common presenting symptoms were headache (69%), fever (69%), altered mental state (58%) and drowsiness (28%). Non-specific symptoms such as nausea/vomiting, anorexia, lethargy, weight loss and cough were present in 35 to 61% of cases. More severe symptoms such as seizures, limb weakness and diplopia were present in less than 20%. The most common physical signs were fever (83%) and neck stiffness (69%). Mental state was abnormal in 65% of patients, but focal signs occurred in less than one-third – intra-cerebral tuberculomas are uncommon and may be asymptomatic or produce focal signs; they may progress to form a brain abscess.

Involvement of the ear in TB is rare.

Ocular involvement may occur in any part, but the cornea and choroidae are most commonly affected. The role of TB in eye disease is an evolving area, and it has been suggested that entities such as relapsing anterior uveitis and ocular vasculitis may be related to TB infection or an immunological reaction to TB infection. In such cases, treatment for TB is sometimes considered in addition to local or systemic corticosteroid therapy. Consultation with an ophthalmologist with a special interest in TB eye disease is advisable.
2.3.7 Cardiovascular TB
Cardiovascular TB is rare, but pericardial involvement is the most common. Tuberculous pericardial effusion usually occurs in extensive disseminated disease and should be considered when there is a substantial tuberculous pleural effusion or when cardiomegaly is present in active TB. A lymphocytic, exudative pericardial aspirate should be considered due to TB unless proven otherwise. Signs of pericardial effusion include oedema, pulsus paradoxus, raised venous pressure and hypotension with a narrow pulse pressure. The role of oral steroid treatment is discussed in Chapter 3. Constrictive pericarditis can be a late complication of TB pericarditis and presents with oedema, ascites and breathlessness.

2.3.8 Other forms of extrapulmonary TB
TB laryngitis usually accompanies extensive, cavitatory pulmonary TB, but isolated TB laryngitis may occur. TB laryngitis is a form of infectious TB with a normal chest radiograph. A cough, voice change and (later) throat pain are the main symptoms. Isolated infiltration of the skin by tuberculous disease is uncommon and skin involvement is more often the result of the extension of TB osteomyelitis or the end of a sinus tract from another more deeply seated focus.

Endocrine involvement by TB includes adrenal, pituitary and thyroid TB. Adrenal TB usually occurs during haematogenous dissemination; adrenal insufficiency is uncommon as most of the adrenal tissue must be destroyed. Pituitary tuberculoma is rare, but hypopituitarism has been observed years after recovery from TB meningitis in childhood. This suggests that its involvement may be silent and easily overlooked during childhood TB meningitis. Thyroid TB is rare.

2.3.9 Disseminated and miliary TB
Disseminated TB involves multiple body systems and results from acute haematogenous spread. Disseminated TB occurs in about 3% of non-HIV TB cases in Western countries.16 Disseminated TB carries an overall mortality rate as high as 38%, but the absence of miliary changes on the chest radiograph, in the presence of multi-system TB, is associated with a mortality rate of around 85%. Malnutrition is common in people with severe or extensive TB.

Miliary TB is the presence of multiple, small and uniformly-sized (usually less than 2 mm in diameter) nodules of active TB throughout the body.17 All miliary TB is disseminated TB, but not all disseminated TB is miliary TB.

2.4 Investigation of tuberculosis
This section describes clinical investigation for active TB disease. Techniques to assist with the early diagnosis of TB are also considered. The extent and severity of TB should always be documented as part of the clinical assessment. Investigation for latent TB infection (LTBI) is described fully in Chapter 8.
2.4.1 Introduction

Clinical investigation for TB initially requires a comprehensive history and physical examination. Important initial tests are a chest X-ray (CXR) and an examination of sputum or other specimens for acid-fast bacilli (AFB) and mycobacterial culture. A Mantoux test or an interferon gamma release assay (IGRA) may also be required.

2.4.2 Chest X-ray

Chest X-ray (CXR) is an essential test whenever TB is considered. Active pulmonary TB cannot reliably be ascertained by CXR features alone, but changes on a CXR may be suggestive.

An outline of common CXR features is shown in Table 2.1.\textsuperscript{18}

| Table 2.1: Typical chest X-ray features in tuberculosis |
|----------------------------------------|------------------|----------------------|
| **Anatomical site** | **Favour active tuberculosis** | **Favour inactive tuberculosis** |
| Lung | Consolidation, variable size: | Linear scarring |
| | - unifocal, commonly | Dense scarring |
| | - ‘soft’, ‘fluffy’ areas with poorly defined margins | Volume loss |
| | Cavities | Destroyed lobe or lung |
| | Nodules: | Calcification |
| | - focal, non-calcified; or | Nodules, calcified (tuberculomas): |
| | - miliary pattern | - Ghon focus (scar from primary infection) |
| | | - secondary (Simon) foci |
| Mediastinum and hilar | Lymphadenopathy* – hilar and/or paratracheal | Calcified lymph nodes |
| | | Pericardial calcification |
| Pleura | Pleural effusion/empyema | Pleural thickening: |
| | | - basal |
| | | - apical (irregular, > 1 cm thickness) |
| | | Pleural calcification |

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.

Radiological criteria for induced sputum testing and bronchoscopy

The usual decision-making process is shown in Table 2.2, but the action taken for an individual case may vary, depending on the patient’s age and the presence or absence of risk factors for reactivation of disease.
Table 2.2: Radiological criteria for detailed mycobacteriological tests*

<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 patients the chest X-ray in tuberculosis may be normal)</td>
</tr>
<tr>
<td>Calcified 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.

A chest X-ray which is normal or lacks the typical features of TB makes a diagnosis of TB unlikely, and invasive tests for TB are unlikely to yield positive results. If TB remains strongly suspected, a repeat film should be obtained 2–3 weeks later. Immunocompromised or patients with HIV infection may have active TB in the presence of a normal chest X-ray or minor/atypical chest X-ray changes, and so immediate sputum testing is justified.

When inactive/fibrotic-type changes are seen on a chest X-ray, they should not be attributed to inactive TB unless detailed mycobacteriological testing for active pulmonary TB has been performed, or previous chest X-rays show that the abnormalities have been stable for at least six months, or up to two years if marked. This is of particular relevance in assessing candidates for ‘immigration clearance’ (see Chapter 10).

It is strongly recommended that subjects undergoing investigation for active pulmonary TB are kept in isolation until disease activity and smear status are determined.

**Chest X-ray in extra-thoracic tuberculosis**

TB pleural effusion is classified as an extra-pulmonary form of TB. The CXR appearance of the lung parenchyma is often normal in active pleural TB. Of 129 cases of TB pleural effusion in a Spanish study, 76% were considered primary, and the lung fields were thus normal. In Malaysia, 61% of 54 cases of TB pleural effusion had no CXR evidence of parenchymal disease.

An abnormal chest radiograph is common in patients with other forms of extrapulmonary TB. CXR suggests current or past intra-thoracic TB in patients with extra-pulmonary TB in:
- 44–69% with meningitis
- 16–44% with superficial lymph node disease
26–50% with bone or joint disease\textsuperscript{26,29}  
8–75% with genitourinary disease\textsuperscript{26,30,31}  
32–78% with peritoneal or abdominal TB.\textsuperscript{26,32–38}

A normal CXR does not exclude extrapulmonary TB, and testing for this should be pursued if there are suggestive systemic or site-specific symptoms.

### 2.4.3 Tuberculin skin test or interferon gamma release assay

The Mantoux test is the form of tuberculin skin test (TST) carried out in New Zealand. TSTs and interferon gamma release assays (IGRAs) are primarily tests for TB exposure and LTBI. They are required only for assistance in the diagnosis of active TB, if culture or histology are negative or inconclusive. These tests are described fully in Chapter 8.

TST and IGRAs are not needed if the diagnosis of active TB has been made or is likely to be easily confirmed (e.g., the CXR is strongly suggestive of infectious TB and the person has a cough and sputum). They should not be performed again if a previous TST or IGRA from within the last month is available, or if the person is known to have had a strongly positive TST reaction or has been treated for TB in the past (see Chapter 8).

Positive TST and IGRA results do not distinguish between active TB disease and LTBI. In addition, false negative TSTs and IGRAs may occur in patients with active TB disease (up to 30% in patients with TB pleuritis in one previous series).\textsuperscript{39} False positive TSTs may also occur in patients with previous BCG vaccination or exposure to non-tuberculous mycobacteria (NTMs); the risk of false positives in this setting is less with IGRAs. The magnitude of the TST reaction does not predict the likelihood of current active TB disease.\textsuperscript{40} Therefore a positive TST or IGRA may help to support a diagnosis of active TB in appropriate clinical circumstances, but is never conclusive.

### 2.4.4 Sputum microscopy and culture

Three (preferably early morning) sputum specimens should be sent for TB testing. In general, all three samples are processed for both smear and culture.

Sputum samples may be incubated in a variety of media (see Chapter 11). Gene probes for \textit{M. tuberculosis} or MAIC may be applied to culture positive samples, to help provide early identification of TB or non-tuberculous mycobacteria. Probes for mutations conferring drug resistance are now available.

Polymerase chain reaction (PCR) for TB is also available (see Chapter 11). A positive result is useful as false positives are relatively rare. However, a negative result does not exclude active TB and so any sample on which PCR is performed should always be sent for TB culture. TB PCR is most commonly performed on nodal aspirates, pleural fluid or biopsies and cerebrospinal fluid (CSF).
2.4.5 Induced sputum

With induced sputum tests, a patient inhales a mist of 3–4% hypertonic saline (through a mouthpiece or face mask) generated by an ultrasonic nebuliser. Although specimens often appear more watery than sputum, these are acceptable for testing.\textsuperscript{41} The procedure has a very high level of patient safety and acceptability.

Induced sputum testing has been shown to be more sensitive than bronchoscopy in the diagnosis of pulmonary TB in subjects who are sputum smear-negative.\textsuperscript{21}

Induced sputum testing for TB is a useful technique, with the following precautions. Respiratory isolation conditions are needed. The procedure must never be carried out in an open clinical area. Infected aerosols persist for a long time in a single room that is not equipped with an air extraction plus a high-efficiency particulate attenuation (HEPA) filtration system (see Chapter 11).

The principal patient safety concern is precipitating worsening of air-flow obstruction. Nebulised bronchodilator should precede the hypertonic saline in people with asthma and chronic obstructive pulmonary disease.

Patients must be supervised by a person who has experience with the procedure. Nursing or physiotherapy expertise is needed to optimise sputum elimination and collection. Staff must wear suitable face masks (see Chapter 11).

2.4.6 Bronchoscopy

Induced sputum is better than bronchoscopy for the diagnosis of active pulmonary TB.

Broncho-alveolar lavage

Expert opinion is that broncho-alveolar lavage (BAL) produces a better yield than ‘bronchial washings’ (the latter using 20–40 ml of lavage fluid), and should therefore be used at bronchoscopy. However, studies have not formally addressed this issue.

Preventing bronchoscopic transmission of tuberculosis

Bronchoscopy carries a greater risk of nosocomial infection from \textit{M. tuberculosis} than induced sputum testing does, provided the latter is performed in respiratory isolation conditions. When bronchoscopy is performed where TB is a possible diagnosis, a room that meets TB isolation ventilation requirements should be used (ie, equipped with HEPA filtration air conditioning and, ideally with negative pressure).\textsuperscript{42,43} When TB isolation ventilation requirements are not available, a portable HEPA filter can be used. The efficacy of HEPA filters is discussed in Chapter 11.

The bronchoscopist and assistants must wear N95 masks, which limit the inhalation of droplets containing TB, when TB is a possible diagnosis (see Chapter 11). Bronchoscopes must be cleaned carefully to prevent the cross-contamination of specimens and cross-infection of patients with \textit{M. tuberculosis}. 

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Indications for bronchoscopy

Bronchoscopy may be required, preferably when the diagnosis of TB has been made and infectious potential has been reduced or removed by treatment, in four circumstances.

- Intra-thoracic cancer needs exclusion.
- Endobronchial or endo-tracheal TB is possible (see section 2.2.1).
- Transbronchial lung biopsy is required because of lung infiltrates that are not typical of TB.
- Miliary changes are present, and sputum and induced sputum are smear-negative for AFB. In this situation, if there are risk factors for drug resistance or other differential diagnoses need exclusion, BAL and transbronchial lung biopsy should be done, provided there is no major contraindication.

Tissue should be sent separately in formalin for histology and in saline for TB culture.

2.4.7 Urine microscopy and culture

Do not perform urine mycobacterial culture unless sterile pyuria is present. There are multiple causes of sterile pyuria so the investigating clinician, whilst considering the possibility of tuberculosis, should also consider investigating and eliminating other common causes first.

Urine microscopy should be a routine test when TB is suspected or active TB needs to be excluded. In people with no urinary tract or abdominal symptoms, sterile pyuria, with or without red blood cells, is the main indication to proceed to early morning urine (EMU) TB tests. TB urine cultures are expensive, so should not be performed on the basis of a single abnormal midstream urine (MSU) test. In miliary TB, EMU tests may be culture positive without an anatomical urinary tract abnormality. EMU may be the only source of positive culture, especially in children.

MSU containing more than 20 white or red cells requires a repeat MSU test. If the abnormality persists, other causes should be excluded (eg, schistosoma serology in people who have resided in endemic areas) before performing urine TB cultures.

If the MSU is abnormal from an obvious cause (eg, menstruation or a bacterial urinary tract infection), repeat the MSU test once the condition has had time to resolve.

Sterile pyuria is also an indication for an intravenous urogram (IVU) or CT IVU, looking especially for urinary tract stenoses and other features of urinary tract TB. An IVU is often superior to ultrasound in this situation.

2.4.8 Gastric aspiration

A gastric aspiration examination is sometimes used in children when TB is suspected (or needs exclusion) and spontaneous sputum cannot be produced (see Chapter 5 for TB in children).
Bronchoscopy is an alternative if available. The choice between performing gastric aspirates and bronchoscopy in infants and children with abnormal CXRs is debated.\textsuperscript{28} Induced sputum examination may also be helpful in children, if tolerated.

2.4.9 Blood culture for mycobacteria

A blood culture for mycobacteria is important in patients with advanced HIV-infection, where 24–64\% of patients with TB have positive blood cultures. In up to 18\%, blood is the only site from which the organism is recovered.

2.4.10 Testing for HIV and other co-morbidities

An HIV test should be offered to every patient diagnosed with, or suspected of having, active TB disease, as each disease affects the course of the other. HIV is the single greatest risk factor for the development of active TB. Classical risk factors for HIV may not always be apparent.

For information on TB and HIV, see Chapter 6.

Patients starting treatment for TB also require baseline haematology, creatinine, liver function, hepatitis B surface antigen, and hepatitis C serology, together with regular monitoring of transaminases (see Chapter 3).

2.4.11 Pleural, pericardial and peritoneal investigations

In 90\% of tuberculous pleural and peritoneal effusions, the fluid is an exudate with a lymphocyte predominance. Other causes of lymphocytic effusions include lymphoma, other malignancies, collagen vascular diseases, and post-coronary artery bypass surgery. Early TB effusions may show neutrophil predominance and an eosinophilic pleural effusion is occasionally seen.\textsuperscript{44} A low pleural fluid glucose level is typical.

The sensitivity of the pleural and peritoneal fluid TB culture (10–35\%) is less than that of pleural or peritoneal biopsy culture (39–65\%). Mycobacterial blood culture bottles are more sensitive than standard TB culture systems for examining these fluids. Histology and culture of pleural biopsies can yield a diagnosis in up to 86\% of cases. Therefore, pleural biopsies are essential. In TB pleural effusions, induced sputum may be culture positive in just over 50\% of cases, so is a useful adjunct to investigations.\textsuperscript{45} Pericardial fluid has similar biochemical properties to pleural fluid, but pericardial biopsies may be required for histology and culture, and need to be obtained surgically.

A recent study of adenine deaminase (ADA) as an indicator of TB in lymphocytic effusions showed only rare false-positive results using an ADA level of 40 U/L or more.\textsuperscript{46} This test is therefore considered a very useful adjunct to diagnosis in suspected TB pleural effusion.\textsuperscript{47}

Thoracoscopic or laparoscopic pleural or peritoneal biopsy may be needed when other specimens (including sputum) fail to confirm a diagnosis especially in people from countries with a high prevalence of drug resistance where the drug susceptibility of the TB organism is essential.
2.4.12 Lymph node tuberculosis

Because pulmonary TB co-exists in 70% of cases of supra-clavicular and cervical TB adenitis, a CXR is indicated. When pulmonary disease is also present it may be easier to confirm the diagnosis with respiratory investigations (see earlier).

A New Zealand study\(^{48}\) showed that a fine needle aspirate (FNA) of tuberculous cervical and supraclavicular nodes was positive in 33% of cases – lower than in many other studies. This may be due to the small number of subjects or because cases present and are investigated earlier in New Zealand than in non-Western countries.

When an FNA is performed, AFB smears are essential and several FNA specimens should be cultured. TB PCR may also be requested. FNA cytology may show necrotic material, multi-nucleate giant cells and other findings suggestive of granulomata; it is important in detecting other causes of lymphadenopathy especially malignancy.

It is always desirable in this era of increasing drug resistance and given the propensity of TB lymphadenopathy to vary in size even during successful treatment, to obtain culture and sensitivity data. Therefore, if FNA smear and culture are negative and there is no clinical urgency, a core biopsy or excision biopsy should be performed with mycobacterial culture and cytology/histology. Treatment should not be started until a positive culture has been obtained or until an abnormal node has been excised and is being cultured for mycobacteria.

In mediastinal adenopathy where TB is strongly suspected, it may be possible to obtain transbronchial needle aspirate (TBNA) or an endobronchial ultrasound-guided TBNA (EBUS TBNA).\(^{49}\) If none of these tests is diagnostic, the patient should have a mediastinoscopy. Intraabdominal lymphadenopathy may be sampled via laparoscopy.

2.4.13 Central nervous system tuberculosis

TB meningitis or CNS disease should be considered in anyone seriously ill with disseminated TB: there should be a low threshold for performing a CT scan and/or lumbar puncture. CT is usually performed prior to lumbar puncture (if available), in order to exclude raised intracranial pressure, posterior fossa disease or obstructive hydrocephalus. It is difficult to exclude these with clinical examination alone, especially as performing fundoscopy may be hazardous in infectious patients.

Characteristic findings on CSF examination include a leucocytosis (usually lymphocyte predominant, although polymorphs may predominate in a minority of patients with early disease), a raised protein in almost all patients, and a low glucose. Acid-bast bacilli are found in less than 20% of cases. TB PCR has excellent specificity but low sensitivity of around 50–60%,\(^{13}\) and up to 45% of patients with presumed TB meningitis have negative CSF cultures. Routine blood test results are non-specific, but hyponatraemia is very common. It is important to search carefully for TB at other sites in patients with suspected CNS TB. Empiric treatment needs to be started early in patients with clinical features of CNS TB and characteristic clinical findings, without waiting for culture results.
2.4.14 Routine laboratory tests

Abnormal results that may be found with TB include the following.

- A mild leukocytosis – occasionally a leukemoid reaction or a leukopaenia or raised monocyte or eosinophil count.
- Anaemia is common, especially with disseminated disease, and iron studies show non-specific features of chronic disease.
- Pancytopenia, which may indicate extensive bone marrow involvement.
- Hyponatraemia, which occurs in about 10% of cases and is due to the production of an anti-diuretic hormone-like substance in diseased tissue. Hypo-adrenalism should be excluded by a short synacthen test.
- Hypercalcaemia in about 5% of cases of TB, but it is usually mild and responds to treatment of the TB.
- Mild hepatic dysfunction, which is common with moderately extensive TB. More severe hepatic dysfunction may be due to co-existing disease such as viral hepatitis or alcoholism.
- Hypoalbuminaemia and other non-specific features of severe chronic disease, especially in disseminated TB.

References


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Chapter 2: Clinical Features, Investigation and Assessment of Active Tuberculosis Disease
Further reading


Chapter 3: Treatment of Tuberculosis Disease

Summary

Management principles in treating TB

The objective of anti-tuberculous treatment is to achieve a lifetime of cure of the disease while preventing resistance.

Treatment regimens must contain multiple drugs to which the organisms are susceptible. Single agents should not be added to an existing treatment regimen, and particularly not to a failing regimen. The addition of two or more drugs is required if treatment failure is suspected.

All patients with MDR-TB or XDR-TB must be treated with daily DOT.

Ciprofloxacin is no longer recommended to treat drug-susceptible or drug-resistant TB.

Standard treatment regimens for susceptible pulmonary TB isolates

Treatment of active TB usually includes two phases. The phases are the:
- intensive phase of treatment (when more drugs are used) – bactericidal phase
- continuation phase (with fewer drugs) – sterilisation phase.

Adults should be treated with a standard six-month regimen consisting of an intensive phase of isoniazid, rifampicin, ethambutol, and pyrazinamide for two months followed by isoniazid and rifampicin for four months (2HREZ/4HR). 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. Once full susceptibility is confirmed, ethambutol can usually be stopped however in patients with a significant disease burden, some clinicians recommend continuing ethambutol for the entire first two months or until smear conversion has occurred. An injectable agent or moxifloxacin may be used instead when ethambutol is not an option provided drug resistance is not suspected, in which case multiple additional agents may be required in the initial regimen.

Directly observed therapy

Wherever possible the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy.

Patients may receive a daily intensive phase followed by a three times a weekly continuation phase (2RHEZ/4(RH)₃), provided that each dose is directly observed.

Alternatively three times weekly dosing throughout therapy (2RHEZ₃/4(RH)₃) may be used provided that every dose is directly observed and that the patient is not living with HIV infection. Thrice-weekly DOT is suitable from the outset of treatment during the intensive phase regimen, only if the patient is non-infectious and has a low burden of disease.

Twice-weekly DOT regimens are no longer recommended.

In the presence of widespread disease or major cavitatory TB, daily therapy should be used initially. Good clinical progress and smear or culture conversion should be demonstrated before switching from daily treatment to thrice-weekly DOT.
Smoking cessation
All patients with TB who smoke should be advised and offered support to quit smoking.

Standard treatment regimens for extra-pulmonary TB
With three exceptions, central nervous system TB, miliary/disseminated TB and bone and joint TB, non respiratory TB is treated with the same regimens as pulmonary TB. Patients with some forms of extra-pulmonary TB may require a more prolonged treatment course. Patients with miliary/disseminated TB should be assessed for evidence of central nervous system TB.

Drug-resistant TB
The most important predictors of drug-resistant TB are:
- a previous episode of TB treatment
- progressive clinical and/or radiographic findings while on TB treatment
- origin from, history of residence in or frequent travel to a region/country with high rates of drug resistance
- exposure to an individual with infectious drug-resistant TB.

Suggested regimens for the treatment of patients with mono- and poly-drug resistance are shown in Table 3.4.

A daily dosing schedule should be used for all patients with drug-resistant TB.
Intermittent dosing schedules must not be used.

All cases of MDR-TB or XDR-TB must be treated in consultation with a tertiary centre experienced in the care of such patients.

Corticosteroid treatment in the management of TB
Corticosteroids should only be given when adequate anti-tuberculosis treatment is also being given. Adjuvant corticosteroids treatment is recommended for both TB meningitis and TB pericarditis and may also provide benefit in life threatening cases of TB.

Monitoring
Patients who are sputum smear–positive before treatment should have repeat sputum tests at least monthly to confirm sterilization. If the specimen at the end of the third month is both smear and culture positive, repeat drug susceptibility testing should be performed. As early detection of drug resistant TB is important, repeat DST after two months of treatment may be appropriate in some patients where there are concerns that acquired drug resistance may have developed.

Baseline blood count, creatinine, alanine amino-transferase (ALT), 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. Depending on the patients risk factors for hepatotoxicity, regular monitoring of either ALT or liver function tests should occur in all patients on treatment for TB.
Drug adverse effects
The prompt recognition and appropriate management of adverse drug reactions is essential. Patients should be advised of common and important side effects such as those associated with hepatitis and ocular toxicity, and to report these promptly.

Monthly monitoring of visual acuity and colour discrimination is recommended for all patients on ethambutol for longer than two months and for any patient with renal impairment.

Four weeks is an arbitrary maximum period for a patient to be off all drugs.

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

Some patients will require a temporary treatment regimen to be started following a drug reaction until the difficulties have been resolved.

Interactions with anti-TB drugs
The interaction of TB drugs with other medications is not uncommon and must always be considered when starting TB treatment.

Special situations
The management of TB in patients with hepatic dysfunction and renal impairment is complex and treatment regimens may require dose adjustment with regular patient monitoring.

Introduction
This chapter includes information on the treatment of TB disease, the monitoring of patients on TB treatment and the treatment of TB in special situations including renal impairment, hepatic impairment and pregnancy. This chapter refers specifically to the treatment of TB in adults. The treatment of TB in children is discussed in Chapter 5.

The treatment of TB in patients with HIV infection is discussed in Chapter 6.

Practitioners who are not familiar with TB and its management are advised to refer patients to a clinician experienced in the field. TB medications are specialist only.

3.1 Management principles in treating TB
The objective of anti-tuberculous treatment is to achieve a lifetime of cure of the disease while preventing resistance. Effective chemotherapy taken over an adequate period of time is the guiding principle of treatment for all forms of tuberculosis. Investigations should be undertaken that give the best possible chance of identifying the organism and its sensitivity pattern. This is particularly important when drug resistance is possible.

Treatment regimens must contain multiple drugs to which the organisms are susceptible. **Single agents should not be added to an existing treatment regimen,** and particularly not to a failing regimen. The addition of two or more drugs is required if treatment failure is suspected. Initial treatment should be modified if drug resistance is suspected (see section 3.5.2).
Clinicians should notify all patients who are treated for TB disease or infection. Relapse of TB, whether this occurs during treatment or not, must be re-notified. Infectious cases of TB must be isolated to prevent further spread of disease. Isolation (in hospital or at home) is discussed in Chapter 12.

Poor adherence to prescribed anti-TB treatment is the most common cause of treatment failure. Directly observed therapy (DOT) is an effective way to monitor adherence to treatment.

**All patients with MDR-TB or XDR-TB must be treated with daily DOT.** Universal provision of DOT is not currently feasible for all patients treated for TB in New Zealand however priority should also be given to the following circumstances (and see Chapter 4):

- suspected or proven drug-resistant organisms
- treatment failure /re-treatment
- social or medical circumstances that are likely to impair adherence to the treatment regimen
- suspected non-adherence or previous non-adherence
- cases that are sputum smear positive for acid-fast bacilli
- people on treatment for both TB and HIV infection
- children.

Completion of therapy is based on the total number of doses administered and not on the duration of therapy alone.¹

### 3.1.1 Phases of treatment and abbreviations of treatment regimens

Commonly used abbreviations for the names of tuberculosis (TB) drugs in treatment regimens are:

- **E** ethambutol
- **H** isoniazid
- **R** rifampicin
- **Rb** rifabutin
- **Z** pyrazinamide

Treatment of active TB usually includes two phases. The phases are the:

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

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.
In a treatment regimen such as ‘2RHEZ/4RH’, the number and letters before the slash 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 and pyrazinamide during the initial 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.

### 3.2 Drug doses and administration

#### 3.2.1 Drug doses

Table 3.1 shows the dosage recommendations for anti-TB medicines. In obese patients, ideal body weight should be used to calculate doses of the first-line TB drugs. Drug doses in obesity are discussed in section 3.11.4.

Ciprofloxacin is no longer recommended to treat drug-susceptible or drug-resistant TB. The most potent available fluoroquinolones in descending order based on in vitro activity and animal models are: moxifloxacin=gatifloxacin > levofloxacin > ofloxacin. If a fluoroquinolone is required to treat a patient with TB, moxifloxacin is currently the preferred agent in New Zealand.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Daily dose</th>
<th>Thrice-weekly dose</th>
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</thead>
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<td><strong>First-line agents</strong></td>
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<td>Maximum dose/day</td>
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<tr>
<td>Rifabutin</td>
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<td>Maximum dose/kg</td>
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<tr>
<td>Maximum dose/day</td>
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<td></td>
</tr>
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<td>Rifampicin§ #</td>
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<tr>
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<td>600 mg</td>
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<tr>
<td>Maximum dose/day</td>
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<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
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<td>3 g</td>
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<tr>
<td>Ethambutol</td>
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Chapter 3: Treatment of Tuberculosis Disease
### Medication

<table>
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<th>Medication</th>
<th>Daily dose</th>
<th>Thrice-weekly dose</th>
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<td><strong>Second-line agents</strong></td>
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<tr>
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</table>

* Sometimes doses up to 450 mg are used.

§ An intravenous form of rifampicin is available.

‖ Prothionamide and ethionamide are given in divided doses.

# Patients >50 kg should be prescribed Rifinah 300 x 2 tablets daily (rifampicin 600 mg daily and isoniazid 300 mg daily); adult patients <50 kg are usually prescribed Rifinah 150 x 3 tablets daily (rifampicin 450 mg and isoniazid 300 mg daily).


### Ethambutol

The daily dose of ethambutol should be 15 mg/kg, unless there is a good reasons for a higher dose.5,6 Ethambutol should be avoided in patients who have renal impairment (section 3.11.1). The risk of optic neuritis is greater with higher doses. Higher doses may be used for treatment with intermittent therapy.

### Pyridoxine with isoniazid and cycloserine

In patients taking isoniazid, it is advisable to also give pyridoxine 10–25 mg/day. This 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 on isoniazid, a pyridoxine dose of 25mg is sufficient as higher doses may interfere with isoniazid activity.6A

In patients taking cycloserine, the pyridoxine dose should be 50 mg for every 250 mg of cycloserine prescribed.4
3.2.2 Administration of amikacin

Aminoglycosides should be dosed once-daily or at extended intervals. This results in a high peak serum concentration, which declines over a 24-hour period and a drug-free period at the end of the dosing interval.

Dose adjustments for weight

The correct dose of amikacin is based on body weight. The weight used to calculate the dose should be the actual bodyweight for non-obese individuals. For these patients the usual daily dose is 15 mg/kg, given by intravenous infusion (or, albeit rarely, intramuscularly). The method of calculating the dosing weight with obese people is discussed in section 3.11.4.

Doses with (stable) renal impairment

Modifications are required to the dose and/or dosing interval when significant renal impairment is present. Prescribers are advised to consult their local guidelines, hospital pharmacist or a clinician experienced in the use of aminoglycosides.

Prolonged treatment with amikacin and normal renal function

Depending on the severity of TB, amikacin is generally given daily for five or six days per week. When necessary, amikacin can be continued at the same dose three times a week after an initial period of daily administration.3

Monitoring of patients on amikacin is discussed in section 3.7.3.

3.2.3 Pharmacological considerations with anti-tuberculosis drugs

The sections below discuss the pharmacological considerations with the anti-TB agents isoniazid, rifampicin, rifabutin, ethambutol, pyrazinamide, protonamide and ethionamide, fluoroquinolones, streptomycin, amikacin, and whether directly observed therapy should occur before or after food.

Isoniazid

Isoniazid is best taken on an empty stomach with no antacids taken for at least two hours afterwards.7 Food and antacids may reduce the absorption of isoniazid.

Rifampicin

Rifampicin is best taken on an empty stomach. The peak serum concentration is reduced by one-third, if rifampicin is taken after a fatty meal. Smaller reductions are seen with carbohydrate meals. Antacids do not affect the absorption of rifampicin.8
Only free rifampicin (not plasma protein-bound rifampicin, which accounts for 75% of the total serum rifampicin level) is available to interact with mycobacteria. Therefore, to produce a concentration of ‘free’ rifampicin of 0.2–0.5 µg/ml (the MIC of rifampicin for M. tuberculosis) a total serum concentration of 0.8–2.0 µg/ml is required. This is usually attained and persists for several hours, even if the drug was administered postprandially.\(^8\)\(^9\)

Rifampicin is excreted in urine, sweat, tears and other bodily fluids and colours those fluids orange. It may permanently discolour soft contact lenses.

**Rifabutin**

Rifabutin should be taken straight after food to enhance serum concentrations of rifabutin.\(^10\) This is opposite to the effect of food on rifampicin blood levels.

**Ethambutol**

Food does not affect the absorption of ethambutol.\(^11\)

**Pyrazinamide**

Food does not impair the absorption of pyrazinamide.

**Protionamide and ethionamide**

Protionamide and ethionamide drugs have a narrow therapeutic side effect profile. They are well absorbed after food. The effect of antacids on absorption is uncertain.

**Fluoroquinolones**

The ingestion of fluoroquinolones\(^12\) with food delays the time to peak serum concentration by one to two hours, but does not change the extent of absorption. Antacids or ferrous sulphate may interfere with the absorption of fluoroquinolones.

**Streptomycin**

Streptomycin must be given parenterally. The peak serum level occurs one hour after an intramuscular dose. The half-life of streptomycin in the blood is about five hours. Excretion is almost entirely renal. Streptomycin enters the cerebrospinal fluid only in the presence of inflamed meninges.

**Amikacin**

Amikacin is usually given by intravenous infusion over half an hour. If given intramuscularly, the peak serum concentration occurs an hour later.

**Directly observed therapy – whether drug taking should be before or after food**

If feasible, a person undergoing directly observed therapy should take their drugs on an empty stomach. However, if this is not possible, the drugs can be taken without fasting,
since the timing is often not critical. However, caution is required; rifampicin levels are lower when the drug is taken after food, especially after a fatty meal. Prescribers should give appropriate advice to people undergoing directly observed therapy.

Before a prescriber starts a person on directly observed therapy, they should ask the person about symptoms of malabsorption. The combination of malabsorption and postprandial administration of rifampicin during directly observed therapy may result in treatment failure or the selection of rifampicin-resistant organisms.\(^{13}\)

### 3.2.4 Drugs in fixed-dose combinations

Fixed-dose combination (FDC) tablets contain two or more medicines within the same tablet or capsule. An advantage of FDCs is the reduced risk of resistance developing, because if a dose is missed, all the drugs are omitted and it is less easy to take an inadequate combination. Other advantages are that fewer medication errors occur with FDCs and fewer prescription items need to be ordered.

A disadvantage of many FDC formulations is reduced bioavailability of some drugs, in particular rifampicin, and the loss of flexibility in obtaining an optimal dose of some agents, such as pyrazinamide; the total number of tablets may not be reduced.

### Rifinah

‘Rifinah 150’ and ‘Rifinah 300’ refer to the dose (mg) of the rifampicin component. The dose of isoniazid in these two preparations is 100 mg and 150 mg respectively. Therefore, to provide a satisfactory dose of isoniazid, use:

- Rifinah 150 (x3 tablets daily) in people weighing under 50 kg
- Rifinah 300 (x2 tablets daily) in people weighing over 50 kg.

### 3.3 Standard treatment regimens for susceptible pulmonary TB isolates

The treatment of active TB usually includes two phases. The phases are the:

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

Adults should be treated with a standard six month regimen consisting of an intensive phase of isoniazid, rifampicin, ethambutol, and pyrazinamide for two months followed by isoniazid and rifampicin for four months (2HREZ/4HR).\(^2\) 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.\textsuperscript{2} Once full susceptibility is confirmed, ethambutol can usually be stopped however in patients with a significant disease burden, some clinicians recommend continuing ethambutol for the entire first two months or until smear conversion has occurred.\textsuperscript{1,2} An injectable agent or moxifloxacin may be used instead when ethambutol is not an option provided drug resistance is not suspected, in which case multiple additional agents may be required in the initial regimen.

2HREZ/4HR is the preferred treatment regimen for all cases of susceptible TB. 2HRE/7HR may also be used when pyrazinamide is not tolerated or if the organism is resistant to pyrazinamide.\textsuperscript{14} Mycobacterium bovis (or BCG related disease) is naturally resistant to pyrazinamide.

All treatment regimens suggested in this chapter give the minimum period of treatment required to achieve cure. Extensive TB, whether pulmonary or multi-system, requires a longer duration of treatment. In patients with cavitatory disease or positive cultures after two months of treatment, the continuation phase of the six-month treatment regimen should be extended so that the patient receives at least nine months of treatment in total. Clinicians should also consider increasing the duration of treatment for patients with extensive TB or slow radiological improvement.

3.3.1 Directly observed treatment

Wherever possible the optimal dosing frequency for new patients with pulmonary TB is daily throughout the course of therapy. There are two alternatives to this recommendation (Table 3.2). Patients may receive a daily intensive phase followed by a three times a weekly continuation phase (2RHEZ/4R3H3), provided that each dose is directly observed. Alternatively three times weekly dosing throughout therapy (2R3H3E3Z3/4R3H3) may be used provided that every dose is directly observed and that the patient is not living with HIV infection. Thrice-weekly DOT is suitable from the outset of treatment during the intensive phase regimen, only if the patient is non-infectious and has a low burden of disease.\textsuperscript{4} Twice-weekly DOT regimens are no longer recommended.\textsuperscript{4}

In the presence of widespread disease or major cavitatory TB, daily therapy should be used initially. Good clinical progress and smear or culture conversion should be demonstrated before switching from daily treatment to thrice-weekly DOT. Intermittent regimens are unproven in the treatment of extra-pulmonary TB.
Table 3.2: Dosing frequency for patients with drug-susceptible pulmonary TB

<table>
<thead>
<tr>
<th>Dosing frequency</th>
<th>Continuation phase</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily phase</td>
<td>Daily</td>
<td>Optimal</td>
</tr>
<tr>
<td>Daily</td>
<td>Daily</td>
<td>Acceptable alternative for any new TB patient receiving directly observed therapy</td>
</tr>
<tr>
<td>Three times per week</td>
<td>Three times per week</td>
<td>Acceptable alternative provided that the patients is receiving directly observed therapy and is not living with HIV infection</td>
</tr>
</tbody>
</table>


A meta-analysis of the dosing frequency for HIV-negative patients on TB treatment outcomes found little evidence of differences in failure or relapse rates with daily or three times weekly regimens. However, rates of acquired resistance were higher among patients receiving three times weekly dosing throughout treatment.

All patients with MDR-TB must receive daily DOT.

3.3.2 Smoking cessation

Recent reviews have shown that smoking is strongly associated with increased rate of both TB infection and the development of pulmonary TB. Smoking also leads to faster progression and poorer prognosis of TB. Smokers are less likely to adhere to TB treatment and are more likely to relapse after successfully completing treatment according to some studies.

All patients with TB who smoke should be advised and offered support to quit smoking.

With regard to smoking cessation, it is important to note that rifampicin increases the clearance of bupropion resulting in decreased levels of bupropion.

3.4 Standard treatment regimens for extra-pulmonary TB

With three exceptions, central nervous system TB, miliary/disseminated TB and bone and joint TB, non respiratory TB is treated with the same regimens as pulmonary TB.

3.4.1 Duration of treatment for extra-pulmonary tuberculosis

Studies on the treatment of extra-pulmonary TB are more limited, but reports on pleural, lymphatic, renal, abdominal, meningeal and bone and joint TB show that outcomes are similar to those of pulmonary TB using similar regimens. However as the ideal therapy for meningitis, miliary/disseminated disease or spinal disease with neurological complications has not yet been defined with certainty, some authorities have recommended longer duration of treatment.
At least 12 months of treatment is usually recommended for meningeal TB and 12 months or longer of treatment for intra-cerebral TB. Patients with disseminated TB should be assessed for evidence of central nervous system involvement and treatment should be extended to 12 months if this is present. Some experts recommend at least 9–12 months of treatment for TB of bones and joints given the difficulties in assessing treatment response.

A longer duration of treatment is also recommended in the presence of severe or extensive disease, drug resistance or clinical or radiological progress that is slower than expected.

A daily dosing schedule is considered optimal for patients with central nervous system TB, miliary/dissemintated TB and bone and joint TB.

### 3.4.2 Management of central nervous system tuberculosis

Table 3.3 shows that isoniazid and pyrazinamide penetrate best into the cerebrospinal fluid. Rifampicin is also an excellent agent if the meninges are inflamed. Rifampicin, isoniazid and pyrazinamide are therefore the most important drugs for the treatment of CNS tuberculosis. Some authorities recommend continuing pyrazinamide beyond two months in the setting of CNS TB.

An aminoglycoside can be used if the meninges are inflamed and can be an additional agent where drug resistance is suspected; isoniazid is the most common agent to which resistance is found. If there is no inflammation, protionamide may also be an option, as this does penetrate into the cerebrospinal fluid. Fluoroquinolones may represent an effective agent for the treatment of TB meningitis, however data concerning their cerebrospinal fluid pharmacokinetics and safety during prolonged therapy are limited.

Table 3.3: Treatment of tuberculous meningitis and intra-cranial tuberculosis

<table>
<thead>
<tr>
<th></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>Drug penetration across the blood/brain barrier:</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• inflamed meninges</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+/-</td>
<td>++</td>
</tr>
<tr>
<td>• non-inflamed 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>
<tr>
<td>Daily drug doses (for adults)*</td>
<td>10 mg/kg</td>
<td>5 mg/kg</td>
<td>25–35 mg/kg</td>
<td>20 mg/kg intramuscular (maximum 1 g)</td>
<td></td>
</tr>
<tr>
<td>Oral steroid</td>
<td>Should be offered to all patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of TB medicines</td>
<td>9–12 months for adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* For information about doses for children, see Chapter 5.
3.5 Drug resistant tuberculosis

3.5.1 Types of drug resistance
The three types of drug resistance are primary, secondary, and naturally occurring resistance.\(^2\)

**Primary resistance**
Primary resistance occurs if the organisms transmitted are resistant to one or more TB drugs.

**Secondary resistance**
Secondary resistance occurs if new resistance develops during treatment.

**Naturally occurring drug resistance**
There is a degree of naturally occurring resistance to anti-TB drugs.\(^{25}\) This resistance varies from drug to drug. The approximate rates of development of resistant organisms in vitro are:

- \(10^{-3}\) for ethionamide, capreomycin, cycloserine and thiocetazone
- \(10^{-5}\)–\(10^{-7}\) for isoniazid, streptomycin, ethambutol, kanamycin and para-aminosalicylic acid
- \(10^{-9}\) for rifampicin
- \(10^{-14}\) for combined isoniazid and rifampicin.

Cavities contain approximately \(10^8\)–\(10^9\) bacilli and there is a significantly higher risk of naturally resistant organisms being present in cavitating TB.\(^{23}\) Due to the occurrence of naturally occurring drug resistant TB it is essential that TB is treated with multiple drugs.

3.5.2 Suspected drug resistance
Additional drugs may be necessary in re-treating TB in people previously treated. If MDR-TB is a possibility and immediate treatment is clinically necessary, sufficient drugs should be used initially to avoid the development of further resistance should the isolate subsequently prove to be resistant to all first-line agents. In practice, this may necessitate use of an MDR regimen at the outset.

Treatment of TB caused by drug-resistant organisms should be done by or in close consultation with an expert in the management of these difficult cases. Second-line regimens often present the patient’s best hope for cure and thus inappropriate management of a drug-resistant case can have life threatening consequences.

The management of drug-resistant TB is often complicated by drug toxicities and long duration of therapy. Successful treatment outcomes for drug-resistant TB are often difficult to achieve compared with drug-susceptible disease, especially when multidrug-resistance is present.
The most important predictors of drug-resistant TB are:

- a previous episode of TB treatment
- progressive clinical and/or radiographic findings while on TB treatment
- origin from, history of residence in or frequent travel to a region/country with high rates of drug resistance
- exposure to an individual with infectious drug-resistant TB.

### 3.5.3 Treatment of drug-resistant TB

The duration of treatment needs to be re-evaluated when drug resistance is encountered. The following treatment periods are a guide and represent the minimum duration of treatment (Table 3.4). A daily dosing schedule should be used for all patients with drug-resistant TB. Intermittent dosing schedules must not be used.

It is essential that exemplary infection control practices are maintained in all case of drug resistant TB.

<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>
</tbody>
</table>

Isoniazid-resistant tuberculosis

Resistance to isoniazid is reported at 0.1 mcg/mL (low level) and 0.4 mcg/mL (high level). If low-level resistance is present, isoniazid should be continued as part of a regimen containing at least three other effective drugs. This is because the determination of isoniazid resistance is based on minimal inhibitory concentrations (MICs), and in practice the serum level could exceed the in vitro MIC.26

Rifampicin-resistant tuberculosis

Isolated resistance to rifampicin is uncommon and should raise the suspicion of MDR-TB. The loss of rifampicin from the treatment regimen requires a longer duration of treatment.

Resistance to rifampicin is associated in most cases with cross-resistance to rifabutin. It is not clear whether laboratory-reported rifabutin susceptibility in the presence of rifampicin resistance is sufficiently reliable to allow use of rifabutin as a substitute for rifampicin. It is recommended that a regimen similar to that used for rifampicin resistance be used.

Pyrazinamide-resistant tuberculosis

*Mycobacterium bovis* (or BCG related disease) is naturally resistant to pyrazinamide. 2RHE/7RH (or 9RH for minor extent of disease) is appropriate for treatment of patients with isolated pyrazinamide-resistant TB.

3.5.4 Multi-drug resistant 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. **All cases of MDR-TB must be treated in consultation with a tertiary centre experienced in the care of such patients.**

Key recommendations for the treatment of MDR-TB include:4

- drug-resistant TB should be promptly diagnosed and appropriate therapy initiated
- patients with MDR-TB should always be treated with a minimum of four or more drugs to which the patient has not been previously exposed and to which the isolate is susceptible
- drug susceptibility testing (DST) should generally be used to guide therapy, however do not depend on DST in individual regimen design for ethambutol, pyrazinamide and group 4 and 5 drugs
- ciprofloxacin should not be used as an anti-tuberculosis agent
- treatment should be continued for at least 18 months past culture conversion
- adverse effects should be treated immediately and adequately
daily DOT is mandatory for all patients with MDR-TB.

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 treatment regimen (Table 3.5). Treatment regimens should be designed with a consistent approach based on the hierarchy of the five groups of anti-tuberculosis drugs.

### Table 3.5: 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, protonamid, cycloserine, 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>


Group 1: Ethambutol and pyrazinamide can be used if there is laboratory evidence of susceptibility but previous use potentially means that these drugs may be less effective. If the laboratory demonstrates low-level isoniazid resistance then high dose isoniazid may be beneficial.

Group 2: An injectable agent should be given to all MDR patients.

Group 3: A fluoroquinolone antibiotic should be included if susceptible. Moxifloxacin is the preferred fluoroquinolone. Ciprofloxacin is no longer recommended for the treatment of TB.

Group 4: Protionamide (or ethionamide) and cycloserine are the two most commonly used agents from this group. Para-aminosalicylic acid (PAS) is the next choice if a third drug is required.

Group 5: The effectiveness of drugs in this group is unclear. They should only be considered when drug options are limited.

In addition to expert consultation, current MDR guidelines published by WHO, Secretariat of the Pacific Community and Francis J Curry National Tuberculosis Center may be useful resources for clinicians involved with the management of patients with drug-resistant TB.

### 3.5.5 Extensively drug-resistant TB

Extensively drug-resistant TB (XDR-TB) is defined as MDR-TB that is resistant to one or more of the fluoroquinolones and injectable agents.
Treatment of XDR-TB will involve Group 5 agents and management should always be in consultation with an expert in the management of drug-resistant TB.

XDR-TB has a very high mortality rate, especially in the setting of HIV co-infection, and a low cure rate.

3.6 Corticosteroid treatment in the management of TB

Corticosteroids should only be given when adequate anti-tuberculosis treatment is also being given. Adjuvant corticosteroids treatment is recommended in the first eight weeks for both TB meningitis and TB pericarditis and may also provide benefit in life threatening cases of TB.

3.6.1 TB meningitis and intra-cerebral tuberculomas

Randomised controlled trials show improved survival with the use of corticosteroids in patients with all stages of severity of TB meningitis.29,30,31,32

All patients with TB meningitis should receive adjunctive corticosteroids regardless of disease severity at presentation.20 The optimal corticosteroid dose is not certain but the following regimen was used in a recent controlled trial; adults were started on treatment with dexamethasone 0.4 mg/kg/24h with a reducing course over six to eight weeks.30

3.6.2 Tuberculous pleural effusion

Oral corticosteroid is no longer routinely recommended for tuberculous pleural effusion, despite the fact pleural thickening with consequent impairment of ventilatory function can result from tuberculous pleuritis. A well-conducted placebo-controlled trial showed that oral corticosteroid, in conjunction with rifampicin, isoniazid and ethambutol, produced benefit in terms of rate of fever resolution and rate of resolution of pleural fluid, but not in the frequency of pleural adhesions.33

A randomised trial of standard TB treatment, with or without corticosteroids, in the treatment of tuberculous pleurisy showed some benefits of steroid treatment (in terms of fluid resorption and pleural thickening) during the first two months. No difference was observed in these parameters after two months of treatment, regardless of whether steroid treatment was used.34

Similarly, Wyser et al (1996)35 showed that earlier symptomatic improvement occurred in their prednisone-treated group, but had no benefit in this regard after the first two months or in the proportion of subjects with pleural thickening at six months. They stressed the importance of early complete drainage of effusions.
Recommendations for managing tuberculous pleural effusions

- Steroid treatment is not routinely indicated for tuberculous pleural effusions.
- Large, loculated effusions that cannot be adequately drained may benefit from steroid treatment. Any benefit is unlikely to occur after two months on steroid.
- Oral steroid may be required to obtain early control of symptoms (pain, fever or malaise).
- Full drainage of tuberculous effusions is desirable. Usually this can be achieved by repeated thoracentesis. In the past, intercostal tube drainage was avoided because of fears of causing a chronic fistula, but this is unlikely with concurrent modern chemotherapy.
- Follow-up is needed after drainage, as an effusion that has been fully drained may recur and need re-aspiration in the first two to three weeks of treatment.

### 3.6.3 Tuberculous ascites

No well-controlled studies are available. In the absence of evidence to support steroid treatment for tuberculous pleural effusion, it is not recommended for tuberculous ascites.

### 3.6.4 Tuberculous pericarditis

Although uncommon, pericarditis is a dire complication of TB. Tuberculous pericarditis is almost invariably fatal without treatment and has up to a 40% mortality rate even with treatment. Early diagnosis and early institution of anti-TB therapy are important in preventing the development of constriction.

Constrictive pericarditis usually occurs early, but can also be a late consequence, and is associated with high morbidity and mortality. Although there have been no controlled trials, early surgical intervention is said to be technically easier and is associated with lower operative mortality and a lower rate of subsequent constriction than late pericardectomy.

The efficacy of corticosteroid treatment in tuberculous pericarditis may vary in the different stages of the disease (effusive, effusive-constrictive and constrictive) and many reports do not distinguish these stages. Oral steroids are unlikely to stop the progression from any stage to constrictive pericarditis, but do improve survival and reduce the need for surgery.36,37

### 3.6.5 Miliary TB, advanced TB, and suspected hypo-adrenalism

There is evidence to support the use of steroid treatment in patients with miliary TB, very advanced TB, and suspected hypo-adrenalism.38 These situations are associated with unexpected death, the causes of which are often uncertain, but may include:

- adrenal insufficiency – potentially, this could be made worse by the introduction of rifampicin, which may reduce the available endogenous cortisol
- the Jarisch-Herxheimer reaction, occurring soon after the start of TB treatment
• sudden death from myocardial TB
• other common medical complications that may be additive and contribute to cardiac arrhythmias and death in people with advanced TB, including electrolyte disturbances (from TB or from other conditions or their treatment), hypoxaemia caused by pulmonary TB, or concurrent chronic air-flow obstruction or coronary artery disease.

Because of the small risk and the potential benefits from steroid treatment, steroid treatment of 20–60 mg/day should be considered:

• if the patient is very ill from TB
• if the CXR shows a miliary appearance
• to reduce the mass effects and obstructive complications from mediastinal lymphadenopathy.

Where clinical or laboratory features are compatible with hypo-adrenalism; a short synacthen test should be done before steroid treatment is started, or dexamethasone should be used until that test has been completed.

In severely ill patients or patients with radiologically advanced disease, steroid cover should start immediately. The duration of steroid treatment will be judged by the clinical circumstances, but may continue for several weeks.

3.6.6 Renal-tract TB
Oral steroid has been used with anti-TB drugs for the treatment of tuberculous renal-tract stenoses, especially if the stenosis was located at the pelvi-ureteric or uretero-vesical junction. The aim has been to avoid permanent stenoses from post-tuberculous scarring. Severe tuberculous cystitis has often been managed in the same way. However, benefits are unproven in both situations. Steroid treatment is likely to be helpful only if narrowing is due to acute inflammation caused by a hypersensitivity response to tuberculo-protein or to the infection.

3.6.7 Oral steroid in the management of drug side effects
Only a clinician expert in the treatment of TB should manage drug side effects with oral steroids.

There is little literature about the management of TB drug side effects with oral steroid treatment. Steroid treatment is not usually needed as the offending drug(s) can be identified and stopped. When appropriate, testing for sensitivity by progressively adding drugs one at a time may be done (see Table 3.7).

3.7 Monitoring

3.7.1 Monitoring infectivity
Patients who are sputum smear–positive before treatment should have repeat sputum tests at least monthly to confirm sterilisation. Eighty-five percent of these patients are expected to be smear- and culture-negative after two months of treatment.
If the specimen at the end of the third month is both smear and culture positive, repeat drug susceptibility testing should be performed.\(^2\) As early detection of drug resistant TB is important, repeat DST after two months of treatment may be appropriate in some patients where there are concerns that acquired drug resistance may have developed.\(^2\)

3.7.2 Radiological monitoring

**Chest X-ray monitoring**

Chest X-ray (CXR) monitoring during treatment is required for all patients with X-ray abnormalities consistent with TB. The intervals between films will depend on the clinical circumstances.

A patient’s chest radiograph that does not show improvement after the patient has received three months’ treatment suggests:

- 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
- the patient may not have followed their medication regimen and secondary drug resistance must be considered
- primary drug resistance may have been present from the outset

**Chest CT scanning**

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.

**Serial imaging and extra-pulmonary sites**

Serial imaging and extra-pulmonary sites: the need for repeat imaging 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.

3.7.3 Monitoring for drug toxicity

**Hepatotoxicity**

**Pre-treatment**

Baseline blood count, creatinine, alanine amino-transferase (ALT), 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. A full panel of liver function tests
should be completed for patients with an elevated ALT, and the case should be discussed with a clinical TB expert.

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

**Monitoring during treatment**

Some overseas experts recommend clinical monitoring *without* regular blood tests in people who are asymptomatic even older people who have a higher incidence of hepatotoxicity.\(^{41}\) However, we recommend regular clinical monitoring of liver function as:

- serious hepatic dysfunction can develop before patients develop symptoms and can happen at any time during the treatment\(^{42,43}\)
- hepatitis B carrier state or sero-positivity for hepatitis C or HIV increases the incidence of hepatotoxicity to TB drugs\(^{44,45}\)
- the prevalence of hepatitis B carriage is 2.5%; it is highest in Māori (5.6%), Asians (6.2%), and Pacific peoples (7.3%)\(^{45A}\)
- risks are greater for those aged over 50 than for those aged 35–50, but for simplicity, 35 or over is the cut off for higher risk
- regular alcohol use is a risk factor for hepatotoxicity
- improvement occurs after removal of the drugs when liver dysfunction is noted\(^{46}\)
- even a rare death from TB-drug induced hepatitis is unacceptable
- iatrogenic hepatic failure sometimes requires liver transplantation.

**Monitoring for hepatotoxicity**

- After baseline screening, adults being treated for latent TB infection should have ALT monitoring at one month and then every two months.
- After baseline screening, 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.
- After baseline screening, adults being treated for TB disease who have risk factors for hepatotoxicity, should have complete liver function tests every month.
- If a patient’s ALT is more than three times the normal level, advice should be sought from a clinical TB expert promptly (see 8.2.5).
- 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 Committee on Adverse Reactions to Drugs.

**Ocular toxicity**

Ocular toxicity is the most important side effect of ethambutol; it is less likely if the dose is 15 mg/kg than if the dose is higher. 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 in people unable to report changes in vision and in people with moderate or severe renal insufficiency.

**Monitoring of patients on amikacin**

**Monitoring serum amikacin trough levels**
Serum amikacin trough levels should be measured regularly just before giving a dose. The trough level should be less than 1 mcg/mL if toxicity is to be avoided. If the estimated creatinine clearance is less than 50 ml/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.

**Monitoring plasma creatinine concentration**
In patients with normal renal function requiring long-term dosing, fortnightly creatinine clearance monitoring is recommended to monitor plasma creatinine concentration.

**Monitoring ototoxicity and vestibular dysfunction**
With long-term 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. 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 nurse every month and a pill count should be completed. Patients must be educated about TB and potential drug side effects and should be instructed to watch for common drug reactions.
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 public health nurse is being carried out.

3.7.4 Therapeutic drug monitoring

Monitoring amikacin levels

See section 3.2.2.

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. In patients with HIV there may be up to a 70% reduction in serum TB drug concentrations compared with control subjects. Sub-therapeutic drug concentrations carry a significant risk of drug resistance developing.
- The patient has ascites (see section 3.11.2.4).
- 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 severely obese (for example, a body mass index of 30 or more; see section 3.11.4).

3.7.5 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.

A paradoxical reaction is thought to result from an immunological host response to mycobacterial products that have been released as a result of treatment-induced bacterial cell death and dissolution and the restoration of part of the host immune response as a result of treatment.

Paradoxical reactions may have local or systemic components or both. Their nature is the same in HIV-infected and non-HIV-infected people, but they occur more frequently...
in HIV-infected people who are receiving TB treatment and then start taking anti-retroviral agents. TB-related paradoxical reactions in people with HIV infection are discussed in Chapter 6.

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
- 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 to detect other possible causes including tissue sampling and repeating TB cultures should be completed.

### 3.8 Drug side effects

Common adverse side effects of TB drugs are listed in Table 3.6.

**Table 3.6:** Adverse effects of tuberculosis drugs

<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>Drug</td>
<td>Side Effects</td>
</tr>
<tr>
<td>--------------</td>
<td>---------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Isoniazid hepatotoxicity:</td>
</tr>
<tr>
<td></td>
<td>Hypersensitivity reactions are unusual.</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy, optic neuritis, fever, hepatitis, ataxia, euphoria, convulsions, tinnitus,</td>
</tr>
<tr>
<td></td>
<td>insomnia, hyperglycaemia, gynaecomastia, dry mouth, epigastric discomfort, urinary retention,</td>
</tr>
<tr>
<td></td>
<td>anaemia, arthralgia. Contraindicated in manic states and porphyria.</td>
</tr>
<tr>
<td></td>
<td>Idiosyncratic reactions may include a (usually reversible) lupus-like syndrome (fever, arthritis,</td>
</tr>
<tr>
<td></td>
<td>pleuritis, pericarditis, positive rheumatoid factors, etc), and, very rarely, a</td>
</tr>
<tr>
<td></td>
<td>rheumatoid arthritis-like syndrome, and agranulocytosis.</td>
</tr>
<tr>
<td></td>
<td>Very rare hypersensitivity reactions include eosinophilia, angitis, toxic psychosis, and</td>
</tr>
<tr>
<td></td>
<td>meningo-encephalitis.</td>
</tr>
<tr>
<td></td>
<td>Toxic doses decrease the synthesis of the inhibitory neurotransmitter gamma aminobutyric acid.</td>
</tr>
<tr>
<td></td>
<td>Central nervous system depression or stimulation may result.</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Gastrointestinal side effects, hyperuricaemia, hepatotoxicity, fever, anorexia, nausea and</td>
</tr>
<tr>
<td></td>
<td>vomiting; precipitation of gout (see section 3.11.2); arthralgias, urticaria, sideroblastic</td>
</tr>
<tr>
<td></td>
<td>anaemia.</td>
</tr>
<tr>
<td></td>
<td>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</td>
</tr>
<tr>
<td></td>
<td>macrolide antibiotics</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Gastrointestinal disturbance, cholestatic hepatic dysfunction, transient elevation of hepatic</td>
</tr>
<tr>
<td></td>
<td>enzymes.</td>
</tr>
<tr>
<td></td>
<td>Danger with intermittent therapy: flu-like syndrome, shock, acute renal failure, death.</td>
</tr>
<tr>
<td></td>
<td>Acute haemolytic anaemia.</td>
</tr>
<tr>
<td></td>
<td>Rare reports of rifampicin-induced light chain proteinuria and renal failure, attributed to</td>
</tr>
<tr>
<td></td>
<td>dehydration associated with fluid restriction for syndrome of inappropriate antidiuretic hormone.</td>
</tr>
<tr>
<td>Thiocetazine</td>
<td>Nausea, vomiting, diarrhoea, bone marrow depression, vertigo, ataxia, tinnitus, occasional</td>
</tr>
<tr>
<td></td>
<td>liver toxicity, cutaneous hypersensitivity.</td>
</tr>
</tbody>
</table>


3.8.1 Dermatological side effects
Skin reactions can occur with any anti-TB drug. Pyrazinamide is the drug that most commonly causes skin reactions; in one study, it caused 26 out of 31 (84%) of all rashes in 1317 patients.50 Pyrazinamide also causes facial flushing or transient pruritis. Isolated skin rash occurs in about 2% of people taking isoniazid, but commonly occurs as part of a wider hypersensitivity reaction. Skin rash due to rifampicin is usually mild, but can take many forms. Photosensitivity can occur with pyrazinamide and the fluoroquinolones.

3.8.2 Hepatotoxicity from TB drug treatment
TB treatment includes several potentially hepatotoxic drugs, including isoniazid, rifampicin and pyrazinamide. Monitoring is discussed in section 3.9. Ethambutol rarely causes hepatic dysfunction.

3.8.3 Toxicity of aminoglycosides
The toxicity of aminoglycosides can be auditory and vestibular toxicity or nephrotoxicity.
Auditory and vestibular toxicity

Aminoglycosides can cause auditory and vestibular toxicity. Auditory damage begins in the basal end of the cochlea and progresses to the apical end. Symptomatic hearing loss begins with high frequency loss and, as administration continues, lower frequency loss occurs. At least half the cases of auditory toxicity are irreversible. Vestibular damage may be reversible. Early detection helps prevent hearing loss in the frequency range that can affect communication, so it is essential to test high-frequency ranges.

High trough serum levels and advanced age are the most important predisposing factors to ototoxicities. Other factors include the duration of administration, the total dosage, having a high fever and bacteraemia, dehydration, and prior renal or ear disease. Ototoxicity occurs independently of nephrotoxicity.

Nephrotoxicity

Nephrotoxicity relates to dose, duration of treatment, and age, and is more likely in patients with pre-existing renal impairment, dehydration or liver disease and in patients receiving loop diuretics or other nephrotoxic agents.

3.9 Management of drug reactions

3.9.1 Need for a new temporary regimen

The patient’s clinical situation determines the acceptable period for which the patient should stay off all TB treatment while awaiting resolution of TB-drug side-effects.

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 likely after 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 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.\textsuperscript{51}

**Agents in the temporary regimen**

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

- **Practice point – managing side effects of TB drugs**
  
The maximum period for a patient 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.

**3.9.2 Management of drug challenges**

When troublesome side effects occur, stop 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 regime 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. The drug challenge doses for mild-to-moderate reactions are shown in Table 3.7.

If you are unfamiliar with conducting drug challenges, consultation with a clinical TB expert should occur.

**Table 3.7:** Drug challenge doses for mild-to-moderate reactions

<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>

Source: NHMRC (1989).\textsuperscript{52}
3.9.3 Management of drug de-sensitisation

Desensitisation should be considered only when suitable replacement drugs are not available. Rapid desensitisation protocols can be used for patients that are sensitive to rifampicin, ethambutol and isoniazid. These guidelines are based on protocols for treating penicillin allergy. Desensitisation should always be carried out cautiously and with full resuscitation resources available.

3.9.4 Management of skin side effects

A minor rash and itchiness are common with anti-TB drugs. Sometimes the skin side effects are short-lived, so the drugs may not have to be stopped. If the drugs are stopped, it is sometimes possible to resume them successfully. Consider the following measures.

- Before assuming the anti-TB drugs are the cause of the symptoms, check the patient has not recently changed their brand of soap.
- Skin moisturisers may help dry, itchy skin
- Pruritis may be helped by:
  - a non-sedating antihistamine such as loratidine, although older antihistamines may be tolerated and are cheaper
  - Pinetarsol gel or solution
  - BK bath oil or lotion.

Major skin rashes require all drugs to be stopped and the patient to be given test doses of each drug until the drug causing the reaction is identified.

3.9.5 Management of drug-induced hepatotoxicity

Generally, drugs that are closely related chemically should not be used if marked hepatotoxicity occurs with one of them. However, rifabutin may be tried cautiously after recovery from rifampicin hepatotoxicity.

If clinical hepatitis occurs (with anorexia, nausea, vomiting, hepatic tenderness and/or jaundice), stop all drugs and refer the patient to a liver unit or gastroenterologist.

Use your clinical judgement before reinstituting a drug that has caused hepatitis. In one series, reintroduction of rifampicin and isoniazid was possible in 41 out of 44 patients after resolution of marked biochemical and clinical hepatitis. Most experienced physicians would try cautiously reintroducing isoniazid and rifampicin after an asymptomatic abnormality of liver function. However, in all but very minor circumstances, consult a clinical TB expert.

3.9.6 Management of uncontrollable vomiting

Nausea is common with anti-TB drug treatment, but it can usually be managed with common agents. Theoretically, drugs such as metoclopramide, which stimulate gastric emptying, may have an effect on anti-TB drug levels, but there is no literature on this...
subject. If prolonged use of such drugs is needed, it may be preferable to use prochlorperazine (Stemetil) or cyclizine (Marzine).

3.9.7 Management of paradoxical reactions
Once a paradoxical reaction has been investigated and other causes excluded, the need for treatment depends on the location and severity of the reaction. Pulmonary reactions may precipitate acute respiratory failure, and an expanding intracranial abscess may result in serious neurological sequelae or death. In these and similar life-threatening situations, corticosteroid treatment may be needed to control cytokine-induced inflammation. Painful, grossly enlarged lymph nodes may need to be excised.

3.10 Interactions with anti-TB drugs
The rifamycin–warfarin interaction and interactions with pyrazinamide are discussed below. For other drug interactions, see Table 3.8.

3.10.1 Rifamycin–warfarin interaction
The rifamycin–warfarin interaction is very important. This interaction can cause sub-therapeutic anticoagulation or a dangerous degree of over-anticoagulation when rifampicin is stopped.

Sub-therapeutic anticoagulation may occur when a patient on warfarin starts rifampicin. Patients who are taking both agents and who have an absolute indication for anticoagulation, need monitoring at least weekly. If warfarin anticoagulation is difficult, use low molecular weight heparin.

Dangerous over-anticoagulation may occur when rifampicin is stopped, thereby effectively reducing the hepatic metabolism of warfarin.

3.10.2 Interactions with pyrazinamide
Allopurinol may paradoxically increase serum urate levels if given with pyrazinamide.

Pyrazinamide may need to be avoided in patients with troublesome gout, as it can precipitate acute attacks. Anecdotally, it may be possible to continue pyrazinamide after recovery from an attack of gout if the patient can tolerate colchicine in a dose of 0.5 mg BID. If successful, the colchicine should be continued, and stopped when the pyrazinamide is discontinued.

3.10.3 Oral contraceptive use
Rifamycins are inducers of certain hepatic cytochrome P450 enzymes. Both oestrogens and progesterones are metabolised through this pathway. As a result, their elimination is accelerated in women taking rifampicin or rifabutin, and contraceptive efficacy is lost for both combined oral contraceptives and progesterone-only pills. Rifampicin is the more potent inducer and the induction of liver enzymes begins six days after commencement of rifampicin and can be observed for up to one month after cessation of the drug.
A second mechanism by which rifamycins lower circulating blood oestrogen levels is by reducing their entero-hepatic circulation. This has been shown to occur with ethinyloestradiol. This mechanism does not operate with progesterone hormones.

An alternative contraceptive method should be used during rifamycin therapy and for one month after stopping, even if rifamycin was for less than a week.\textsuperscript{57C,57D}

Injectable progesterone, depot medroxyprogesterone acetate is considered an effective contraceptive. The standard recommendation is a 12-weekly injection. It is uncertain whether a greater frequency is needed when rifamycins are being taken. The usual recommendation is to reduce the dosing interval to 10 weeks (one source advises eight weeks) in women taking rifampicin or rifabutin.\textsuperscript{57E}

### 3.10.4 Rifampicin-corticosteroid interaction

Induction of hepatic enzymes due to rifampicin can result in a profound reduction in corticosteroid levels. Patients on corticosteroids therefore should have the dose of corticosteroid increased by two to three fold when rifampicin is commenced. Clinicians should also be aware that enzyme induction may persist for two to three weeks after the discontinuation of rifampicin.

#### Table 3.8: Clinically important interactions with tuberculosis drugs

<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>Inhibition of carbamazepine hepatic metabolism has been described</td>
<td>Monitor carbamazepine blood levels</td>
</tr>
<tr>
<td></td>
<td>- carbemazepine</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>- phenytoin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Possible increased plasma haloperidol</td>
<td>Adjust dose if needed</td>
<td></td>
</tr>
<tr>
<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>
<td></td>
</tr>
<tr>
<td>Anti-fungals</td>
<td>Ketoconazole</td>
<td>Possible decreased antifungal blood level</td>
<td>No problem using Fluconazole</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>Marked rise in cyclosporin levels</td>
<td>Monitor cyclosporin blood levels</td>
<td></td>
</tr>
<tr>
<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>
<td></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>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>
<td></td>
</tr>
<tr>
<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>
<td></td>
</tr>
<tr>
<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>
<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>Monitor response</td>
</tr>
<tr>
<td>• dispyramide</td>
<td></td>
<td></td>
<td>Monitor serum level; may increase antifungal dose</td>
</tr>
<tr>
<td>• mexilitine</td>
<td></td>
<td></td>
<td></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>Raised rifabutin level</td>
<td></td>
<td>Monitor serum level; may increase antifungal dose</td>
</tr>
<tr>
<td>• fluconazole</td>
<td>Reduced absorption, halving the rifampicin level</td>
<td></td>
<td>Give at least 12 hours apart; check rifampicin level</td>
</tr>
<tr>
<td>• ketoconazole</td>
<td></td>
<td></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>
</tbody>
</table>
### Chapter 3: Treatment of Tuberculosis Disease

<table>
<thead>
<tr>
<th>Tuberculosis drug</th>
<th>Interacting agent</th>
<th>Effect</th>
<th>Advice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytion concurrent isoniazid</td>
<td>Markedly reduced anti-epileptic effect, especially in fast acetylators Isoniazid counteracts lowering of serum phenybin by rifampicin</td>
<td>Monitor diabetic control.</td>
<td></td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• tobutamide</td>
<td></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>
</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></td>
<td></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>

### 3.11 Special situations

#### 3.11.1 Renal impairment and treatment of TB

Isoniazid, rifampicin, pyrazinamide, ethionamide and protonamide are eliminated almost entirely by non-renal routes (ie, by metabolism or biliary secretion). When prescribing TB drugs in a person with significant renal impairment, monitoring of blood levels may be required.
Renal impairment, without dialysis

Isoniazid
It has been estimated that isoniazid of 5–6 mg/kg/day given to a slow acetylator with severe renal impairment would be equivalent to a dose of 7–9 mg/kg/day in a normal subject. Therefore, standard doses of isoniazid should be given in people with renal failure. If side effects occur, therapeutic drug monitoring is indicated (see section 3.9).

Rifampicin
Up to 30% of rifampicin is excreted in urine (possibly as a result of the biliary route becoming saturated) but less than half of this is unaltered. Although the half-life of 600 mg rifampicin increases 30–40% in patients with renal insufficiency, it is well tolerated and no dosage adjustment is required.

Ethambutol
About two-thirds of the dose of ethambutol is excreted unchanged in urine. Ethambutol should be avoided if possible in the setting of renal impairment. However, if ethambutol is given, the frequency of dosage should be reduced according to the severity of renal impairment. Alternatively, the daily dosage adjustment can be based on the glomerular filtration rate (GFR) but note the following:

- With normal renal function, corrected creatinine clearance is the best indicator of GFR.
- In the early stages of glomerular failure the corrected creatinine clearance remains the most sensitive indicator of GFR. Because of the hyperbolic relationship between creatinine clearance and serum creatinine, the clearance will fall significantly during a period in which the serum creatinine remains normal.
- Once renal failure is established and the serum creatinine is significantly elevated (above 0.2–0.3 mmol/L, depending on muscle mass), the serum creatinine becomes a more sensitive indicator of any further deterioration of the GFR. The serum concentration will rise rapidly while the creatinine clearance will show little further change.

Pyrazinamide
Pyrazinamide is primarily metabolised by the liver to pyrazinoic acid and other metabolites, 3% appearing unchanged in the urine and 30–40% as pyrazinoic acid. Consequently, mild-to-moderate degrees of renal impairment do not require any adjustment of dose or frequency of administration.

Fluoroquinolones
The mode of excretion varies among the fluoroquinolone family, so drug management varies in the presence of renal impairment.

Moxifloxacin is excreted both by renal (20–30%) and biliary pathways, so no dose adjustment is needed, with or without haemodialysis.
Aminoglycosides
Streptomycin, kanamycin, amikacin and capreomycin are excreted almost exclusively by the kidney, and dosages must be adjusted according to the degree of renal impairment. Serum concentrations of drugs should be monitored. However, these drugs are best avoided in renal impairment.

Table 3.9: Doses of major anti-tuberculosis agents and renal impairment

<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>Ethambutol¹</td>
<td>Avoid unless absolutely necessary GFR 20–50: Dose as in normal renal function GFR 10–20: 15mg/kg every 24–36 hours GFR &lt; 10 ml/min: 15 mg/kg every 48 hours or 5–7.5 mg/kg daily</td>
<td>Avoid unless absolutely necessary 15 mg/kg every 48 hours or 5–7.5 mg/kg daily</td>
<td>Avoid unless absolutely necessary 25 mg/kg three times a week, after dialysis or 5–7.5 mg/kg/day</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.
¹ Ethambutol should be avoided in renal impairment unless absolutely necessary.


Peritoneal dialysis
It is acceptable to give the normal dose of rifampicin and isoniazid even in slow isoniazid acetylators. Ethambutol should be avoided unless absolutely necessary.

Haemodialysis
Isoniazid, rifampicin and ethambutol are not significantly removed by haemodialysis.

Isoniazid and rifampicin
Isoniazid and rifampicin can be given in their usual daily doses. Conventional doses are safe and effective.

Ethambutol
Ethambutol should be used with caution in renal impairment. Blood levels of ethambutol can vary from one patient to another due to variable absorption. This
variation in levels may be the result of pre-dialysis fluid overload, and better absorption may be achieved with post-dialysis dosing.

The recommended dose of ethambutol with haemodialysis is 15–25 mg/kg given three times a week after dialysis, when dialysis is given at that same frequency.

If ethambutol is used, serum levels of ethambutol must be monitored and regular ophthalmology assessments are essential.

**Pyrazinamide**

Pyrazinamide is significantly removed by haemodialysis. Doses of 25–30 mg/kg must be given after haemodialysis, three times a week. Pyrazinoic acid, which is the primary metabolite of pyrazinamide, is partially removed by haemodialysis, but the extent of removal is uncertain.

**Timing of doses**

Rifampicin, isoniazid and ethambutol may be administered after haemodialysis, and this may facilitate directly observed therapy.

**Other tuberculosis drugs**

Ethionamide and para-aminosalicylic acid are not significantly dialysed.

Cycloserine is significantly removed by dialysis, so doses should be given after dialysis. Usual doses, given three times a week after dialysis, are recommended.

Ethionamide is rapidly metabolised by the liver, so dose adjustment for renal failure or dialysis is unnecessary. The absorption of ethionamide may be delayed in long-term dialysis patients.

Clofazimine should be given in its usual dose of 100–200 mg daily, administered after dialysis.

Moxifloxacin can be given in usual doses with haemodialysis.

### 3.11.2 Hepatic dysfunction (and ascites) and TB treatment

The monitoring of hepatotoxicity of TB drugs is discussed in section 3.8.2. Sometimes liver dysfunction is detected before treatment is started.

**Causes of abnormal liver function tests**

Hepatic dysfunction before TB treatment 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 when TB is diagnosed may also cause abnormal liver function.
Tests before starting treatment

Section 3.7.3 discusses the investigations of liver function that should be obtained before starting treatment. If tests are abnormal, investigations should include appropriate clinical evaluation; an ultra-sound may be indicated if an obstructive pattern is present.

Regimens when major liver disease is present before treatment

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 in icteric patients can occur. Although 50% of quinolone clearance occurs in the liver, its serum concentration is not substantially altered in hepatic disease.

In renal disease, indices of renal function correlate with estimates of residual renal function, but this is not true of hepatic dysfunction where transaminase levels usually do not correlate with the ability of the liver to metabolise drugs.

If a person with active TB has major hepatic dysfunction, 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 may be added one at a time. Rifampicin would be the next agent of choice to add. Consultation with a TB clinical expert and a hepatologist is strongly recommended. Therapeutic drug monitoring may be helpful.

Ascites

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 (see section 3.7.4).

Hepatitis B, hepatitis C and HIV infected patients

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 than other people.

3.11.3 Pregnancy and lactation

Pregnancy

The risk of untreated TB to a pregnant women is far greater than the risk of toxic effects from the drugs used in its treatment. When active TB is diagnosed in a pregnant women it is essential that prompt, effective treatment is administered.

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 latent TB may be delayed until after the birth unless the infection has been recently acquired or the women has other medical conditions such as HIV infection that places her at higher risk of developing TB disease.

Little is known about the safety of second-line agents during pregnancy. These drugs should only be used in specific instances after consultation with a TB specialist.

**Isoniazid, rifampicin and ethambutol**

The use of isoniazid, rifampcin and ethambutol have been well studied and are considered safe in pregnancy. All pregnant women on isoniazid should receive pyridoxine to prevent neurotoxicity in the foetus.

**Pyrazinamide**

There is a lack of controlled data on the safety of pyrazinamide during pregnancy and international guidelines differ in their recommendations.

The World Health Organization and the International Union Against TB and Lung Disease both recommend the routine use of pyrazinamide during pregnancy and toxicity to the foetus has not been documented. The American Thoracic Society and Centers for Disease Control guidelines however do not recommend the general use of pyrazinamide with drug-susceptible TB due to a lack of controlled data in pregnancy. The Francis J Curry National Tuberculosis Center guidelines for Drug-resistant tuberculosis recommend that for women with HIV co-infection or drug-resistant disease, pyrazinamide should be included in the TB regimen if the isolate is susceptible. In cases with drug resistance, the risk of taking pyrazinamide is less than the risk of not curing TB.

Pregnant women with TB should be counselled appropriately and if pyrazinamide is not used the minimum duration of treatment is nine months.

**Streptomycin, amikacin, capreomycin and kanamycin**

Aminoglycosides are potentially ototoxic to the foetus. Streptomycin and kanamycin have been implicated as the cause of mild to severe bilateral congenital deafness in up to 17% of pregnancies. For that reason, amikacin and capreomycin are also not recommended during pregnancy but have been used safely in some reports for the treatment of drug-resistant TB.

**Ethionamide and prothionamide**

Ethionamide and prothionamide are considered potentially teratogenic, so should not be used during pregnancy.
Rifabutin, cycloserine and PAS

Rifabutin, cycloserine and PAS have not been studied extensively but animal models and anecdotal human reports have not shown toxicity.

Lactation

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 affects in the newborn.\textsuperscript{72}

It is therefore important to note that because of the low concentrations of anti-tuberculosis drugs in breast milk, they do not provide an effective treatment for disease or latent TB infection in a breastfed infant.

3.11.4 Obesity and TB drug doses

Antimicrobial dosing in obese patients is complex and poorly understood, but some issues are discussed in a review by Wurtz et al (1997).\textsuperscript{73} 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.

Doses of first-line TB medicines in obesity

Maximum doses of the standard TB medicines are discussed in section 3.2.

With short obese adult, 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.

References

Guidelines for Tuberculosis Control in New Zealand 2010
Chapter 3: Treatment of Tuberculosis Disease


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**Guidelines for Tuberculosis Control in New Zealand 2010**  
**Chapter 3: Treatment of Tuberculosis Disease**
Chapter 4: Adherence to Treatment and Directly Observed Therapy

Summary
Tuberculosis (TB) control requires a high level of adherence to the treatment regimen. If adherence is poor, drug resistance, prolonged infectiousness or reactivation may develop. Healthcare staff must support patients and enable them to adhere to the full course of treatment.

This chapter discusses the different levels of supervision for treatment, including the use of directly observed therapy (DOT). It is primarily intended for public health nurses and clinicians with TB patients.

Clinical and public health services providing treatment and follow-up for TB must provide:

- a free service
- free TB medications
- good case management
- appointment reminders and follow up of non-attendance
- a comfortable clinic environment with minimal waiting times
- clear advice about side effects
- clear communication, including written and oral health education materials
- interpreters and culturally appropriate workers, if required.

TB programmes need to use multiple strategies to ensure patient adherence to the treatment regimen. The most successful programmes combine outreach workers, supervised therapy, thorough case management, excellent patient–provider communication, and additional assistance or incentives to patients if required. In the case of treatment for LTBI, shorter courses of medication offer the possibility of improved completion of therapy.

Public health offices should ensure that information on DOT is carefully completed on the EpiSurv Case Report form.

4.1 Adherence

4.1.1 Introduction
Adherence refers to the extent to which a patient follows the instructions given for prescribed treatment. Adherence is critical for successful TB control. Patients who do not adhere to their treatment regimen remain infectious longer, take longer to complete treatment and are more likely to relapse or develop drug resistance than patients who do adhere.

Low adherence with any prescribed treatment is common, with typical adherence rates estimated to be about 50%. A meta-analysis of interventions to improve adherence with long-term medication found that almost all the effective interventions were complex, including drug combinations, information, counselling, reminders, self-monitoring, reinforcement, family therapy, and other forms of additional supervision or attention.
4.1.2 Adherence and tuberculosis medication

Patients need support to adhere to a course of TB medication because:

- it is difficult to remember to take long courses of treatment
- the pills prescribed are sometimes hard to swallow
- large numbers of pills have to be taken
- the medication can have unpleasant side effects
- patients must abstain from or reduce their intake of alcohol
- stigma and negative attitudes associated with TB can affect the patient’s acceptance of diagnosis and willingness to adhere to treatment
- medication for other conditions may result in a very large total number of tablets and interactions may compound difficulties
- the patient usually feels better long before the treatment has been completed.

These factors are also relevant in the treatment of latent tuberculosis infection (LTBI), where the patient does not even feel unwell before starting treatment (see Chapter 8).

Factors influencing adherence include:
- the accessibility and responsiveness of the health service (health care factors)
- the nature of the treatment (treatment factors)
- stigma and cross-cultural concepts of TB (cultural factors)
- the existence of more pressing personal problems (patient factors).

A New Zealand study of older people found that the public health nurse, resourced to deliver a patient-centred model of care, is a key support during TB treatment.2

4.2 Assessing adherence

Risk factors for non-adherence must be formally assessed for each patient at the beginning of treatment to determine the optimal level of supervision.

4.2.1 Risk factors for non-adherence

Recognised risk factors for non-adherence to the treatment regimen include:
- homelessness
- a history of TB
- substance abuse
- denial of diagnosis
- living alone
- patients believing that they are likely to have poor adherence.3,4

It is difficult for healthcare workers to predict a patient’s adherence with accuracy. Demographic variables such as age, gender and ethnicity do not predict adherence.
4.2.2 Determining the initial level of supervision

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 (see Table 4.1).

Table 4.1: Recommended level of supervision

<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 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 (eg, substance abuse, denial 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 observed therapy</td>
</tr>
<tr>
<td>Psychiatric illness</td>
<td></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 diseases</td>
<td></td>
</tr>
<tr>
<td>None of the above risk factors</td>
<td>Self-administered treatment</td>
</tr>
</tbody>
</table>

4.3 Monitoring adherence

All patients on TB medication must be systematically monitored for adherence to their treatment regimen.

4.3.1 Methods for monitoring adherence

Monitoring methods include patient interviews, pill counts and, rarely, urine assays.

Record-keeping sheets help public health nurses to record pill counts and detect adherence problems (see Appendix 4.1).

4.3.2 Levels of supervision and treatment contracts

Levels of supervision

There are three levels of treatment supervision. Treatment may be delivered as:

- self-administered treatment
- treatment under close supervision
- DOT.

A process for determining the level of supervision is shown in Figure 4.1.
The type of treatment and the required level of supervision may change during the course of treatment.

**Treatment contracts**

Treatment contracts can be used at all levels of supervision, if the patient’s adherence is doubtful. A treatment contract includes:

- the time and place for delivery of supplies of medication (or delivery of DOT)
- the patient’s agreement to contact the case worker if plans change
- the patient’s intention to attend all appointments.

After the patient has dated and signed the treatment contract, the public health nurse or medical officer of health should date and countersign the contract.
4.3.3 Self-administered treatment

Self-administered treatment is possible if there are no risk factors and regular monitoring confirms good adherence. The patient self-administers medications daily with oversight by a public health nurse. Table 4.2 shows the routine requirements for monitoring when there are no concerns about adherence.
**Table 4.2:** Routine activities for monitoring adherence

<table>
<thead>
<tr>
<th>Clinical activities</th>
<th>Public health activities</th>
<th>Clinical and public health activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring of:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• clinic non-attendance</td>
<td></td>
<td>Good communication among case workers, clinicians and patient</td>
</tr>
<tr>
<td>• adherence (physician assessment)</td>
<td></td>
<td>Rapid communication if concerns about adherence</td>
</tr>
<tr>
<td>• rate of clinical response to medication</td>
<td></td>
<td>Regular case review meetings between clinical and public health services</td>
</tr>
<tr>
<td></td>
<td>Regular assessment of patient by public health nurse, which includes:</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• discussing progress and problems, including side effects and adherence</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• making monthly pill counts or syrup volume checks</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• checking medications are dispensed as prescribed</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• monitoring changes to risk factors for non-adherence</td>
<td></td>
</tr>
</tbody>
</table>

### 4.3.4 Close supervision

Under close supervision, the patient self-administers medications daily, but has frequent, usually weekly, visits from an outreach worker, generally a public health nurse. The worker explores and tries to alleviate barriers to adherence.

Trigger points that might lead to closer supervision (or DOT) include:

- the patient did not attend one clinic visit
- the patient was not present for one pre-arranged public health nurse visit
- the public health nurse or hospital staff were concerned about adherence
- pill counts indicate consistent missing doses (more than 15%).

### 4.4 Directly observed therapy (DOT)

#### 4.4.1 Definition

The WHO DOTS strategy stands for Directly Observed Therapy, Short Course. This includes a comprehensive strategy for tuberculosis which is relevant for developing countries.

DOT, as discussed here, describes the process where a trained supervisor watches the patient swallowing the medication for all doses during the course of treatment. It is one component of the DOTS strategy.

The DOT supervisor may be a health worker or a trained and supervised community member. DOT may be given daily or intermittently. Chapters 3 and 8 outline accepted regimens. WHO recommends that intermittent regimens should be thrice weekly rather than twice weekly as the consequences of missed doses are likely to be less serious.\(^5\)
4.4.2 Directly observed therapy rates in New Zealand

Universal DOT is not required in New Zealand, which has high rates of treatment completion and low rates of drug resistance and relapse.\textsuperscript{6,7,8}

In New Zealand, about 32% of notified TB cases received DOT in 2002–07.

Only people who received DOT for the whole duration of their treatment are classified on the EpiSurv case report form as having received DOT. An additional question has now been added: ‘Did the case receive DOT throughout the intensive phase of treatment’.\textsuperscript{9}

Public health services need to ensure that information on DOT use is collected and entered on EpiSurv.

4.4.3 Effectiveness of directly observed therapy

Some literature shows that DOT produces superior treatment completion rates to those achieved by non-supervised interventions. DOT also leads to decreased relapse and drug-resistance rates.\textsuperscript{10,11,12} However, randomised trial evidence for the effectiveness of DOT is limited,\textsuperscript{13,14,15} and DOT may not always lead to better treatment outcomes than self-administered treatment.\textsuperscript{16,17,18}

4.4.4 Adherence to treatment of latent tuberculosis infection

Treatment for LTBI requires a long course of treatment in a well person. Adherence is even more difficult than in cases on full treatment for active TB disease. No one strategy has been found to be successful for improving adherence to treatment for LTBI.\textsuperscript{19} It has been found that shorter courses of treatment for LTBI are associated with better adherence.\textsuperscript{20} Offering the patient the choice of medication regimen for LTBI is also associated with better adherence.\textsuperscript{21}

DOT is associated with higher completion rates of LTBI treatment.\textsuperscript{22,23} It should be considered if the client has risk factors for non-adherence and one or more of the following apply:

- Full DOT treatment of TB disease is being given at the same time to a person in the same household or neighbourhood.
- The patient is aged under five years.
- There are risk factors for progression from infection to disease (see Chapter 8).
- The patient is a contact of a multi-drug-resistant (MDR-TB) TB case and treatment has been recommended.

DOT should always be used for intermittent regimens (thrice-weekly doses).
4.5 Practical problems during DOT

4.5.1 Temporary inability to give DOT

Self-administration of thrice-weekly treatment is not acceptable and can be authorised only by a medical officer of health or a clinical TB specialist and only in exceptional circumstances.

If a patient is going overseas and cannot be given DOT, he or she must change to daily treatment. If the patient is travelling around New Zealand, he or she should try to continue DOT through another public health office; if this is not possible, daily treatment should be prescribed.

4.5.2 Missed DOT doses

There are no published data (for daily or intermittent regimens) on how much treatment a person can miss and still be cured, but the medical officer of health should be advised if the patient misses:

- more than one DOT dose per month (for intermittent treatment)
- more than one DOT dose per week (for daily treatment).

If the patient misses a dose, the medical officer of health should meet the patient to discuss any obstacles to adherence to the DOT regimen. If adherence cannot be achieved in a patient who poses a risk of infection to others, the patient may need to be detained under section 16 of the Tuberculosis Act 1948.

Any missed doses of DOT must be added on to the end of treatment.

4.5.3 Non-traditional DOT workers

Community DOT workers are people without formal healthcare training. Community DOT workers need training and supervision in the provision of DOT.

In some circumstances health professionals from outside the public health workforce can be recruited to administer DOT.

In either situation, the public health nurse remains the case manager with overall responsibility for DOT, and close communication is essential.

4.6 Detention order

4.6.1 Section 16 of the Tuberculosis Act 1948

If all attempts to enable a patient to adhere to their treatment regimen fail, the local medical officer of health may seek a three-month detention order under section 16 of the Tuberculosis Act 1948.
A detention order is only applicable where it is necessary to isolate an infectious pulmonary (or laryngeal) TB patient who is posing a risk to others (ie, if a patient is non-adherent but does not pose an infectious risk to others, a detention order is not applicable).

### 4.6.2 When may a detention order be sought

It is important to involve the medical officer of health as soon as it is apparent that a detention order may be necessary.

Before seeking a detention order, ensure that every effort has been made to ensure that barriers to adherence have been minimised and there is good communication. This may include using cultural advisors, other health workers, or any other people who can engage with the patient.

The Ministry of Health has produced a guide for medical officers of health, explaining the protocol for detaining patients: *A Guide to Section 16 of the Tuberculosis Act 1948.* The guide outlines the legal implications and steps to follow when considering whether and how to detain a patient.

### 4.7 Optimising tuberculosis health services to improve adherence

**Code of Health and Disability Services Consumers’ Rights**

The Code of Health and Disability Services Consumers’ Rights (the Code of Rights) describes a series of rights for all users of health services in New Zealand (including the right to be treated with respect, to effective communication, to full information and to confidentiality). These rights are part of best clinical practice.

**Free services**

The local medical officer of health can write an order (a letter) under section 9 of the Tuberculosis Act 1948 requiring a person suspected or known to have TB to undergo compulsory investigation and treatment, if patients refuse to do so voluntarily. The District Health Board is then obliged to provide free TB diagnosis and treatment to these patients (including to non-resident patients ineligible for publicly funded health care who do not have health insurance).

The services are free in accordance with the Minister of Health’s gazetted notice *2003 Direction of the Minister of Health regarding eligibility for publicly-funded health and disability services in New Zealand.*

**Medications**

Anti-TB medication is free to all patients, regardless of their eligibility for publicly funded health care.

Blister packs are recommended to aid adherence.
Case management

Ideally, a designated physician and a single case worker (usually a public health nurse) will communicate regularly with the patient and each other.

Patient reminders should be issued for follow-up of non-attendance at clinics. A copy of the appointment should be sent to the public health service, as the public health staff may know about changes affecting the patient’s ability to attend.

Clinic visits

The case worker should ensure that the clients are reminded and supported to attend all clinic visits.

Advice about side effects

Clients need clear instructions (written and oral) about the potential side effects of medication, and what they need to do and who to contact should these occur.

A poor understanding of side effects has been reported in regard to treatment of LTBI.26,27

Language

Effective communication, given in a form, language and manner that the patient understands, is one of the rights in the Code of Rights. At the first contact with the health service, any patient whose first language is not English should be assessed to establish whether or not an interpreter is needed. If there is any doubt, an interpreter should be used.

When an interpreter is needed, a professional interpreter (ie, an interpreter with specialised training) should be used whenever possible. In general, untrained interpreters (eg, family members or friends) should not be used except in emergency situations, as this compromises the patient’s confidentiality and there is a risk of miscommunication.

A telephone interpreting service can sometimes be used.

Tips for communicating through an interpreter

- Speak slowly and clearly, using one or two sentences at a time.
- Focus your attention on the patient, not the interpreter.
- Use simple English — try to avoid medical terms and colloquialisms.
- Avoid conversation with the interpreter in front of the client. If this cannot be avoided, try to include the client or explain what is happening.

Source: Ministry of Health (2001).28
Ensure that written information is available in the patient’s language to complement verbal information.

‘Incentives and enablers’: measures that help a patient to overcome barriers and improve adherence

Incentives and enablers can increase adherence with DOT. These can include:

- discussions of barriers and attempts to overcome them
- more intensive supervision
- text message reminders
- additional information sessions
- assistance with transport, food, phone top-ups, or other goods
- monetary incentives.
### Appendix 4.1: Sample medication record for patients on self medication

**Medication record for patients on self medication**

<p>| | | | | | | | | | | | | |</p>
<table>
<thead>
<tr>
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<td>Date</td>
<td>No. of days since last visit</td>
<td>Prescribed dose</td>
<td>No. of tabs in a dose</td>
<td>No. of tabs left last visit</td>
<td>No. of doses left last visit (E/D)</td>
<td>No. of doses today plus no. dispensed today</td>
<td>No. of doses present today (G/D) plus no. dispensed today</td>
<td>Expected doses today (F–B)</td>
<td>Doses missed (H–I)</td>
<td>Percentage of doses missed (J/B%)</td>
<td>PHN/PHA initials</td>
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**Comments:**

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**Guidelines for Tuberculosis Control in New Zealand 2010**

**Chapter 4: Adherence to Treatment and Directly Observed Therapy**
References


Chapter 5: Tuberculosis in Children

Summary

Clinical and diagnostic differences from adult tuberculosis

- The same basic principles that apply to diagnosis and management of TB in adults apply to children. However, there are some important clinical and diagnostic differences.
- Children have a higher risk of progressing from infection to disease than adults and a higher risk of developing severe forms of disease (miliary and meningeal).
- Younger children < 5 years have a higher risk of developing extrapulmonary disease particularly miliary or meningeal TB.
- TB in children is usually an immediate complication of primary infection with a closed caseous paucibacillary lesion. Cavitory TB is rare in children.
- Majority of TB in young children occurs within one year of infection, meaning that TB disease in a child is a marker of recent transmission of the organism.
- Most children are infected from an infectious adult within their own immediate or extended family.
- Majority of children with intrathoracic TB have minimal symptoms and signs.
- Early suspicion and diagnosis is a crucial part of detection of TB in children.
- Diagnosis of TB in children is usually based on history and examination along with a combination of positive tuberculin skin test, known contact with adult case of TB and clinical or radiological features suggestive of TB.
- Miliary TB has a high risk of meningeal involvement in over 50% of cases, so many experts would recommend all children < 5 years with miliary TB should undergo a lumbar puncture to rule out meningitis.
- Bacteriological confirmation is particularly important if an isolate from a source case is not available, if the child has HIV, if there is suspected drug resistance or known drug resistance in the probable source case, in severe disease, and if the diagnosis is unclear.
- The vast majority of children with TB are not infectious, although all new/suspected cases should be isolated initially if hospitalised.

Basic principles of treating tuberculosis in children

For paucibacillary childhood TB, a three drug intensive phase is sufficient, if resistance is not suspected. More complicated disease requires a four drug intensive phase.

Optimal treatment regimens and dosages are not known for children, but most children using current regimens have good outcomes.
Management of tuberculosis in children

Many studies have confirmed that the regimen of 6/12 of isoniazid rifampicin, with pyrazinamide in the first two months cures over 99% cases of drug susceptible pulmonary TB.

As most cases of TB in children do not have an isolate available, the treatment regimen is based on sensitivities from source case.

Children with severe forms of TB should be hospitalised, including cases of miliary and meningeal TB, often for most of the intensive phase, as well as children with airway obstruction, some bone and joint disease and severe adverse reactions.

In most case of extrapulmonary disease excluding lymphadenopathy, 9–12 months treatment may be required.

Early discussion with a paediatric TB expert should be undertaken in cases:
- of disseminated TB
- poor or slow resolution of TB despite adequate treatment
- presence of comorbidities, especially HIV co-infection
- cases of suspected or proven drug resistance
- neonatal TB.

Monitoring

Clinical and radiological follow-up are used to evaluate a child’s response to treatment.

Clinical follow-up should include assessment of growth, symptomatology, adherence and adverse events, as well as dose adjustments for weight gains.

Chest X-ray – radiological changes usually require longer than six months to resolve. A normal CXR is not necessary for discontinuing anti-TB medication.

Adverse events are less common than in adults.

Management of neonates

Congenital TB is rare.

Transmission is most likely to occur in women with miliary TB, untreated smear positive disease or diagnosis in late pregnancy or post delivery. Greater than four months of treatment of the mother will protect foetus.

Breastfeeding does not transmit TB.

Consider TB when evaluating an unwell infant with symptoms not able to be explained by other causes and born to a mother at high risk for TB.

If the diagnosis is suspected a Mantoux test, chest X-ray, lumbar puncture and appropriate cultures should be performed.

Perinatal TB from airborne spread from an adult case including health care worker has been well documented over the years.

Management of a neonate will depend on stage of maternal disease.
Introduction

TB in children under 15 years of age accounts for approximately 5–10% of all disease in New Zealand, although this can be as high as 40% in some developing countries. (see chapter epidemiology, Shingadia 2003) This means that many clinicians in New Zealand will rarely diagnose a case of TB disease. Along with this, paediatric TB disease has some distinct characteristics, particularly in the young infant, which can make it a challenge to diagnose and treat.

Young children are more likely to develop active disease after exposure to TB and this can progress rapidly within weeks. Once disease occurs it is also more likely than in adults to progress to severe disseminated or meningeal disease, with significant morbidity and mortality. Tuberculosis in many young children may present with few or non-specific symptoms. Obtaining appropriate specimens can be difficult and other clinical investigations can also be difficult to interpret due to the paucibacillary nature of disease in young children.

An approach which includes awareness of the diagnosis, epidemiological information, clinical findings and appropriate investigations will help to make an early and accurate diagnosis. As TB in children is an indicator of recent acquisition and a marker of ongoing transmission in a community, it needs to be diagnosed early to identify source cases and prevent further transmission.1,2

Other chapters will include details of management of exposure of a child to a case of active TB (Chapter 7), management of latent TB infection in children (see Chapter 8) and drug specifics (see Chapter 3). BCG vaccination is now covered in the Immunisation Handbook (MoH website).

5.1 Clinical and diagnostic differences from adult tuberculosis

The same basic principles that apply to diagnosis and management of TB in adults apply to children. However, there are some important clinical and diagnostic differences.

- Children have a higher risk of progressing from infection to disease than adults and a higher risk of developing severe forms of disease (miliary and meningeal) with high rates of disability and death. Reasons for this relate to a relative immaturity of immune function.3,4

- Younger children < 5 years have a higher risk of developing extrapulmonary disease particularly miliary or meningeal TB. A child < 1 year old has a 10–20% chance of developing disseminated TB or tuberculous meningitis compared with a child >2 years of age who has only a 0.5% chance.4

- TB in children is usually an immediate complication of primary infection with a closed caseous paucibacillary lesion. Cavitatory TB is rare in children and is more likely to occur in children >10 years of age.3,4,5 Uncomplicated hilar adenopathy is the most common disease manifestation seen in children.
Prior to the use of chemotherapy, studies found that children under 2–3 years of age with primary infection progressed to serious disease within the first 12–24 months without significant prior symptoms. This progression rarely occurred in those age 2 to 10 years, but when it did they usually had significant symptoms.6,7

Children with HIV infection or other immunocompromising condition can have similar progression to young children.1

The majority of TB in young children occurs within one year of infection, meaning that TB disease in a child is a marker of recent transmission of the organism. In infants the time period can be as short as a few weeks.2

Most children are infected from an infectious adult within their own immediate or extended family.8,9

Just over half of TB occurs in infants and children <5 years of age and a second peak again in late childhood and adolescence. TB is much less common between 5–14 years.

5.1.1 Signs and symptoms

Majority of children with intrathoracic TB have minimal symptoms and signs.10 Over one-half of children will have no symptoms or signs, but have significant changes on chest x-ray. The younger the age the more likely the child will have symptoms. Non-productive, unremitting cough, mild dyspnoea and fever are the most common symptoms and young infants may have failure to thrive or lack of weight gain.11 Findings on chest examination are uncommon. The characteristic X-ray finding is lymphadenopathy with or without parenchymal involvement. A recent study from South Africa found significant limitations in interpretation of mediastinal adenopathy on chest X-ray and suggests caution in interpretation of radiographic lymphadenopathy.12 Further imaging maybe required.

Miliary disease results from lymphohaematogenous spread and occurs early after infection within first two to six months. The clinical manifestations are variable with onset that can be insidious (malaise, anorexia, low grade fever, weight loss) and non-specific or rapid and overwhelming. TB meningitis can also have an insidious onset over several weeks, but is universally fatal without treatment and delayed diagnosis can result in significant morbidity.1

Early suspicion and diagnosis is a crucial part of detection of TB in children. There have been a number of large outbreaks reported due to delayed diagnosis in the source case. A number of these have involved schools.3,13

Superficial lymph node enlargement is more commonly due to non-tuberculous mycobacteria in children in New Zealand, particularly in the under five year olds, but TB needs to be excluded particularly if overseas born or born to a family from a high prevalence country.
5.1.2 Diagnosis

- Diagnosis of TB in children is usually based on history and examination along with a combination of positive tuberculin skin test, known contact with adult case of TB and clinical or radiological features suggestive of TB. Positive cultures are uncommon in children and the above three factors are the mainstay of the diagnosis despite introduction of new diagnostic tests.\(^2,4\) The role of IGRA tests in diagnosis of active TB disease in young children is yet to be clarified\(^{14}\) (see Chapter 8).

- As sputum is rarely available from young children (< 7 years), alternatives are three early morning gastric aspirates on consecutive days, at least one induced sputum\(^{15,16}\) and bronchial secretions, preferably used in combination with gastric aspirates, from bronchoscopy if available. Bronchoscopy is invasive and should be used with caution in the unwell child with respiratory compromise but may be useful if other diagnosis are under consideration. A recent study from South Africa suggests that induced sputum can be done even in young infants, although this depends on the expertise being available and appropriate infection control precautions.\(^{17}\)

- Biopsy of appropriate tissue specimen for microscopy culture and PCR should be undertaken if possible, eg, pleura/CSF/lymph node. Miliary TB has a high risk of meningeal involvement in over 50% of cases, so many experts would recommend all children < 5 years with miliary TB should undergo a lumbar puncture to rule out meningitis.\(^{18}\)

- PCR will frequently be negative in pulmonary TB in children due to the low bacillary load, but can be very useful in diagnosis of extrapulmonary TB.\(^{16}\)

- Bacteriological confirmation is particularly important:
  - if an isolate from a source case is not available
  - if the child has HIV
  - if there is suspected drug resistance or known drug resistance in the probable source case
  - in severe disease
  - if the diagnosis is unclear.\(^{18}\)

- Even under ideal circumstances cultures are often negative in children as a result of paucibacillary disease. Negative cultures never exclude TB in a child.\(^2\)

- In many cases of TB in children there will be no positive culture so a decision to treat requires careful consideration prior to initiation of a complete treatment course. Most children have smaller mycobacterial loads than adults with good treatment outcomes provided treatment is started promptly. The risk of developing drug resistance during drug treatment is less.

5.1.3 Isolation requirements

- It is recommended to isolate all hospitalised children with TB and their caregivers and visitors initially, as although cases are rarely infectious an undiagnosed relative may be the source case.\(^{3,8,14}\)
The vast majority of children < 10 years old with TB are not infectious. The reasons for this are that most children have no significant cough, lack tussive force necessary to spread disease; rarely produce sputum, low concentration of organisms in endo-bronchial secretions. Any child who develops adult-type TB including upper lobe infiltrates or cavities have a higher load of organisms and can be infectious as well as acquire resistance to treatment.

Children that require isolation include children with: cavitatory TB, positive sputum AFB smears, laryngeal involvement, extensive pulmonary infection, congenital TB undergoing procedures that involve the airway.

5.2 Basic principles of treating tuberculosis in children

Children usually have paucibacillary disease with cavitatory disease being uncommon in those <10 years, but children develop extrapulmonary disease more often than adults including miliary and meningeal disease with infants < 3 years particularly at risk. For paucibacillary childhood TB, a three drug intensive phase is sufficient, if resistance is not suspected. If no isolate is available from source case or for complicated disease, including miliary and meningeal disease four drugs should be started.

Basic principles of drug treatment in children are same as for adults. However:

- due to different patient pharmacokinetics, children’s dosage are based on mg/kg
- medication dose needs to be adjusted for weight increases with growth to prevent under dosing
- in younger children it is better to dose at the higher end of recommended ranges
- children have lower risk of adverse effects
- limited paediatric drug formulations can result in difficulties with administration
- children are dependent on caregivers for adherence.

5.2.1 Management of tuberculosis in children

Early discussion with a paediatric TB expert should be undertaken in cases:

- of disseminated TB
- poor or slow resolution of TB despite adequate treatment
- presence of comorbidities, especially HIV co-infection
- cases of suspected or proven drug resistance
- neonatal TB.

Optimal treatment regimens and dosages are not known for children, but most children using current regimens have good outcomes. Treatment regimens are available from a number of different international organisations (see chapter treatment). Many studies have confirmed that the regimen of 6/12 of isoniazid rifampicin, with pyrazinamide in the first two months cures over 99% cases of drug susceptible pulmonary TB.
In cases where pyrazinamide is not tolerated, isoniazid and rifampicin for 9/12 is adequate, but this should be reserved for only mild cases.

- As most cases of TB in children do not have an isolate available, the treatment regimen is based on sensitivities from source case. Usually three drugs alone are started, but if a fourth drug is required ethambutol is most common, but penetrates poorly into CSF except in the presence of inflamed meninges.\(^{18}\)

- A fourth drug would be recommended in all cases of disseminated and meningeal TB, severe disease, co-infection with HIV, and smear positive pulmonary TB if no source case identified. A fourth drug should also be considered if there is a high risk of drug resistance based on epidemiologic characteristics of the child or source case.\(^{2}\)

- In cases of meningitis an alternative is prothionamide which has good penetration into the CNS, both normal and inflamed meninges, and is generally well tolerated. Rifampicin also penetrates poorly into CSF and longer continuation phase (10 months, ie, 12 months total) is recommended for miliary and meningeal TB by some experts.\(^{7,18}\)

- Intermittent treatment regimens have been used in children but these studies have enrolled children with less severe disease.\(^{19}\) In both intensive and continuation phase treatment can be given daily or intermittently three times weekly. Although twice weekly regimens have been used in children they are not recommended by the WHO and are not used in New Zealand.\(^{1}\)

- Children with severe forms of TB should be hospitalised, including cases of miliary and meningeal TB, often for most of the intensive phase, as well as children with airway obstruction, some bone and joint disease and severe adverse reactions. Occasionally hospitalization will be required for difficulties with medications, eg, palatability.

- In most case of extrapulmonary disease excluding lymphadenopathy, 9–12 months treatment will be required.

- For treatment of HIV infected children with TB – see HIV chapter.

- Adherence issues are the same as for adults – see chapter on DOT.
Table 5.1: Dosage recommendations for anti-tuberculosis agents for children

<table>
<thead>
<tr>
<th>Medication</th>
<th>Daily dose</th>
<th>Thrice-weekly dose</th>
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<tbody>
<tr>
<td></td>
<td>mg/kg (range)</td>
<td>mg/kg (range)</td>
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<tr>
<td><strong>First-line agents</strong></td>
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<tr>
<td>Isoniazid</td>
<td>5* (5–15)</td>
<td>10# (8–12)</td>
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<tr>
<td>Maximum dose/day</td>
<td>300 mg</td>
<td>900 mg</td>
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<tr>
<td>Rifampicin</td>
<td>10 (8–12)</td>
<td>10# (8–12)</td>
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<tr>
<td>Maximum dose/day</td>
<td>600 mg</td>
<td>600 mg</td>
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<tr>
<td>Pyrazinamide</td>
<td>25</td>
<td>35</td>
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<tr>
<td>Maximum dose/day</td>
<td>2 g</td>
<td>3 g</td>
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<tr>
<td>Maximum dose/day</td>
<td>2.5 g</td>
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<tr>
<td><strong>Second-line agents</strong></td>
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<tr>
<td>Prothionamide and ethionamide</td>
<td>15–20</td>
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<tr>
<td>Maximum dose</td>
<td>1 g</td>
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<tr>
<td>Rifabutin</td>
<td>10–20</td>
<td>10–20</td>
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<td>Maximum dose/day</td>
<td>300 mg</td>
<td>300 mg</td>
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<tr>
<td>Moxifloxacin</td>
<td>7.5–10</td>
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<td>Maximum dose</td>
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<tr>
<td>Streptomycin</td>
<td>15 (12–18)</td>
<td>15 (12–18)</td>
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<td>Maximum dose, intramuscular, intravenous</td>
<td>1 g</td>
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<tr>
<td>Amikacin</td>
<td>15–22.5</td>
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<td>Maximum dose, intramuscular, intravenous</td>
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<td>Kanamycin</td>
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<tr>
<td>Amount/kg</td>
<td>15–30</td>
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<tr>
<td>Maximum dose, intramuscular, intravenous</td>
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<tr>
<td>Capreomycin</td>
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<tr>
<td>Maximum dose intramuscular</td>
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<tr>
<td>Cycloserine</td>
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<tr>
<td>Maximum dose</td>
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<tr>
<td>P-aminosalicylic acid (4 g sachets)</td>
<td>150 mg</td>
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<tr>
<td>Maximum dose</td>
<td>12 g</td>
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* Younger children less than five years INH dose of 10 mg/kg.
# Dose range of isoniazid 20–30 mg/kg (maximum 900 mg) and rifampicin 10–20 mg/kg (maximum 600 mg) for 3x weekly regimen is recommended in some guidelines.14

5.2.2 Formulations/administration

- For ease of administration tablets may be crushed and mixed with water immediately prior to administration. Choice of agent used as the mixing agent needs to be approved as some agents can reduce bioavailability of drugs.1
- The addition of vitamin C containing products to antituberculous drug suspensions should be avoided. When vitamin C is added to a suspension, it may reduce the concentration of the anti-TB drug.21 Reduced serum levels have also been found when isoniazid is given with apple sauce.
- Non-proprietary suspensions are prepared extemporaneously by pharmacists for multi-dose use. They are based on non-validated formulae, often use non-funded excipients and have a limited period before expiry. These suspensions should rarely be needed.
- Rifampicin, isoniazid and pyrazinamide should never be put in a suspension together, because the rifampicin becomes unstable.
- Families may have problems administering medications to young children, due to swallowing difficulty, number of medications, taste and limited formulations. People with experience helping families in this circumstance should work with families early to resolve any problems. If problems are not resolved early, significant delays and interruptions in therapy can result, which may negatively affect the adequacy of treatment.

5.2.3 **Pyridoxine**
Isoniazid peripheral neuritis is rare in children, so most do not require pyridoxine supplementation. Pyridoxine (5–10 mg/day) should be given to:
- breastfeeding infants
- adolescents (because of their rapid growth)
- malnourished children or children with inadequate diets (eg, meat- or milk-deficient diets)
- breastfeeding infants whose mothers are taking isoniazid
- HIV-infected children
- children who develop paraesthesiae.

5.2.4 **Corticosteroids**
Corticosteroids may be used for some cases of TB, although limited evidence is available.¹⁴ These include cases of TB meningitis, airway obstruction secondary to enlarged lymph nodes, severe miliary disease and pericardial TB.²²
- Prednisone dose of 2 mg/kg per day (maximum 60 mg/day) for four weeks and then reduce over 1–2 weeks.
- Corticosteroids should only be given with appropriate antituberculosis therapy.¹⁸

5.2.5 **Monitoring**
Clinical and radiological follow-up are used to evaluate a child’s response to treatment.
- Clinical follow-up should include assessment of growth, symptomatology, adherence and adverse events, as well as dose adjustments for weight gains. As a guide this should occur two weeks after initiation of treatment, at the end of the eight-week intensive phase and two-monthly after that. This will vary according to a number of factors including age of child, severity of disease and tolerance of medication.
- Chest X-ray – radiological changes usually require longer than six months for complete resolution, but improvement would be expected in the healthy host after three months. A normal CXR is not necessary for discontinuing anti-TB medication.
- Long-term complications such as development of bronchiectasis are uncommon but awareness of this risk is needed.
- Adverse events are less common than in adults.
Most common is development of hepatotoxicity which can be caused by isoniazid, rifampicin and pyrazinamide. If liver function tests are normal at initiation, serum liver enzymes do not need to be monitored routinely in most children as an asymptomatic elevation (<5 x normal) is not an indication to stop treatment.\textsuperscript{18,23} If symptoms suggestive of liver toxicity occur, all potentially hepatotoxic medication should be stopped. Liver function tests should be done and if significantly elevated, other tests to evaluate causes of hepatitis should be undertaken (see chapter treatment).

There has been longstanding concern over the effect of acetylator status on isoniazid metabolism. Recent work has found that younger children eliminate isoniazid faster than older children.\textsuperscript{24} It is now recommended that young children \(<\) 5 years should receive an isoniazid dose of at least 10mg/kg to ensure that faster acetylators of INH are exposed to adequate serum concentrations of isoniazid.

Recent reviews suggest ethambutol is safe at recommended doses. The WHO guidelines recommend higher doses of ethambutol in children at 20 mg/kg/day (15–25 mg/kg/day) because pharmacokinetics are different, with peak serum concentrations lower in children than in adults receiving the same dose.\textsuperscript{18} Renal function should be monitored if child has, or is at risk of renal impairment, as ethambutol is renally excreted.\textsuperscript{1}

Prothionamide causes gastrointestinal discomfort and vomiting in 50%. This can be modified by starting with a twice daily dose.

5.3 Management of neonates

Congenital TB is rare.\textsuperscript{25,26} Congenital TB is defined by tuberculous lesion in the infant and one or more of following revised criteria of Cantwell and colleagues:
- tuberculous lesions evident in first week of life
- primary hepatic complex or caseating hepatic granulomas
- evidence of tuberculous infection of the maternal genital tract
- exclusion of the possibility of postnatal transmission of disease.

Primary TB rather than reactivation of TB in mother is more likely to lead to congenital TB. A neonate may acquire TB in-utero through direct spread through the umbilical cord, haematogenous spread or aspiration of infected amniotic fluid or vaginal secretions.

Transmission is most likely to occur in women with miliary TB, untreated smear positive disease or diagnosis in late pregnancy or post delivery.\textsuperscript{25} Greater than four months of treatment of the mother will protect foetus.

Breastfeeding does not transmit TB.

Symptoms of TB in the neonate are non-specific; lethargy, poor feeding, low birth weight, unresolving or recurrent pneumonia and may mimic other congenital viral infections or bacterial sepsis. The commonest reported symptoms are hepatosplenomegaly and respiratory distress, less commonly fever and lymphadenopathy. The diagnosis can be difficult but should be considered in the child not responding to broad-spectrum antibiotics, negative tests for other congenital infections and in whom TB is suspected in the mother. Overt expression of disease often does not occur until the second to third week of life.
• A high index of suspicion should be kept when evaluating an unwell infant with symptoms not able to be explained by other causes and born to a mother at high risk for TB.

• If the diagnosis is suspected a Mantoux test, chest X-ray, lumbar puncture and appropriate cultures should be performed. The tuberculin skin test is unhelpful if negative as it can take up to three months to become positive. Most infants will have an abnormal chest X-ray, although it can be normal immediately after birth. Diagnosis is usually made on clinical suspicion and microscopy and culture from gastric aspirates, biopsy tissue (lymph nodes, bone marrow, liver) or placental tissue. CSF is also recommended.

• Newborns with pulmonary TB requiring ventilation can transmit TB to contacts.

• Perinatal TB from airborne spread from an adult case including health care worker has been well documented over the years.\textsuperscript{27}

5.3.1 Management of neonate exposed to maternal TB

Management will depend on stage of maternal disease.\textsuperscript{25,28} Case management can be complex and should be discussed with an expert in paediatric TB.

Mother with active disease

If the newborn presents with symptoms the infant should be assessed for congenital TB. For the asymptomatic infant (when congenital TB has been excluded):

• isoniazid (10 mg/kg) for three months (if maternal isolate is known to be sensitive)

• at 3/12 Mantoux – if negative Mantoux with normal chest X-ray and asymptomatic infant, stop isoniazid and consider BCG vaccination

• if Mantoux positive assess for TB disease, if negative treat for six months isoniazid

• breastfeeding is recommended irrespective of mothers TB status. First-line antituberculous drugs cross into breast milk in variable amounts, although at an inadequate level to treat the infant and is considered safe

• the decision to separate mother and infant is difficult. The American Academy of Paediatrics recommends separation until the mother has been fully evaluated or until both mother and child are on treatment. However some experts permit contact if the mother wears a mask and follows infection control measures.\textsuperscript{14,27} Once the infant is receiving isoniazid separation is not necessary.

• separation is suggested if the mother has MDRTB, or has poor adherence.\textsuperscript{14,25}

Mother with latent TB infection, but no disease

The neonate of a mother with latent TB infection but no disease is not at risk and requires no special evaluation or treatment.\textsuperscript{14}

Household contacts should be evaluated for an infectious source case.
References

Chapter 6: HIV-associated Tuberculosis

**Summary**

**Epidemiology**

Human immunodeficiency virus (HIV) is the single greatest risk factor for the development of tuberculosis (TB) disease and TB is the most common opportunistic infection of people infected with HIV. People with HIV infection are at high risk of TB if they are latently infected with *M. tuberculosis* or are contacts of infectious cases.

In New Zealand, from 2004 until 2009, 2% of the patients notified with TB disease had HIV infection.

**HIV-associated tuberculosis: immunopathology**

With progression of HIV infection, CD4+ lymphocytes are depleted resulting in a weakened response to *M. tuberculosis*. The natural history of HIV infection is also altered by TB. People with active TB experience increased viral replication and an accelerated course of HIV infection.

**HIV-associated tuberculosis: clinical aspects**

It is recommended that all patients diagnosed or suspected to have TB should be offered HIV testing.

There should be a high index of suspicion for TB in patients with HIV infection. TB may present in HIV infection at any CD4+ lymphocyte count. The clinical presentation of TB in HIV infection is influenced by the degree of immune-suppression. With increasing immunosuppression, particularly when the CD4+ count falls below 200 cells/mm³, the clinical presentation becomes less typical. Pulmonary manifestations are often atypical and extra-pulmonary TB becomes more common, either alone or concurrently with pulmonary disease.

Efforts should always be made to prove the diagnosis unequivocally with culture and drug susceptibility.

Infectious patients should be appropriately isolated. The same guidelines apply as for HIV-negative infectious cases (see Chapter 12). Infection control processes must be rigorously applied in settings where HIV-infected people may come into contact with infectious TB cases.

**Treatment of tuberculosis in HIV-infected patients**

Of paramount importance in the co-infected patient is appropriate and adequate treatment of TB. 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 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 extra-pulmonary TB unless there is central nervous system disease or bone and joint TB, which may require 12 months of treatment.

Intermittent dosing regimens of TB drugs less than three times weekly may result in poor outcomes in some HIV-infected groups. All patients with HIV-associated TB should
receive daily therapy for the first eight weeks of treatment. For the continuation phase, the optimal dosing frequency is also daily. If daily continuation phase treatment is not possible, three times weekly dosing during the continuation phase may be used in selected cases.

Adverse events are common in TB patients with HIV infection. Directly observed therapy (DOT) is recommended for HIV-infected patients with TB disease. It is paramount that patients do not miss doses of TB treatment.

The optimal time to start Anti-retroviral Therapy (ART) in relation to the start of TB treatment is not yet clear. One randomized controlled trial provides some evidence for early initiation of ART in terms of reduced all-cause mortality, improved TB outcomes and reduced incidence of immune reconstitution inflammatory syndrome (IRIS). In 2009, the recommendations of World Health Organisation and Centre for Disease Control are that TB treatment should be commenced first and ART subsequently commenced as soon as possible and within the first eight weeks of starting TB treatment.

The treatment of HIV-associated TB is complex and requires expertise in the management of both HIV disease and TB. There are significant drug–drug interactions between the rifamycin drugs (rifampicin and rifabutin) and both the protease inhibitors (PIs) and the non-nucleoside reverse transcriptase inhibitors (NNRTIs).

Drug-resistant tuberculosis in HIV infection

In patients with advanced HIV and CD4+ counts below 100, there is an increased risk of acquired rifamycin resistance if these drugs are given once or twice weekly and these regimens should not be used. Multi-drug–resistant TB is a serious threat to patients with HIV infection and outcomes may be improved by ART and immune recovery.

Prevention of tuberculosis in HIV-infected patients

HIV is the single greatest risk factor for the reactivation of TB and therefore screening for latent TB infection (LTBI) should form part of the regular evaluation of all HIV-infected individuals. A Mantoux test or IGRA should be performed in all HIV-positive people.

Preventive treatment for LTBI should be given to HIV-infected patients with a Mantoux ≥ 5 mm or positive IGRA, previously documented positive Mantoux and no prior LTBI treatment, minor or slight chest X-ray (CXR) abnormalities consistent with old TB (but consider the need for full preventive treatment) or a documented recent exposure to a smear-positive case.

The efficacy of treatment of LTBI in HIV-infected people has been proven in placebo-controlled trials. The preferred regimen for LTBI in a patient with HIV infection is nine months of daily isoniazid (9H).

Introduction

The management of human immunodeficiency virus (HIV) and tuberculosis (TB) co-infection is complex, so this chapter provides a broad overview of the field. The information elsewhere in these guidelines is largely applicable to the HIV-infected patient, but certain issues are unique to this population and warrant special attention.

The chapter provides a brief epidemiological overview of the global and local situation with respect to co-infection, highlighting those areas where clinical features may differ from those found in the HIV-negative patient. A review of the treatment of TB in HIV
infection is presented, with particular emphasis on the issues and decisions required with the concurrent use of anti-retroviral therapy and anti-TB therapy.

Co-infected patients should be managed by clinicians experienced in the management of both HIV and TB or in close liaison with an infectious diseases physician.

Several review articles and guidelines have been published on this topic, and the reader’s attention is drawn to these for additional detail.[1–10]

6.1 Epidemiology

6.1.1 The world
HIV is the single greatest risk factor for the development of TB disease. The HIV epidemic has compounded the worldwide problem of TB, which is the most common opportunistic infection of people infected with HIV.

Despite significant public health advances in some of the countries hardest-hit by the HIV epidemic, new infections continue at an alarming rate. The United Nations Joint Programme on HIV/AIDS and the World Health Organization (WHO) estimated there were 2.7 million new infections in 2008, with 33 million people living with HIV worldwide.11 It is estimated that one-third of these are also infected with *Mycobacterium tuberculosis*.3

6.1.2 New Zealand
New Zealand has relatively low rates of HIV infection compared with most of the world, but infected people here remain at high risk of TB if they are latently infected with *M. tuberculosis* or are contacts of infectious cases. From the beginning of the HIV epidemic until the end of December 2009, 2,248 people in New Zealand were known to have been infected with the HIV virus.12

In New Zealand, from 2004 until 2009, 2% of the patients notified with TB disease had HIV infection (Table 6.1).

Table 6.1: Number of patients with HIV-associated TB in New Zealand, 2004–2008

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of TB disease notifications*</th>
<th>Number (%) of patients with HIV-associated TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>376</td>
<td>10 (2.7)</td>
</tr>
<tr>
<td>2005</td>
<td>344</td>
<td>8 (2.3)</td>
</tr>
<tr>
<td>2006</td>
<td>355</td>
<td>10 (2.8)</td>
</tr>
<tr>
<td>2007</td>
<td>288</td>
<td>4 (1.4)</td>
</tr>
<tr>
<td>2008</td>
<td>297</td>
<td>8 (2.7)</td>
</tr>
</tbody>
</table>

* TB disease notifications in EpiSurv at time of data downloaded to send to AIDS Epidemiology Group to identify HIV co-infected cases.

Source: ESR

The majority of patients with HIV-associated TB were born outside New Zealand, mostly in parts of the world with high rates of TB.
6.1.3 Surveillance of tuberculosis–HIV co-infection

HIV-infection rates in people with tuberculosis

Surveillance of HIV-associated TB is important because of the significant interactions in pathology and treatment between the two infections. From 1995 to 2004, 45 out of 3772 (1.2%) notified TB cases in New Zealand were diagnosed with HIV infection, and from 2004 until 2009, 40 out of 1660 (2.4%) of notified TB cases had HIV infection. These data were obtained by comparing anonymised HIV surveillance data and anonymised TB surveillance data. The TB case report form does not collect information on HIV status and so this rate of co-infection may underestimate the proportion of people with TB disease who have HIV infection. This rate also does not capture the proportion of people with latent TB and HIV infection.

Tuberculosis infection rates in HIV-positive people

The proportion of HIV-infected people in New Zealand who have also been infected with *M. tuberculosis* is not known. Although clinical awareness of the possibility of co-infection and a low threshold for testing for both infections have been encouraged, the extent of dual testing is not known.

6.2 HIV-associated tuberculosis: immunopathology

One of the components of host immunity critical to defence from TB is the CD4+ lymphocyte. Antigen-specific type 1 CD4+ T helper lymphocytes provide stimulatory signals (e.g., the cytokine gamma-interferon) that activate TB-infected macrophages to limit intra-cellular replication of *M. tuberculosis*. HIV also targets these cells, which become infected and are ultimately destroyed by the virus.

With progression of HIV infection CD4+ lymphocytes are depleted, which results in a weakened response to *M. tuberculosis*. The range of clinical manifestations of TB in HIV-infected people reflects the variability of the impaired host response to the infecting organism. The CD4+ lymphocyte count is a useful marker of the degree of immune-deficiency in HIV-positive patients, and clinical features of TB in HIV infection correlate to a degree with CD4+ count.

Conversely, the natural history of HIV infection is also altered by TB. In studies of HIV-associated TB in environments without effective anti-viral therapy, higher rates of death were seen in those with co-infection. This occurred during treatment for TB, but also after successful treatment. Death was seldom attributable to TB but rather to other complications of HIV infection, suggesting an accelerated course of HIV infection in those with active TB.
The concentration of HIV in the blood (the HIV viral load) is elevated in TB disease, and it has been demonstrated in vitro that HIV replication is increased in alveolar macrophages and peripheral lymphocytes on exposure to *M. tuberculosis* antigens.\textsuperscript{19–21} The inflammatory cytokines tumour necrosis factor alpha (TNF-\(\alpha\)) and interleukin-1 (IL-1) are implicated as mediators of this enhanced viral replication, and both are released during the host response to mycobacterial infection.\textsuperscript{20,21} It is suggested that these pro-inflammatory cytokines lead to an increase in viral replication with a subsequent decline in the CD4+ lymphocyte count.

### 6.3 HIV-associated tuberculosis: clinical aspects

#### 6.3.1 HIV testing in tuberculosis

TB is an important indicator illness for HIV infection. An *HIV test should be offered to every patient diagnosed or suspected* to have TB because classical risk factors may not be apparent.\textsuperscript{3}

#### 6.3.2 Susceptibility

It is clear from reports of nosocomial outbreaks of TB among HIV-positive patients that HIV infection leads to much greater susceptibility to TB infection progressing to disease.\textsuperscript{22–25} HIV can radically alter the natural history of primary TB infection with a high proportion of infections resulting in disease and potentially a very short time between exposure and the development of symptoms.\textsuperscript{23}

**Practice point**

Infection control processes must be rigorously applied in settings where HIV-infected people may come into contact with people with infectious TB.

#### 6.3.3 Clinical presentation

*There should be a high index of suspicion for TB in the context of HIV infection.* TB may present in HIV infection at any CD4+ lymphocyte count, including those within the normal range. The clinical presentation of TB in HIV is influenced by the degree of immune-suppression (see Figure 6.1).\textsuperscript{1,5,15}

With normal or moderately reduced CD4+ counts (ie, more than 200 cells/mm\(^3\)) the presentation is more ‘typical’, with pulmonary disease likely and radiological findings including an upper lobe distribution and cavity formation. With increasing immune-suppression, especially when the CD4+ lymphocyte count falls below 200 cells/mm\(^3\), the clinical presentation becomes less typical. Pulmonary manifestations alter and extra-pulmonary TB becomes more common, either alone or concurrently with pulmonary disease.\textsuperscript{1,5,15,26,27} A chest X-ray (CXR) may show lower zone infiltrates and unilateral or diffuse bilateral shadowing, and may even be normal despite culture-positive or even smear-positive sputum.\textsuperscript{27}
Mediastinal and hilar lymphadenopathy and disseminated disease are seen with increasing frequency at low CD4+ lymphocyte counts, a situation similar to primary disease in the HIV-negative population. Pleural effusions occur at a range of CD4+ counts and seem to be more common than in HIV-negative cases.

A variety of CXR findings have been found in TB with advanced HIV infection, including:

- hilar and mediastinal adenopathy with localised parenchymal shadowing
- diffuse opacities, usually bilateral
- localised coarse nodular opacities
- miliary pattern
- pleural effusion
- a normal CXR.

In advanced HIV infection cavities are not usually seen on chest X-ray. Rapid progression may occur and radiological deterioration can occur on treatment.

These types of presentation in the severely immune-compromised are explained by both the high rates of progression to disease following primary infection and reactivation of latent TB infection (LTBI) in the context of impaired immunity, leading to a weak delayed-type hypersensitivity response.

Tuberculin reactivity is lost as immunodeficiency progresses, also due to the loss of an effective delayed-type hypersensitivity response to mycobacterial antigens. A negative Mantoux should not discourage active investigation for possible TB, especially when the CD4+ lymphocyte count is low (see also section 6.5.2).
TB should be considered in any HIV-infected person with respiratory symptoms. Sputum smears should be examined for acid-fast bacilli and sent for mycobacterial culture.

In a patient with unexplained fever, occult sites of extra-pulmonary TB infection should be sought, particularly when the CD4+ count is low. Abdominal TB can be difficult to diagnose and, at low CD4+ counts, tends to present with visceral involvement and adenopathy rather than the peritoneal TB typically seen in HIV-negative patients.\textsuperscript{28}

As with all TB, it is important to confirm the diagnosis with culture of the organism so that the identity can be confirmed and drug susceptibility testing undertaken.

### 6.3.4 Infectivity

Infectious patients should be appropriately isolated, and the same guidelines apply as for HIV-negative infectious cases (see Chapter 12).

A meta-analysis concluded there is no evidence that HIV-positive cases are intrinsically more infectious to their contacts than HIV-negative cases.\textsuperscript{29}
6.4 Treatment of tuberculosis in HIV-infected patients

6.4.1 Drug treatment: general principles

Drug regimens

The drug treatment of TB in the context of HIV infection follows the same approach as in HIV-negative individuals. However, the approach may need to be modified, depending on concurrent anti-retroviral medication (see below for information on TB treatment while on anti-retroviral therapy (ART)).

Duration of therapy

The American Thoracic Society and Centers for Disease Control and Prevention’s most recent guidelines on the treatment of TB recommend that six-month regimens are appropriate for fully sensitive pulmonary disease in patients co-infected with HIV and TB.30 However, controversy remains about short-course rifampicin-containing regimens in HIV-infected people due to concerns about relapse.31 A recent meta-analysis of randomised controlled trials and cohort studies to evaluate the impact of duration of rifamycin showed a trend toward higher relapse rates if rifamycins were used for only six months compared with ≥ 8 months.32

Before completion of therapy, careful evaluation is required to ensure TB has been completely resolved. If there has been inadequate response, treatment should be continued. Six-month regimens are considered appropriate only for patients with fully sensitive TB with minimal disease. However, treatment should be extended to a minimum of nine months for patients with extensive disease, including cavitary disease or where the response to treatment has been slow. In most cases, a six- to nine-month regimen is recommended for extra-pulmonary TB unless there is CNS disease or bone and joint TB where 12 months of treatment may be required.

Daily compared with intermittent dosing; self-administration compared with directly observed therapy

Intermittent dosing regimens of TB drugs less than three times weekly may result in poor outcomes in some HIV-infected groups. Acquired resistance has been observed in patients on both twice-weekly rifampicin and rifabutin-based regimens.33–36

All patients with co-infection should receive daily therapy for the first eight weeks of treatment. For the continuation phase, the optimal dosing frequency is also daily. If daily continuation phase treatment is not possible, three times weekly dosing during the continuation phase may be used in selected cases.32
Directly observed therapy (DOT) is strongly recommended for HIV-infected patients with TB disease. Adverse events are common in HIV infected patients treated for TB disease. Anti-retroviral therapy regimens may be complex and DOT reduces the number of medications the patient must assume direct responsibility for administering. Study of ART regimens has confirmed the relationship between pill burden and missed doses, and avoiding missed doses of anti-TB drugs is paramount. DOT is appropriate for a large proportion of patients and should be used in the majority of cases, including all children. However, if self-administration is chosen, patients should be monitored closely with regular community supervision.

6.4.2 Anti-retroviral therapy and tuberculosis treatment

Anti-retroviral therapy (ART), which uses highly active combinations of drugs, consists of combination therapy with at least three anti-retroviral agents, usually with a ‘backbone’ of two nucleoside analogue reverse transcriptase inhibitor (NRTI) drugs combined with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI).

Efficacy of combination anti-retroviral therapy

The development of ART has dramatically altered the natural history of HIV infection, with a reduction in the frequency of opportunistic infections and a decline in the rate of death from AIDS. ART aims to suppress HIV replication with a subsequent recovery in CD4+ lymphocyte count. This is achieved, at least initially, in the majority of recipients of this treatment.

The natural history of TB–HIV co-infection in the ART era has not been studied in the same detail as in untreated HIV infection, but evidence suggests that effective viral suppression and immune reconstitution will impact favourably and reduce the incidence of reactivation disease and new infection.

Issues with anti-retroviral therapy and tuberculosis treatment

The treatment of HIV-related TB is complex and requires expertise in the management of both HIV disease and TB. The key issue with respect to treatment of HIV and TB is that there are significant drug–drug interactions between the rifamycin drugs (rifampicin and rifabutin) and the PI and NNRTI anti-retrovirals. Both the PIs and NNRTIs act as substrates for cytochrome P-450 (CYP450) isoenzymes, and, depending on the drug, may induce or inhibit CYP450. The rifamycins are inducers of CYP450 (rifampicin more so than rifabutin). The net result of co-administration is a reduction in the serum level of the anti-viral agent, the extent of reduction varying between agents. HIV resistance develops in an environment of sub-therapeutic anti-viral drug concentrations, and this situation must be avoided whenever possible.

Practice point

Allow two to three weeks after discontinuation of rifampicin before starting potentially interacting anti-virals, because of the risk of persisting enzyme induction.
ART regimens that include an NNRTI have fewer interactions with rifampicin-based TB treatment than regimens that include a PI. For patients on treatment for TB disease, starting ART with an efavirenz containing regimen is preferred due to fewer interactions and evidence to support the use of this drug with rifampicin based TB treatment. Some authors recommend increasing the dose of efavirenz to 800mg daily in patients over 60 kilograms but other experts suggest that no dose adjustment is necessary. Inferior virological outcomes have been observed when nevirapine based antiretroviral therapy is commenced while taking anti-tuberculosis treatment. It has been suggested that this relates to sub-therapeutic nevirapine levels in the initial two week lead in period as the cytochrome P450 enzyme system has already been induced by rifampicin. Despite these concerns one study has shown 80% virological suppression at 18 months in patients receiving TB treatment and subsequent nevirapine. If nevirapine is used with rifampicin the lead-in phase is not required and full-dose nevirapine may be used from the start.

Use of protease inhibitors with rifabutin results in reduced metabolism of rifabutin, resulting in significantly increased serum rifabutin levels with a potential increase in toxicity (eg, uveitis). Hence, the dose of rifabutin should be reduced, especially if the PI is boosted with ritonavir.

Rifampicin is not recommended for patients on PIs due to its induction of PI metabolism. The use of saquinavir–ritonavir or lopinavir–ritonavir with rifampicin has been associated with high incidence of hepatotoxicity in healthy volunteers, so these combinations should be avoided.

There are no significant drug–drug interactions between the NRTIs and the rifamycins. However, several clinical studies of triple-NRTI regimens have shown suboptimal anti-HIV activity, so this combination is generally not recommended.

Table 6.3 summarises current recommendations about the concurrent use of rifamycins and PI and NNRTI drugs. Rifabutin levels are increased by all PIs and dose reduction is required, as indicated, to avoid toxicity. Careful clinical monitoring of the patient is also mandatory. Careful follow-up is required with attention to both TB response and HIV suppression.

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.

Data on the drug-drug interactions with the new antiretroviral drugs are limited and further studies are awaited. Etravirine should not be used together with rifampicin because of rapid metabolism. Limited pharmacodynamic studies predict that the combination of rifampicin, and possibly rifabutin, will result in decreased levels of maraviroc and raltegravir. Recent guidelines, however, suggest raltegravir does not require dose adjustment when given with either rifampicin or rifabutin and that maraviroc should be increased to 600 mg twice daily when given with rifampicin but no dose adjustment is required when given with rifabutin. However, until further data are available these drugs should be avoided or used with extreme caution in combination with rifamycins.
Table 6.2: Recommendations for using non-nucleoside reverse transcriptase inhibitor (NNRTI) anti-retrovirals with rifampicin, and protease inhibitor (PI) and NNRTI anti-retrovirals with rifabutin

<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>NNRTI</strong></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>Protease inhibitor</strong></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).

Ensuring adequate tuberculosis treatment and adequate anti-viral treatment in co-infection

The optimal time to start ART in relation to the start of TB treatment is not yet clear but there is increasing evidence to support early treatment. One randomised controlled trial provides some evidence for early initiation of ART in terms of reduced all-cause mortality, improved TB outcomes and reduced incidence of immune reconstitution inflammatory syndrome (IRIS). In 2009, the recommendations of World Health Organization and Centre for Disease Control are that TB treatment should be commenced first and ART subsequently commenced as soon as possible and within the first eight weeks of starting TB treatment.
6.4.3 Paradoxical reactions during therapy

Paradoxical reactions are the worsening of signs or symptoms of TB or the development of new manifestations of TB in people on appropriate anti-TB chemotherapy.\[^{1,5,42,55}\] This phenomenon is observed in the HIV-negative population (about 2%), but it has been noted to be more common in HIV-infected TB patients. Estimates of frequency range from 7% to 36%, and the highest incidence has been seen in patients receiving anti-retroviral therapy.\[^{55}\]

Clinically, in patients with HIV infection, paradoxical reactions most commonly involve lymph nodes, with progressive lymphadenopathy. Fever and worsening or development of pulmonary infiltrates may be seen, and the reaction usually occurs within a month of starting anti-retroviral therapy.\[^{55,56}\]

In general, paradoxical reactions are self-limited and last 10–40 days. They are not an indication to stop either anti-TB or anti-retroviral therapy, but if severe may require investigation to exclude other causes of deterioration, and even symptomatic treatment with corticosteroids.\[^{42,55,56}\]

6.4.4 Tuberculosis-related immune reconstitution syndrome

Reconstitution syndromes are a group of disorders that can occur during ART treatment of HIV. In many respects the phenomenon is analogous to the process described above and is thought to reflect restoration of competent CD4+ and CD8+ responses directed against latent infection with a variety of pathogens. Reconstitution syndromes have been most commonly described secondary to *Mycobacterium avium intracellulare* complex and cytomegalovirus, but can also occur with TB.\[^{42}\] In patients with HIV, who are treated with ART within six weeks of starting anti-TB treatment 11–45% develop immune reconstitution inflammatory syndrome (IRIS). The risks of IRIS developing are low baseline CD4+ count, high baseline viral load, good CD4+ and HIV response to ART and extra-pulmonary disease.\[^{57,79}\]

TB-related IRIS may manifest as lymphadenitis or pneumonitis, typically with low bacillary numbers. Most patients can be managed conservatively however anti-inflammatory agents or corticosteroids may be required to control troublesome inflammatory symptoms.\[^{42}\]

6.4.5 Drug-resistant tuberculosis in HIV infected patients

Treatment of drug-resistant TB in HIV-infected patients applies the same principles as in non-HIV-infected people (see Chapter 6). Well-documented outbreaks of multi-drug-resistant disease among HIV-infected people have highlighted the difficulties of treating this group with drug-resistant isolates.\[^{24}\]

A higher-than-expected rate of rifampicin mono-resistance has been noted by some investigators in HIV-infected individuals. Different studies have noted both primary and acquired rifampicin resistance and risk factors for acquired resistance, included diarrhoea, advanced immune-suppression and non-compliance.\[^{58,59}\]
6.4.6 Cotrimoxazole preventive therapy

Cotrimoxazole preventive therapy (CPT) has been shown to improve survival in TB patients with HIV infection in several studies from sub-Saharan Africa. In that setting, the benefit of CPT has been ascribed to decreasing the incidence of malaria, Pneumocystis pneumonia and a variety of bacterial infections.\textsuperscript{60–64}

WHO guidelines recommend CPT for all people with both TB and HIV regardless of CD4 count.\textsuperscript{65} The epidemiology of opportunistic infection in New Zealand differs from that in developing countries and local experts do not recommend CPT in TB and HIV co-infected patients with CD4 counts greater than 200 cells/mm\textsuperscript{3}.

6.5 Prevention of tuberculosis in HIV-infected patients

6.5.1 Co-ordination of control measures

TB prevention should be a key component of the care of HIV-infected patients.\textsuperscript{2,42} Identification and treatment of LTBI and prevention of severe immunodeficiency by the appropriate use of ART are all strategies that might be expected to reduce the mortality and morbidity of HIV-associated TB.\textsuperscript{1}

6.5.2 Screening for latent tuberculosis infection in HIV-infected patients

HIV is the single greatest risk factor for the reactivation of TB, so screening for LTBI should be part of the evaluation of all patients with HIV-infection and a Mantoux test or interferon gamma release assay (IGRA) obtained in all HIV-positive people.

Induration of 5 mm or greater in response to a standard 5 TU purified protein derivative test, (or positive IGRA – see Chapter 2), irrespective of prior Bacillus Calmette-Guérin (BCG) vaccination, should be regarded as positive in this population. In view of the high risk of developing disease, treatment of LTBI should be offered.\textsuperscript{1,2,5,42,66} A previously documented positive Mantoux with no record of preventive therapy is also an indication for treatment.

With increasing immune-deficiency the likelihood of a negative Mantoux increases due to impaired delayed-type hypersensitivity response, but anergy testing is no longer recommended as an adjunct to Mantoux testing.\textsuperscript{2} There is no evidence for benefit of treatment for LTBI in anergic HIV-positive people solely on the basis that they are at high risk for TB infection.\textsuperscript{2,67}

<table>
<thead>
<tr>
<th>Practice points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preventive treatment for LTBI should be given to HIV-positive patients with:</td>
</tr>
<tr>
<td>• Mantoux $\geq$ 5 mm or positive IGRA</td>
</tr>
<tr>
<td>• previously documented positive Mantoux and no prior LTBI treatment</td>
</tr>
<tr>
<td>• minor or slight CXR abnormalities consistent with old TB (but consider full preventive treatment)</td>
</tr>
<tr>
<td>• documented recent exposure to a smear-positive case.</td>
</tr>
</tbody>
</table>
6.5.3 Investigation of inactive pulmonary tuberculosis

A CXR should be completed for all patients with:

- with respiratory symptoms
- with a positive Mantoux or IGRA
- with a history of pulmonary disease or tuberculosis
- at risk of exposure to tuberculosis.

This is especially important in people from countries with a high incidence of TB. A CXR may show changes consistent with prior, inactive TB (see Chapter 2). These people should be investigated to exclude active disease, including induced sputum or bronchoscopy if they have little or no spontaneous sputum. If microbiological tests show no evidence of active disease, they should be considered for preventive treatment of inactive TB disease (see Chapter 8).

6.5.4 Treatment of latent tuberculosis infection in HIV infection

The efficacy of treatment of LTBI in HIV-infected people has been shown in placebo-controlled trials.\(^67\text{–}^69\) A systematic review has confirmed the benefits of treating LTBI in the context of HIV infection.\(^70\) A recent Cochrane review showed an odds ratio for active TB of 0.38 in people with a positive Mantoux, based on 12 trials and 8578 patients.\(^71\) Regimens include 6H, 12H, 3RH and 3RHZ.\(^*\)

The current preferred regimen for the treatment of LTBI with HIV infection is 9H, but the following should be noted.

- The 9H regimen has no relevant interactions and can be introduced after ART is established.
- To overcome adherence issues shorter courses of treatment have been used. 2RZ was recommended as an alternative in 2000 based on data from patients with HIV infection. Despite reports that the combination of rifampicin and pyrazinamide appeared to be safe in HIV-infected patients in contrast to those who were HIV-negative, the American Thoracic Society and Centers for Disease Control and Prevention have revised their recommendations and recommend that this regimen should generally no longer be offered to patients.\(^72\) Cases of hepatotoxicity in HIV-infected patients have been subsequently reported.\(^73\)
- Rifampicin for four months is an acceptable alternative for treatment of LTBI in HIV-negative individuals. No studies demonstrate the efficacy or safety of this regimen in individuals with HIV infection, and the use of rifampicin is often limited by the co-administration of ART.
- The dose adjustments outlined in Table 6.3 when combining rifamycins with PI–NNRTI drugs also apply in this situation.

\* The number in front of the letters is the number of months of the treatment regimen, the letters stand for the drugs (R = rifampicin; H = isoniazid; Z = pyrazinamide), so 6H = six months of daily isoniazid; 12H = 12 months of daily isoniazid; 3RH = three months of daily rifampicin and isoniazid; and 3RHZ = three months of daily rifampicin, isoniazid and pyrazinamide. For more information about treatment regimens, see Chapter 3.
6.5.5 BCG vaccination in HIV-infected patients

The Global Advisory Committee on Vaccine Safety recommends that the BCG vaccination should not be used in any children who are known to have HIV infection due to studies showing an increased risk of their developing disseminated BCG disease.\textsuperscript{74, 75} BCG vaccination is also not recommended for adults with HIV infection.\textsuperscript{6}

References


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Chapter 5: Tuberculosis in Children


Chapter 7: Contact Investigation

Summary
This chapter provides guidance on conducting a contact investigation, including extent of follow-up, medical assessment of contacts exposed to tuberculosis (TB), and the importance of communication and liaison.

All contact tracing exercises should be supervised by the medical officer of health of the district in which the index case is notified. The chapter is intended to guide public health and other health staff who may be involved in contact tracing, including DHB occupational health and infection control staff. General practitioners and other clinical staff should not undertake contact tracing activity for TB, but may find the chapter useful if one of their patients has been identified as a TB contact.

The aim of contact investigation is to minimise morbidity resulting from transmission of tuberculosis (TB). The objectives of contact investigation are to:

- identify infected contacts who may require treatment of TB disease or latent TB infection (LTBI)
- identify uninfected contacts under the age of five years who may benefit from BCG vaccination
- identify the source case if not known
- identify environmental factors that may be contributing to the transmission of TB
- educate contacts about TB.

Contact tracing activity should be audited periodically to ensure quality and consistency with guidelines and to inform future work.

7.1 Contact investigation

7.1.1 Structuring a contact investigation programme
Refer to the Centers for Disease Control and Prevention 2005 Guidelines for the Investigation of Contacts of Persons with Infection Tuberculosis for more detailed information if required.1

Establishing priorities
The estimated probability of transmission (section 7.2.2) will influence the priority, rapidity and extent of contact investigation.

Classifying contacts
The first step is to allocate contacts into groups with higher and lower risk of infection.

Members of the immediate household and others who have shared accommodation with the index case are close contacts and are usually the top priority. However, contacts in work, leisure or other settings are not always ‘casual’ contacts.
Work sites should be visited: if there is overcrowding and poor ventilation these contacts may be considered ‘close’. Other settings such as church groups may also result in significant exposure. Contact tracing is often unnecessarily extensive in schools, but a large outbreak in a New Zealand school required the whole school to be screened.

See section 7.4 for more information on contact tracing in special circumstances.

Establishing limits for contact investigations
The concept of the ‘stone in the pond’ or ‘concentric circle’ is used to limit contact investigations (see Figure 7.1).

By initially evaluating the higher-risk contacts for evidence of TB infection and/or disease, the infectiousness of the index case can be inferred. To limit the extent of a contact investigation follow these guidelines.

1. Start with higher-risk contacts. If there is no evidence of recent transmission of infection in this group, do not extend the investigation.

2. If investigations suggest recent infection in the higher-risk group, extend to progressively lower-risk contacts until the levels of infection detected approximate the likely levels of infection in the local community.

3. Periodically review the findings to determine whether to stop or extend the investigation.

Figure 7.1: Concentric circle approach to contact tracing

Source: Reprinted from Etkind and Veen (2006), courtesy of Marcel Dekker Inc.
7.1.2 Determining the period of infectiousness

Contact investigation should extend back to the date of onset of cough in the index case or for three months if the date of onset of cough is unknown or there is no history of cough.\(^8\)\(^-\)\(^10\) The period of inquiry about contact exposure may also need to be extended if the source case is highly infectious (see section 7.2.2).

7.1.3 Identifying contacts to be assessed

Screening of contacts by the public health service should begin as soon as possible after notification. The recommended timeframes for starting contact assessment after notification are within:

- three working days for contacts of a smear-positive pulmonary case
- three working days for child contacts (under five years of age) of any pulmonary case
- seven working days for contacts of a smear-negative pulmonary case
- seven working days for all other cases.

As soon as the case is notified, a public health nurse should inform the household that a contact investigation will be taking place soon and reassure them that there is no immediate threat to their health. The household should be given an estimated date for the public health nurse’s first visit.

At the initial interview with the index case, explain why infected contacts need to be identified. Ask the index case for a list of all close and casual contacts during the period of infectiousness. This question should be asked again in subsequent weeks, as a patient may not remember every contact at the first interview or may initially be reluctant to divulge names and details.

7.2 Assessing risks

Consider risk factors for infection and for progression to disease separately.\(^11\)

7.2.1 Assessing contacts’ risks for progression to disease

The risk factors for each contact should be assessed. Factors increasing the risk of progression to disease include very young or old age, immuno-suppression and certain concurrent medical conditions. These conditions are listed in Chapters 2 and 8. They must be taken into account when planning a contact tracing exercise.

A contact who is at relatively low risk of infection but at high risk of disease (if infected) warrants careful follow-up. For example, a relatively low dose of inhaled organisms may pose a serious risk of disease to an HIV-positive person with a low CD4 count.
7.2.2 Assessing the risk of infection

Source case characteristics

Important source case characteristics indicating a higher risk of transmission include:
- sputum status – large numbers of acid-fast bacilli on direct smear
- extensive pulmonary disease
- cavitatory disease
- frequent cough
- laryngeal TB.\(^{12,13}\)

In the case of MDR-TB, contacts should be rapidly identified and evaluated. Close contacts of an infectious MDR-TB case, especially those who are aged under five years or are immunocompromised, are especially important to screen.

Duration and proximity of contact

Risk of infection is greatest for contacts who have been closest to the source case for the longest time.

Usually it takes many hours or days to transmit an infectious dose, but casual exposures may lead to transmission if the case is sufficiently infectious and the environmental air conditions are favourable or if the contact is at high risk of infection.\(^{14,15}\)

Environmental air factors

Droplet nuclei are transported from the source through the air; the greater the concentration in air, the greater the risk to contacts. The degree of ventilation or filtration in the environment is important (see Chapter 12).

7.3 Medical assessment and management of contacts

7.3.1 Overview of medical assessment

Contacts are investigated by:
- inquiring into symptoms of TB disease
- assessing the risk profile and BCG vaccination status
- Mantoux or interferon gamma release assay (IGRA) testing
- chest X-ray (CXR) examination, if appropriate.

The results of the investigation determine:
- whether the contact is likely to have been infected
- if the contact is infected, whether investigation for possible active or inactive TB is needed or treatment for latent TB infection is appropriate
- the type of TB education that should be offered.
An overview of contact investigation is shown in Figure 7.2.

**Figure 7.2:** Contact investigation flow chart

![Flowchart of contact investigation](image_url)

* Consider chest X-ray as a precaution if contact is aged over 60 years or if there is a possibility the Mantoux/IGRA may be falsely negative (see Chapter 8).

** If aged under five years and no previous BCG vaccination.

### 7.3.2 Mantoux or interferon gamma release assay testing

The Mantoux reaction takes up to eight weeks to convert after exposure.\(^{16}\) If the contact is identified more than eight weeks after their last exposure to the case, only one test is necessary. IGRA tests also require a 'window period' of at least eight weeks.\(^ {17}\)

If the contact is identified less than eight weeks after their last exposure to the case, then it may be possible to demonstrate conversion. Two Mantoux or IGRA tests are necessary: one as soon as the contact is identified and, if that is negative, a second test eight weeks after the last exposure to the infectious case. However, if the person develops symptoms of possible TB disease during this interval, second test should be administered without delay and investigations for TB disease started.
If the contact has a pre-existing documented Mantoux or IGRA result within the past 12 months, an initial baseline test is not necessary (see Chapter 8). If the person has previously had TB disease, or an earlier Mantoux of 15 mm or more, screening will need to be with IGRA and CXR.

7.3.3 Children aged under five years

In young children (aged under five), the risk of developing TB disease after infection is as high as 40%, especially in infancy, and disease can develop within weeks of infection.

Mantoux rather than IGRA is recommended for children aged under seven years.

Close contacts

Refer all children aged under five years who are close contacts of pulmonary cases to a specialist.

If Mantoux-positive, a child under five should receive treatment for presumed latent TB infection (LTBI).

If Mantoux-negative (< 5 mm), preventive treatment for possible LTBI should be given for eight weeks, when a second Mantoux test is done.

If the Mantoux converts, a CXR is done and treatment is continued until complete. If the Mantoux increases by less than 10 mm (so does not reach the criteria for conversion) the paediatrician should consider continuing treatment until complete, especially if the child is under two years of age.

If the Mantoux remains negative, treatment is stopped and BCG vaccination offered.

Casual contacts

Children with casual exposure to a pulmonary case should be referred to a paediatrician only if the tuberculin test is positive or becomes positive on a second test.

Mantoux or IGRA positive individual in a house containing an infant

If a Mantoux or IGRA positive individual is found in a house containing an infant (under one year old), enquire about TB symptoms in all adults and adolescents in the household in case there is a source case who may infect the infant.

7.3.4 Pregnancy

The Mantoux test is safe in pregnancy. Mantoux or IGRA positive contacts need investigation.

- if there are no symptoms of TB disease, CXR can usually be deferred until after the pregnancy, or at least until after the first trimester. CXR should be done with shielding
discuss with a TB specialist if there are concerns about symptoms or the risk factor profile in those with a Mantoux test > 15 mm or positive IGRA. The public health and clinical TB specialists should discuss with the lead maternity carer and woman to determine if the risk justifies investigation for TB disease or treatment of LTBI.

7.3.5 Initial chest X-rays
Contacts require a CXR if:
- they have symptoms of TB
- they have a positive Mantoux or IGRA or a conversion
- the contact is a child aged under five who is a contact of pulmonary case (such children should have a CXR before starting treatment irrespective of their Mantoux reaction)
- a false-negative Mantoux or IGRA is suspected, especially in patients with immunosuppression or age over 60 (see Chapter 8).

7.3.6 Treatment of latent tuberculosis infection (LTBI)
People who are Mantoux or IGRA positive must be considered for treatment of LTBI (see Chapter 8).

7.3.7 Monitoring of people not being treated
People at higher risk of developing TB disease, who have declined treatment or for whom the decision has been made not to treat for LTBI, should be monitored with CXRs at six, 12 and 24 months. This group includes:
- children aged under five who are close contacts of smear- or culture-positive cases
- HIV-positive contacts
- contacts of multi-drug-resistant (MDR-TB) source cases
- people with inactive fibrotic scars on CXR.

CXR monitoring of other people who are untreated for LTBI is not usually recommended.

7.3.8 Contacts of MDR-TB cases
The balance of benefits and harms associated with treatment of LTBI in people exposed to MDR-TB is unclear. Whether they are treated for LTBI or not, all contacts of MDR-TB cases should be educated about the need for lifelong awareness of the symptoms and signs of active TB disease, and should be monitored closely for at least two years.
7.3.9 Contacts with TB symptoms who refuse follow-up

If a person has symptoms and/or signs of active TB disease, especially if it is suspected that the person may have pulmonary TB, but is refusing to be investigated further, this should be brought to the attention of the medical officer of health. This situation may apply if contacts of active TB cases refuse to be investigated or followed up. The medical officer of health can write an order (a letter) under section 9 of the Tuberculosis Act 1948, requiring such a person suspected to have TB disease to undergo compulsory investigations to determine whether or not they have active TB disease.

7.3.10 BCG vaccination

A BCG vaccination should be offered to unvaccinated Mantoux-negative contacts (< 5 mm) aged under five years.

If two Mantoux tests are needed to test for conversion, a BCG vaccination should not be given until after the second test has been confirmed to be negative.

7.3.11 Non-tuberculous mycobacteria

Patients with non-tuberculous mycobacterial disease, such as Mycobacterium avium-intracellulare, are of negligible infectivity and do not represent a disease threat to healthy contacts. They do not need public health follow-up.

If the notifying physician suspects that the diagnosis might be non-tuberculous mycobacterial disease, the public health service should be told this at the time of notification so contact tracing can be restricted until the diagnosis is confirmed.

7.4 Contact investigations in special circumstances

7.4.1 Hospitals and other healthcare facilities

If a case of pulmonary disease has been in a hospital or other healthcare facility before diagnosis of TB and isolation, staff and patients may need assessment. Good communication between the public health service and the infection control and occupational health services in the facility is needed to clarify roles and responsibilities.

A risk assessment should be undertaken which takes into account:
- the degree of infectivity of the index case
- the length of time before the infectious person was isolated
- whether other patients are unusually susceptible to infection
- the proximity of contact.

Contact tracing and testing should only be carried out for patients for whom the risk is regarded as significant.21

In general, patients should be regarded as at risk of infection if they have spent more than eight hours in the same bay or room as an inpatient with smear-positive TB who had a cough.
NICE guidelines advise that such patients should be given ‘inform and advise’ information and their general practitioner informed. If patients were exposed to a patient with sputum smear-positive TB for long enough to be equivalent to a household contact, or an exposed patient is known to be particularly vulnerable to infection, they should be managed as close contacts.

Exposed patients may have been discharged by the time the contact investigation begins and public health should follow up these contacts.

Healthcare workers may be less likely to comply with screening recommendations than non-health professionals, so management support may be needed. If a healthcare worker, who has a documented Mantoux or IGRA test result within the past 12 months, is exposed to infectious TB, only one test is necessary to detect conversion. This test should be done eight weeks after the date of last exposure.

The medical officer of health must maintain an overview of the investigation, both of patients and staff. Data on the outcome of contact investigation in hospitals should be supplied to the medical officer of health, who should also provide feedback to hospital infection control and occupational health staff about the outcome of contact investigations, so that all parties have the same picture of the infectivity of the source case.

7.4.2 Schools

TB in schools requires particular care because of the potential for spread of infection and the likely level of anxiety among parents and staff. Following diagnosis of TB in a school pupil or staff member, and after discussion with the patient and family, the public health service should make contact with the school principal. Prevention and control activities will need to be clearly explained to staff, parents and if necessary the media.

If a pupil has sputum smear-positive TB, the rest of his or her class (if there is a single class group) or the rest of the year group who share classes should be assessed as part of contact tracing.

If a teacher has sputum smear positive TB, the pupils in his or her classes in the preceding three months should be screened.

Consider extending the contact tracing on the basis of:

- high infectivity of index case
- length of time of contact
- whether contacts are unusually susceptible to infection
- the proximity of the contact.

If an index case cannot be found among the case’s household or other close contacts, consider extending the screening to all staff to search for a source case.
7.4.3 Correctional facilities

See Chapter 9. When an infectious TB case is discovered in prison, the clinician should alert Department of Corrections and public health teams about the infectious potential and treatment plan.

The prison medical service and public health service need to liaise closely throughout the period of treatment and follow-up, and communications must be well documented.

Public health staff are responsible for conducting education and contact investigation among staff and prisoners. Prison contacts will often be released before their investigation and management is complete. Good liaison between prison services and public health will allow identification and education of families at risk for TB exposure.

7.4.4 Aircraft contact investigations

Transmission of TB on aircraft has been documented, but the risk is very low. Only contacts seated within two rows of an infectious case, on flights lasting longer than eight hours, need to be traced. Although a recent review suggests that even this level of screening is not required,\textsuperscript{24} this remains the current WHO recommendation.\textsuperscript{25}

Passenger information can be divulged to the medical officer of health under Principle 11 of the Privacy Act 1993. The aircraft seating diagram and passengers’ seat numbers can be obtained from the airline. Passenger arrival cards (often with limited address information) can be obtained from the New Zealand Customs Service. Details of exposed passengers who are no longer in New Zealand can be referred to an overseas public health service for follow-up (see section 7.5.8).

7.4.5 Outbreaks

An outbreak of TB is defined as two or more cases known to be linked by epidemiological investigation or DNA fingerprinting. (A cluster of cases all living in a single household is not considered an outbreak.) Such clusters need to be identified early. Outbreak control activities that must be considered include:

- workforce planning
- communications with the affected group
- inter-district communication
- communication with the Ministry of Health
- media management
- notification of the outbreak on EpiSurv.

7.5 Practical aspects of contact investigation

7.5.1 Documentation

Collect data about each contact as shown in the suggested form in Figure 7.3. Compile a summary of the full contact investigation, as shown in Figure 7.4, preferably electronically.
7.5.2 Education
Contacts should be provided with information about the:
- contact investigation procedures and role of public health in supervising community treatment
- symptoms of TB disease
- transmission of TB
- difference between TB disease and LTBI
- success of treatment for TB infection and disease
- importance of early medical assessment of TB symptoms
- principles of privacy, confidentiality and their rights as a health care consumer.

At the end of screening, contacts with abnormal findings should be given a summary of their results. Stress the importance of lifelong awareness of the symptoms of TB for infected contacts (even if treated for LTBI) and the need to seek medical attention promptly if symptoms occur.

7.5.3 Cross-cultural communication
Public health workers conducting contact investigations should be trained and ready to address cross-cultural issues in their interactions with clients. If necessary use a trained interpreter.

7.5.4 Public health follow-up of non-infectious tuberculosis
During the public health follow-up of non-infectious TB cases, it is important to consider whether it is necessary to search for the person who is the source of this TB case’s infection. This is particularly important if the case is a young child.

Different public health follow-up is advised in the following three scenarios.

**Scenario 1: Adult case, normal chest X-ray, non-respiratory tuberculosis (such as bone or kidneys)**
A source case is unlikely to be found because the infection leading to the TB disease probably occurred many years ago. The search for a source case is confined to asking whether any of the current close contacts of the case have symptoms of TB, such as fever, sweats, chronic cough, weight loss. Anybody answering ‘yes’ to these questions should be offered a Mantoux or IGRA test and CXR. Otherwise, Mantoux or IGRA testing and CXRs for the case’s social circle are not necessary.

Contact tracing is not necessary because the case is not infectious.
**Scenario 2: Paediatric case, with or without pulmonary disease**

The child is likely to have been recently infected by an adult so an urgent search for a source case is essential. All those in the child’s immediate social circle should be screened. It is efficient to focus screening for the adult source on adults with a history of TB or symptoms of TB.  

Contact tracing is seldom necessary. Children aged under 12 years with pulmonary disease seldom infect others, because:

- the natural history of primary TB means children rarely form cavities
- children are usually diagnosed relatively early
- younger children do not generate a sufficiently powerful cough to disseminate many acid-fast bacilli.

However, it is incorrect to assume that a child can never transmit disease. The paediatrician must assess the infectious potential of children with pulmonary disease and discuss with the public health service.

**Scenario 3: Person placed on preventive treatment for inactive tuberculosis with up to four drugs**

A person placed on preventive treatment for inactive tuberculosis may have had active pulmonary disease in the past. Treatment is given preventively because the prescribing clinician is concerned about a possibility of relapse.

It is unnecessary to search for a source case or to undertake a contact investigation because it is likely the case has been non-infectious for a long time. As a precaution, current close contacts should be asked about symptoms of TB, such as fever, sweats, chronic cough and weight loss. Contacts with these symptoms should be offered a Mantoux or IGRA test and CXR. Contacts without symptoms do not need investigation.

7.5.5 Repeat contact tracing for re-exposed contacts

It is possible to develop disease following re-infection with TB. Therefore, people re-exposed to infectious TB must be re-evaluated, even if they have been treated for LTBI in the past. See Chapter 8.

7.5.6 DNA fingerprinting

DNA fingerprinting is discussed in detail in Chapter 11. Its purpose is to detect clusters of TB of the same typing. The results of DNA typing need to be regularly reviewed at the district and national levels as clusters may require further investigation and action.

7.5.7 Source cases discharged into community while smear-positive

All contacts newly exposed to a case who is still smear-positive after discharge from hospital should be identified and receive two Mantoux or IGRA tests eight weeks apart.
Any conversions should be drawn to the attention of the medical officer of health, who should discuss with the clinician treating the case the need for a review of treatment efficacy and for induced sputum testing.

7.5.8 Communication

Communication between districts

The public health office in the district in which a case is notified must co-ordinate and finalise the contact investigation and enter all data onto EpiSurv. They must ensure:

- contacts are followed up if they move to another district
- complete assessment information is obtained on the outcome of screening in all districts.

When requesting that a public health service in another district investigates contacts in their district, provide a fully completed TB case report form on the index case and communicate culture and sensitivity results as soon as available.

When asked by another public health service to investigate contacts residing in your district, supply interim and final outcome information to the requesting district (see Figure 7.4). Do not enter these cases or contacts onto EpiSurv in your district.

General practitioners

Contact investigation and medical evaluation are specialised tasks and should be provided by public health. General practitioners who are consulted by contacts need to refer those contacts to the local public health service.

Medical officers of health need to:

- ensure general practitioners in their districts are aware of the local TB policy and procedures
- provide information and support to general practitioners to ensure smooth and effective service delivery for patients
- advise a general practitioner if the public health service is investigating any of the practice’s patients as a TB contact and communicate any abnormal results, hospital referrals and problems
- alert the general practitioner to the possibility of future TB in all Mantoux- or IGRA-positive contacts, particularly those not receiving treatment for LTBI, and the need for a repeat CXR if the person develops symptoms.

General practitioners should:

- understand the process the public health service follows for contact investigation
- refer contacts to the medical officer of health and not to the clinician managing the treatment of the index case
- know the indications for BCG vaccination and the availability of community BCG clinics.
DHB and private specialists

All specialists treating cases of TB disease must contact the local public health service to notify the case and enable appropriate contact investigation.

Notification to overseas health authorities

Medical officers of health must notify overseas health authorities about:
- TB cases diagnosed in New Zealand who temporarily or permanently travel overseas
- overseas contacts of cases who have recently arrived in New Zealand
- overseas source cases of TB diagnosed in New Zealand.

This is done via the Ministry of Health Focal Point and is a requirement of the International Health Regulations 2005.

7.5.9 Media management

Responsibility for media comment should be agreed between those involved and should usually be carried out by the medical officer of health.

7.5.10 Reviewing local findings

Regular audits are important to ensure screening activities are optimal and to avoid unnecessary screening. Medical officers of health should collect and periodically analyse contact investigation data to evaluate local screening activities.
Figure 7.3: Contact record form

| Name ............................................................................................. | NHI number ................................................ |
| Address ................................................................................................ | |
| Age ....................  DOB ...................  Sex M / F  Ethnicity ...................................................................... |
| General practitioner .................................................................................................. |
| Interpreter details ..................................................................................................... |
| Previous BCG: Y / N  Symptoms of TB: Y / N |

**Risk factors**

**Risk factors for infection**

<table>
<thead>
<tr>
<th>Source case</th>
<th>Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear-positive pulmonary: Y / N</td>
<td>Close: Y / N (eg, lives with case)</td>
</tr>
<tr>
<td>Cough: Y / N</td>
<td>Prolonged: Y / N (eg, many hours exposure)</td>
</tr>
<tr>
<td>Cavity: Y / N</td>
<td>Unventilated environment: Y / N (eg, closed windows)</td>
</tr>
</tbody>
</table>

**Risk factors for progression to TB disease**

- Age < 5 years or documented Mantoux conversion: Y / N
- Immuno-suppressed by disease or treatment: Y / N
- Undernourished: Y / N

*The more YES responses you have circled, the higher the risk for this contact.*

What is the cutting point for a positive Mantoux in this person?

**Results** *(see following pages for key to codes)*

<table>
<thead>
<tr>
<th>1st Mantoux mm</th>
<th>R</th>
<th>LTF</th>
<th>NR</th>
<th>2nd Mantoux mm</th>
<th>R</th>
<th>LTF</th>
<th>NR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st IGRA</td>
<td></td>
<td></td>
<td></td>
<td>2nd IGRA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXR 1 result</td>
<td>N</td>
<td>TB</td>
<td>R</td>
<td>LTF</td>
<td>NR</td>
<td></td>
<td></td>
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<td>CXR 2 result</td>
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<td>TB</td>
<td>R</td>
<td>LTF</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXR 3 result</td>
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<td>R</td>
<td>LTF</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CXR 4 result</td>
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<td>R</td>
<td>LTF</td>
<td>NR</td>
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<td></td>
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<td>Assessment</td>
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<td>LTBI</td>
<td>TB</td>
<td>TBO</td>
<td>U</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Actions</td>
<td>Dis</td>
<td>TB</td>
<td>X-ray</td>
<td>BCG</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: The key to this table is under Figure 7.4.
**Figure 7.4:** Summary of contact information

<table>
<thead>
<tr>
<th>Contact name</th>
<th>Assessment</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Surname first)</td>
<td>N</td>
<td>Dis</td>
</tr>
<tr>
<td></td>
<td>LTBI</td>
<td>TB</td>
</tr>
<tr>
<td></td>
<td>TB</td>
<td>X-ray</td>
</tr>
<tr>
<td></td>
<td>TBO</td>
<td>BCG</td>
</tr>
<tr>
<td>(Surname first)</td>
<td>N</td>
<td>Dis</td>
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<tr>
<td></td>
<td>LTBI</td>
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<td>TB</td>
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<td></td>
<td>TBO</td>
<td>BCG</td>
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<tr>
<td>(Surname first)</td>
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<td></td>
<td>LTBI</td>
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<td>TB</td>
<td>X-ray</td>
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<td></td>
<td>TBO</td>
<td>BCG</td>
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<tr>
<td>(Surname first)</td>
<td>N</td>
<td>Dis</td>
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<td></td>
<td>LTBI</td>
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<td></td>
<td>TB</td>
<td>X-ray</td>
</tr>
<tr>
<td></td>
<td>TBO</td>
<td>BCG</td>
</tr>
</tbody>
</table>

When investigation is complete, please return this to the infectious diseases clerk at the public health unit.

Key to Figures 7.3 and 7.4 – tuberculosis contact tracing

<table>
<thead>
<tr>
<th>Mantoux test</th>
<th>Chest X-ray (CXR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R</td>
<td>Refused testing</td>
</tr>
<tr>
<td>LTF</td>
<td>Lost to follow-up; cannot be located</td>
</tr>
<tr>
<td>NR</td>
<td>Not required (ie, not medically indicated)</td>
</tr>
<tr>
<td>N</td>
<td>No evidence of current or past TB</td>
</tr>
<tr>
<td>TB</td>
<td>Consistent with current or past TB</td>
</tr>
<tr>
<td>R</td>
<td>Refused CXR</td>
</tr>
<tr>
<td>LTF</td>
<td>Lost to follow-up</td>
</tr>
<tr>
<td>NR</td>
<td>Not required (ie, not medically indicated)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>No evidence of TB infection or disease</td>
</tr>
<tr>
<td>Dis</td>
<td>Discharge. Use this code if lost to follow-up or refuses testing.</td>
</tr>
<tr>
<td>LTBI</td>
<td>TB infection but not disease; normal CXR</td>
</tr>
<tr>
<td>TB</td>
<td>Active TB disease</td>
</tr>
<tr>
<td>TBO</td>
<td>‘Old’ or ‘inactive’ TB disease</td>
</tr>
<tr>
<td>BCG</td>
<td>BCG given</td>
</tr>
<tr>
<td>U</td>
<td>Unknown because complete assessment was not possible. Did not complete testing because of loss to follow-up or refusal or another reason.</td>
</tr>
</tbody>
</table>
References


Chapter 8: Diagnosis and Treatment of Latent Tuberculosis Infection

Summary
This chapter deals with the diagnosis and management of latent TB infection (LTBI). It is primarily intended for specialist medical practitioners and public health service staff who treat people with LTBI.

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

The diagnosis of LTBI depends on finding evidence of TB infection in the absence of active or inactive TB disease. In LTBI the chest X-ray (CXR) is normal or shows trivial and stable evidence of past TB (eg, a small scar or patch of calcium). People with LTBI are asymptomatic and non-infectious.

The tests used to diagnose LTBI are tuberculin skin tests (TSTs) such as the Mantoux test and interferon-gamma release assays (IGRAs) such as the QuantiFERON-TB Gold In-tube assay (QFT-G IT).

If untreated, adults with LTBI have a 5–15% chance of developing active TB disease at some point in their lives. However the risk is greater in some groups of people with LTBI, including recently infected people and people with risk factors for progression to active TB disease (including children under five years of age, people living with HIV and people with other predisposing immuno-suppressive medical conditions and/or immuno-suppressive treatments).

Treatment of LTBI in an individual at high risk of developing active TB disease is effective in reducing the individual’s future risk of developing TB disease. There are a number of recommended drug regimens for the treatment of LTBI in HIV-negative and in HIV-positive people.

Treatment of LTBI is a specialised task, and should be undertaken by specialist medical practitioners with knowledge and experience in this area (including appropriate medical and nursing staff in public health services). General practitioners (GPs) should consult with an appropriate specialist regarding any patients they identify who may have LTBI and are at high risk of developing TB disease.

Introduction
This chapter deals with the diagnosis and management of latent TB infection (LTBI). The diagnosis of LTBI depends on finding evidence of TB infection in the absence of active or inactive TB disease. The tests used to diagnose LTBI are tuberculin skin tests (TSTs) such as the Mantoux test and interferon-gamma release assays (IGRAs).

LTBI is ‘latent’ because live, dormant (not reproducing) Mycobacterium tuberculosis organisms are sequestered in the tissues, although they are not clinically apparent. In LTBI the chest X-ray (CXR) is normal or shows trivial and stable evidence of past TB (eg, a small scar or patch of calcium). The number of TB organisms is low.
Worldwide about one third of the population is thought to have LTBI. The prevalence of LTBI in New Zealand is not known. However the prevalence will vary in different subgroups within the New Zealand population, eg, in different age and ethnic groups.

If untreated, adults with LTBI have a 5–15% chance of developing active TB disease at some point in their lives. However the risk is greater in some groups of people with LTBI, including people living with HIV and children under five years of age. Factors determining the risk of progression from LTBI to TB disease include time since infection, age, the dose of infectious agent, and the immune status and general health of the infected person.

Treatment of LTBI in an individual at high risk of developing active TB disease is effective in reducing the individual's future risk of developing TB disease. The only way to prevent LTBI is by preventing TB transmission through early identification and treatment of people with infectious TB disease.

The Centers for Disease Control and Prevention’s Targeted tuberculin testing and treatment of latent tuberculosis infection is a useful reference document.1

8.1 Diagnosis
The diagnosis of LTBI depends on finding evidence of TB infection in the absence of active or inactive TB disease. In LTBI the chest X-ray (CXR) is normal or shows trivial and stable evidence of past TB (eg, a small scar or patch of calcium). People with LTBI are asymptomatic and non-infectious.

8.1.1 Who should be tested for LTBI
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.

Practice points
The following groups of people should be tested for LTBI:

- People likely to have been infected recently (see Table 8.1): primarily contacts of a patient with recent diagnosis of active infectious TB disease; refugees aged under 16 years.
- People who have an increased risk of developing active TB disease if they have LTBI, due to impaired immunity (see Table 8.2): eg, people living with HIV infection, chronic renal failure, solid organ transplantation, anti-tumour necrosis factor (TNF) alpha treatment and various other chronic conditions and treatments.
- Health care workers (HCWs), because they are at increased risk of exposure to people with active infectious TB disease (see Chapter 12).

Note that the investigation of inactive TB disease (where there is radiographic evidence of old, healed TB disease but no history of prior TB treatment, and which requires full multi-drug treatment) is covered in Chapter 2.
8.1.2 Risk factors for infection and developing TB disease

Risk factors for infection

Risk factors for infection are summarised in Table 8.1. TB is almost always transmitted by active pulmonary or laryngeal TB in adults or adolescents. Almost without exception, transmission does not occur from people who only have extrapulmonary TB, such as lymph node, renal or bone disease.

Table 8.1: Risk factors for infection

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closeness of contact with a source case</td>
<td>Close contacts are at highest risk.</td>
</tr>
<tr>
<td>Duration of exposure to a source case</td>
<td>Brief exposures usually carry low risk.</td>
</tr>
<tr>
<td>Sputum status of source case</td>
<td>Risk is highest if source case is smear-positive; less if smear-negative and culture-positive; minimal if culture-negative.</td>
</tr>
<tr>
<td>Extent of pulmonary disease of source case</td>
<td>Cavitation and productive cough indicate higher risk. Laryngeal tuberculosis (TB) is often highly infectious.</td>
</tr>
<tr>
<td>Cough frequency of source case</td>
<td>Treatment leads to a sharp decline in cough frequency, which is associated with a decline in infectivity. However, cough frequency is a less statistically significant indicator of infectivity than extent of disease or bacteriologic status.</td>
</tr>
<tr>
<td>Delay in diagnosis or appropriate treatment of source case</td>
<td>Effective chemotherapy of the source case rapidly and progressively reduces infectiousness (and therefore risk to contacts).</td>
</tr>
<tr>
<td>Recent conversion of the tuberculin reaction</td>
<td>This is a marker of recent infection, rather than a risk factor per se; the possibility of the infection having progressed to TB disease should also be considered.</td>
</tr>
<tr>
<td>Open skin TB abscess</td>
<td>Dressing or irrigation of an open abscess can lead to transmission of infection, but this is very rare.</td>
</tr>
<tr>
<td>Institutions</td>
<td>Residents of rest homes, long-stay hospital patients, residents of shelters for the homeless, and prison inmates are at increased risk, probably as a result of increased exposure and closeness of contact.</td>
</tr>
<tr>
<td>Age: Prevalence increases with age, but incidence is highest in young children</td>
<td>These differences in risk probably reflect differences in exposure, but may be due to intrinsic differences between individual contacts.</td>
</tr>
<tr>
<td>Sex: Males at higher risk than females after adolescence</td>
<td></td>
</tr>
</tbody>
</table>

Note: Numbers refer to references at the end of the chapter.

Risk factors for developing TB disease following infection

People with LTBI have widely varying risks of progression to TB disease, depending on the factors listed in Table 8.2.

Other factors that are possible risk factors for LTBI progressing to TB disease, but for which there are variable amounts of evidence, include the following.
• Socioeconomic status: The relationship between socioeconomic status and TB is complex. The clear relationship between TB and poverty\textsuperscript{8,9} may be mediated through many factors, such as crowding, infectivity of source case, access to medical services, and attitudes and priority given to health. A study of paediatric TB in new Zealand from 1992 to 2001 found that poverty was strongly associated with TB.\textsuperscript{10} A recent ecological study using TB surveillance and census data showed that TB incidence in New Zealand is associated with household crowding at the census area unit (CAU) level.\textsuperscript{11}

• Gender differences in TB risk are also complex. They vary across cultures and countries, differ between LTBI and TB disease, and are probably due more to socioeconomic factors than to biological differences in susceptibility.\textsuperscript{8,12}

• No ethnic differences in TB risk have been documented in studies with appropriate control for confounders.\textsuperscript{8}

• Twin and blood-group studies suggest some genetic predisposition.\textsuperscript{8}

• Emotional or physical stress may increase risk.\textsuperscript{8}

Table 8.2: Risk factors for developing TB disease following infection

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since infection</td>
<td>Inverse association: Risk is highest in the first year after infection, but continues, albeit at a decreasing rate, thereafter.\textsuperscript{13} Therefore, documented recent Mantoux conversion following exposure to an infectious case indicates significant risk. Conversely, the risk is lower in people who have been infected in the remote past (eg, those who have lived or grown up in high TB-incidence countries but have resided in New Zealand for some years).</td>
</tr>
<tr>
<td>Age</td>
<td>Inverse association: Peaks in risk occur in the preschool years and adolescence and early adulthood. The lifetime risk of progressing from infection to active TB is:</td>
</tr>
<tr>
<td></td>
<td>• 5–15% in adults\textsuperscript{8}</td>
</tr>
<tr>
<td></td>
<td>• inversely proportional to age:</td>
</tr>
<tr>
<td></td>
<td>• 23–43% in infants under 1 year of age</td>
</tr>
<tr>
<td></td>
<td>• 11–24% in children aged 1–5 years</td>
</tr>
<tr>
<td></td>
<td>• 8–25% in children aged 6–10 years</td>
</tr>
<tr>
<td></td>
<td>• 16% in children aged 11–15 years.\textsuperscript{14}</td>
</tr>
<tr>
<td>Dose of infection</td>
<td>The risk is highest if the source case is smear-positive; less if smear-negative or culture-positive; minimal if culture-negative.\textsuperscript{8}</td>
</tr>
<tr>
<td>Size of tuberculin reaction</td>
<td>The larger the reaction, the greater the risk of subsequent disease. However, there is a substantial degree of variation in the extent of increased risk associated with larger tuberculin reactions.\textsuperscript{15–17}</td>
</tr>
<tr>
<td>Predisposing medical conditions</td>
<td>HIV is the strongest risk factor (see Chapter 6). Other risk factors include diabetes, alcoholism and drug addiction, silicosis, gastrectomy, intestinal bypass and chronic malabsorption syndromes, and immuno-suppressive diseases (leukaemia, lymphoma and end-stage renal disease).\textsuperscript{1}</td>
</tr>
<tr>
<td></td>
<td>Underlying illnesses such as diabetes mellitus, renal failure, chronic obstructive pulmonary disease, and HIV infection are also strong predictors of death from TB.\textsuperscript{18}</td>
</tr>
<tr>
<td>Immuno-suppressive treatment</td>
<td>Current or recent oral steroid therapy (over 15 mg prednisone or equivalent per day for two to three weeks); anti-Tumour Necrosis Factor (TNF) alpha treatment; some cancer chemotherapy; immuno-suppressive drugs used in solid organ transplantation.</td>
</tr>
<tr>
<td>Risk factor</td>
<td>Comments</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Immigrants who have recently arrived from a high-incidence country</td>
<td>Risk for migrants is highest in the first 1–2 years of being in New Zealand.19, 20</td>
</tr>
<tr>
<td>Body weight</td>
<td>Increased risk in underweight or malnourished individuals.8</td>
</tr>
<tr>
<td>Smoking</td>
<td>Increased TB incidence in smokers (lowest risk in never smokers, intermediate in ex-smokers, highest in current smokers).21,22</td>
</tr>
</tbody>
</table>

Note: Numbers refer to references at the end of the chapter.

### 8.1.3 Tests used to diagnose 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. The Mantoux test is a TST using an intradermal injection of 5 tuberculin units (TU) of purified protein derivative (PPD), which is derived from cultures of *M. tuberculosis*. In a person previously infected with *M. tuberculosis* a hypersensitivity reaction occurs at the site of injection. The Mantoux test is the only TST currently used in New Zealand. See section 8.1.5 for further information regarding Mantoux testing.

IGRAs have been developed as an alternative to Mantoux tests for the diagnosis of LTBI. IGRAs work on the principle that if a person is infected with *M. tuberculosis*, T-lymphocytes circulating in their blood will produce interferon-gamma (IFN-gamma) if re-exposed to TB antigens in vitro. See section 8.1.6 for further information regarding IGRAs, including a summary of some selected recent literature on the cost-effectiveness of IGRA, the use of IGRA in migrants, and a study on the prognostic value of IGRA for the progression from LTBI to TB disease.

### 8.1.4 Which test to use

While the Mantoux test has been used for many years, IGRAs are much newer tests and evidence for 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, as outlined below. It is important to note that the limitations of both tests are similar, in particular that false negative results (and indeterminate results in the case of IGRAs) can occur, and are more likely to occur in immuno-compromised people.

Advantages of IGRAs compared with TST include that they have better specificity.23 require only one patient visit for the test, have the potential for more rapid availability of results, are not subject to inter- and intra-operator variability, are not subject to boosting and sensitisation, are not affected by previous BCG vaccination or by infection with most non-tuberculous mycobacteria (NTM) and have results that can be stored in the laboratory system. Disadvantages of IGRAs compared with TSTs are that they have higher upfront cost, require laboratory expertise and have a relative lack of evidence upon which to base decision-making, although research in this area is expanding.
The USA Centers for Disease Control and Prevention guidance recommends that QFT-G may be used in all circumstances in which TSTs are used. The UK National Institute for Health and Clinical Excellence (NICE) TB guidelines recommend that Mantoux testing should be done, and that in people with positive Mantoux tests, IGRAs should then be considered (if available).

Contact screening for LTBI

**Practice points**

Contacts aged seven years and under: use Mantoux test.  
Contacts aged over seven years: use Mantoux test or IGRA or Mantoux test followed by IGRA (if Mantoux positive).  
An IGRA is particularly recommended:  
- in BCG-vaccinated people  
- in immuno-compromised 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.

**Rationale**

The recommendation to use the Mantoux test in children aged seven and under is based on a review of the literature and on expert opinion. Phlebotomy is relatively invasive for children, and studies have shown a relatively high rate of indeterminate results with IGRAs in children aged under five. New Zealand has a good level of expertise in the administration and interpretation of Mantoux tests in children.

The specificity of IGRAs is higher than that of Mantoux tests in people who have had a BCG vaccination.

Studies indicate that IGRAs are more sensitive than Mantoux tests in people who are immuno-compromised.

**Interpretation of results in contacts**

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

If an IGRA is negative or indeterminate, or a Mantoux test is negative and:
- the person is asymptomatic and not immuno-compromised, no further action is required
- the person is symptomatic or immuno-compromised, the person should be referred for further investigation.
Healthcare worker screening for LTBI

**Practice point**
Use IGRAs to screen healthcare workers for LTBI.

**Rationale**
There are relatively high rates of BCG-vaccinated individuals and immigrants among healthcare workers in New Zealand.

Healthcare workers (HCWs) are at risk of occupational exposure to TB, so may need multiple tests to screen for LTBI during their working life. Use of IGRAs avoids the need for baseline two-step testing, as well as the occurrence of boosting and sensitisation that can be complications of serial Mantoux testing.

IGRA results will be stored in the laboratory system, which should facilitate the transfer of information between District Health Boards should HCWs move between regions.

**Interpretation of results in healthcare workers**
If an IGRA is positive, the HCW should be referred for further investigation and assessed on a case-by-case basis to determine their history of TB exposure, and therefore likelihood of progression to active TB disease, and to agree a management plan.

If an IGRA is negative or indeterminate *and*:
- the HCW is asymptomatic and not immuno-compromised, no further action is required
- the HCW is symptomatic or immuno-compromised, they should be referred for further investigation.

Note that care must be taken when interpreting the results of serial testing with IGRAs. Debate exists in the international literature about the most valid cut-off point for defining a true IGRA conversion in the context of serial testing. In line with guidelines from the Centers for Disease Control and Prevention, a change from a negative to positive result should be considered as a conversion and the person must be referred for further investigation. However, as more information becomes available this definition of an IGRA conversion may be amended.

**Refugee screening for LTBI**

**Practice points**
Refugee children aged seven years and under: use Mantoux test.
Refugee children aged 8–15 years: use Mantoux test *or* IGRA *or* Mantoux test followed by IGRA (if Mantoux positive).
An IGRA is particularly recommended:
- in BCG-vaccinated children
- in immuno-compromised children.

Refugees aged 16 years and older are not currently screened for LTBI in New Zealand. However if in future a policy decision is made to screen this group, either Mantoux test or IGRA should be used (as for refugee children aged 8–15 years).

Rationale
As for contact screening for LTBI (see above).

Interpretation of results in refugees
If an IGRA or a Mantoux test is positive, the person should be referred for further investigation and assessed on a case-by-case basis to determine their history of TB exposure, and therefore likelihood of progression to active TB disease, and to agree a management plan.

If an IGRA is negative or indeterminate, or a Mantoux test is negative and:
- the person is asymptomatic and not immuno-compromised, no further action is required
- the person is symptomatic or immuno-compromised, the person should be referred for further investigation.

Screening for LTBI in immuno-compromised people

Practice points
Use IGRAs to screen immunocompromised people where indicated eg, prior to starting anti-TNF alpha therapy or other immuno-suppressive therapies, in people with renal failure, prior to solid organ transplantation, etc.

In some situations, a clinician may elect to use both a Mantoux test and an IGRA to screen for LTBI in an immuno-compromised person.

Rationale
IGRAs have been shown to be more sensitive than Mantoux tests to screen for LTBI in immuno-compromised individuals, including people living with HIV and people with immune compromising conditions, including conditions requiring anti-TNF alpha therapy.30–32, 35

Interpretation of results in immuno-compromised people
If an IGRA or a Mantoux test is positive (i.e. only one test was done), the immuno-compromised person should be treated for LTBI.
If IGRA and Mantoux test results are discordant in an immuno-compromised person (i.e. both tests were done, and the Mantoux test is positive but the IGRA is negative or the IGRA is positive but the Mantoux test is negative), the clinician should consider treating the person for LTBI.

Even if an IGRA is negative or indeterminate or a Mantoux test is negative, the immuno-compromised person should be assessed on a case-by-case basis to determine their history of TB exposure, likelihood of having acquired LTBI and if so, of progression to active TB disease, and considered for treatment of LTBI accordingly.

8.1.5 Mantoux test

Administering and reading the Mantoux test

Those administering and reading the Mantoux test must be trained in the technique and should follow the technical guidance in the Ministry of Health’s *Technical Guidelines for Mantoux Testing and BCG Vaccination*. Medical officers of health should work with organisations offering Mantoux tests to facilitate the initial and ongoing training of those undertaking Mantoux tests.

**Practice points**

Read a Mantoux test as close as possible to 72 hours after placement.

The exception to this is the second step of a two-step Mantoux test, which should be read at 48 hours (see section below on the two-step Mantoux test).

A Mantoux test is read by measuring the presence or absence of induration (not redness). The result should be recorded in millimetres (mm).

If it is not possible to read a Mantoux test at 72 hours, a reading at 48 hours is acceptable. If this is not possible, readings may be done between 72 hours and seven days. However, all the literature regarding the risk of developing TB is based on reading Mantoux tests at 48–72 hours, the interpretation of Mantoux tests that are read between 72 hours and seven days is uncertain.

Definition of positive Mantoux reactions in New Zealand

The predictive value of Mantoux readings in different clinical situations allows the establishment of ‘cutting points’. There are no New Zealand data, so data collected in similar communities such as Canada must be used to establish appropriate points for New Zealand. Readings at the cutting points or higher are defined as positive. The cutting points are summarised in Table 8.3.

Children are at greater risk of severe and life-threatening TB disease than adults, so the cutting points shown in Table 8.3 are conservative.
Table 8.3 shows that previous BCG vaccination affects the cutting point in New Zealanders who have not resided in high-incidence countries. However, previous BCG vaccination does not affect the cutting point of a person who has resided in a high-incidence country.

Table 8.3: Definition of a positive Mantoux test in New Zealand (cutting points)

<table>
<thead>
<tr>
<th>Category</th>
<th>Adults (≥ 15 years)</th>
<th>Older children (5–14 years)</th>
<th>Younger children (&lt; 5 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Zealand born</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No BCG vaccination</td>
<td>≥ 10 mm</td>
<td>≥ 10 mm</td>
<td>≥ 5 mm</td>
</tr>
<tr>
<td>• Previous BCG vaccination</td>
<td>≥ 15 mm</td>
<td>≥ 10 mm</td>
<td>≥ 10 mm</td>
</tr>
<tr>
<td>Following residence in a high-incidence country*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No BCG vaccination</td>
<td>≥ 10 mm</td>
<td>≥ 10 mm</td>
<td>≥ 5 mm</td>
</tr>
<tr>
<td>• Previous BCG vaccination</td>
<td>≥ 10 mm</td>
<td>≥ 10 mm</td>
<td>≥ 10 mm</td>
</tr>
<tr>
<td>With immuno-suppressive illness or taking immuno-suppressive drugs (with or without BCG vaccination)</td>
<td>5–10 mm†</td>
<td>≥ 5 mm</td>
<td>≥ 5 mm</td>
</tr>
<tr>
<td>HIV/AIDS (with or without BCG vaccination)</td>
<td>≥ 5 mm</td>
<td>≥ 5 mm</td>
<td>≥ 5 mm</td>
</tr>
<tr>
<td>Close contacts of smear-positive cases (any origin)</td>
<td>≥ 10 mm</td>
<td>≥ 5 mm</td>
<td>≥ 5 mm</td>
</tr>
<tr>
<td>(with or without BCG vaccination)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* As per the BCG chapter of the Ministry of Health’s Immunisation Handbook.
† See the discussion following the table.

In adults with immuno-suppressive illness or taking immuno-suppressive drugs, the degree and duration of immune suppression should be documented and the appropriate cutting point selected as described here.

The 5 mm cutting point is appropriate with:
- immuno-suppressive treatment for organ transplantation
- aggressive immuno-suppressive cancer treatment
- cytotoxic immuno-suppressive agents such as cyclophosphamide or methotrexate
- systemic corticosteroid treatment that is prolonged (for example, for more than six weeks) and in a dose of prednisone of 15 mg or more per day (or equivalent with another steroid); the higher the dose, the greater the risk of reactivation of TB
- combinations of immunosuppressive conditions (for example, prednisone of less than 15 mg per day plus diabetes mellitus (on treatment), moderate or severely advanced malignancy, or malnutrition (this advice is empirical, not evidence-based)
- end-stage renal failure.

The 10 mm cutting point is appropriate with:
- doses of prednisone less than 15 mg per day long term
- diabetes mellitus (including insulin-dependent)
- alcoholism
- malnutrition
- disseminated malignancy.
Situations in which people should not receive a Mantoux test

The following people should not receive a Mantoux test (incorporating guidance from the Canadian Tuberculosis Standards):42

- those with documented active TB or a documented history of adequate treatment for LTBI or TB disease in the past (because the test is of no clinical utility and discomfort is likely)
- those with documented Mantoux reactions ≥ 15 mm or greater in the past (because no new diagnostic information will be gained and discomfort is likely)
- those with severe blistering Mantoux reactions in the past, or with extensive burns or eczema present over Mantoux testing sites (because of the greater likelihood of adverse reactions or severe reactions)
- those with major viral infections
- those who have received measles vaccination within the past four weeks (because this has been shown to increase the likelihood of false-negative Mantoux results; no data are available regarding the effect on Mantoux results of other live virus vaccinations – mumps, rubella, varicella and yellow fever – but it would seem prudent to follow the same guidance; however, if the opportunity to perform the Mantoux test might be missed, the test should not be delayed for live virus vaccines, as these are theoretical considerations; note that a Mantoux test may be administered before or on the same day as live virus vaccinations, but at a different site).43

Situations in which people can receive a Mantoux test

The following people can receive a Mantoux test (incorporating guidance from the Canadian Tuberculosis Standards):42

- those with a common cold
- those who are pregnant or are breastfeeding
- those immunised with any vaccine on the same day
- those immunised within the previous four weeks with inactivated vaccines
- those who give a history of a positive Mantoux reaction (other than blistering) that is not documented
- those taking low doses of systemic corticosteroids (< 15 mg prednisone (or equivalent) daily; it generally takes a steroid dose equivalent to ≥ 15 mg prednisone daily for 2–4 weeks to suppress Mantoux reactivity).

Serial Mantoux testing: boosting, conversion and reversion

Repeated Mantoux tests can result in larger reaction sizes, which can be due to non-specific variation, boosting or true Mantoux conversion.38 Non-specific increases occur because of differences in administration, reading and minor variation in the individual’s response. Increases due to non-specific variation are small, between 2 to 3 mm. Increases of 6 mm or more represent either boosting or conversion.
Boosting

The boosting phenomenon is seen when there has been sensitisation to mycobacteria (tuberculous or non-tuberculous) many years earlier, in which case an initial Mantoux test may produce a negative or a weakly positive response (below the positive cutting point). This is thought to occur because there are too few sensitised lymphocytes in circulation to produce a significant local response. If the test is repeated, a larger reading may be obtained due to the immune response being ‘recalled’ or ‘boosted’ by the first test.

The second boosted reading is the correct one (that is, the second result should be used for decision-making or future comparison). Boosting is maximal if the second test is placed one to five weeks after the initial test and it may continue to be observed for up to two years.38

The boosting phenomenon is common, especially in older people and in populations with a high prevalence of BCG vaccination and/or exposure to non-tuberculous mycobacteria (NTM).38,44,45

Two-step Mantoux test

In people who may need to have serial tests for LTBI (such as healthcare workers), IGRA’s are recommended, if available, as IGRA’s are not subject to boosting. However, if IGRA’s are not available, the two-step Mantoux test should be done as part of the initial testing, as it will help to distinguish boosting from conversion on subsequent testing.

The two-step Mantoux test utilises the boosting phenomenon and is performed when a true baseline Mantoux reaction needs to be established. Because boosting lasts up to two years, two-step testing is unnecessary in someone who has been tested in the preceding two years.

The second Mantoux test is needed only if the initial reading is negative. The two tests should not be given at the same site because this can result in increased reaction size.38

In a two-step Mantoux test, the second test should be undertaken one week after the first test, and should be read at 48 hours, wherever possible, especially in subjects with previous BCG vaccination. In a small study of United Kingdom health service employees previously vaccinated with bacille Calmette-Guérin (BCG), boosting was maximal if the second test was read 48 hours after placement (injection) compared with after 72 hours and 96 hours.45

Two-step testing is not necessary for the initial Mantoux test in contacts exposed to TB. If contacts have had significant exposure to a person with infectious TB, they will have already been boosted by the time the first test is placed.

Practice points
If IGRAs are not available, use the two-step Mantoux test to establish a true baseline Mantoux reaction in people who may need to have serial tests for LTBI, eg, healthcare workers, and travellers prior to travelling to high-incidence countries to live or work for more than six months (especially if they are likely to have contact with people with active TB disease in that country).

In a two-step Mantoux test, the first test should be placed and should be read 72 hours later. The second test should be placed, at a different site, one week after the first test was placed, and should be read 48 hours later.

Example of the value of two-step testing

A 25-year-old nurse is new to a hospital. The nurse reports having had a BCG vaccination as a student at age 18. The nurse has a doubtful BCG scar. The nurse’s first Mantoux result is 3 mm. When the Mantoux test is repeated a week later, the result is 10 mm (that is, the correct, ‘boosted’, reading is 10 mm).

Six months later the nurse has unprotected exposure to a highly infectious case of pulmonary TB where diagnosis was delayed. The nurse provided care to the patient for several days. Eight weeks after exposure the nurse is again Mantoux tested and the reaction is 14 mm. There is no evidence of new TB infection, because the change from 10 mm to 14 mm is less than the 10 mm change required to demonstrate conversion.

Had the two-step test not been used when the nurse joined the hospital, an incorrect change in Mantoux from 3 mm to 14 mm would have been recorded and the nurse would have been managed as a Mantoux conversion.

Mantoux conversion

Mantoux conversion is the development of new or enhanced hypersensitivity due to infection with tuberculous or non-tuberculous mycobacteria, including BCG vaccination. By comparison, boosting is a recall of the hypersensitivity response in the absence of new infection.

Mantoux conversion is defined as an increase in the Mantoux reaction of 10 mm or more within a two-year period. Mantoux conversion has been associated with an annual incidence of TB disease of 4% in adolescents and 6% in contacts of smear-positive cases. People who have a Mantoux conversion should be investigated for TB disease (see Chapter 2). If the need for full treatment is excluded, they should be considered for treatment of LTBI.

Mantoux conversion occurs within eight weeks of infection. Therefore, when testing contacts of infectious TB cases for conversion, the first Mantoux test should be done as soon as possible and the second Mantoux test should be done eight weeks after the date of the last contact with the source case.

If a person has had a documented Mantoux test result within the past 12 months and is exposed to infectious TB, the documented pre-exposure result may be used as the baseline in testing for conversion. Therefore only one Mantoux test is necessary to
detect conversion. This test should be done eight weeks after the date of last exposure. Positive reactions older than 12 months may wane, so cannot be relied on as a valid baseline.

Increase in the Mantoux reading of less than 10 mm

If the Mantoux test increases between tests by less than 10 mm, the second test is the correct reading. Depending on the applicable cutting point, sometimes the second test may be positive, but the change in diameter of induration does not meet the criterion for conversion. There is no evidence to guide a decision regarding whether or not to treat these cases (see section 8.2.1 for the Tuberculosis Working Group of the Ministry of Health’s recommendations in this situation).

Mantoux reversion

A Mantoux reversion is the change to a negative Mantoux result after a previous positive result. This phenomenon is uncommon in healthy individuals, occurring in less than 10% of people with a previously positive Mantoux.

Reversion is more common in older adults (estimated at 8% per year), when the initial Mantoux was less than 14 mm and in people whose initial positive Mantoux reaction was a boosted result (identified by two-step testing). There is no clinical or epidemiological information available to interpret the significance of a Mantoux reaction that reverts to negative and then becomes positive again.

Interpretation of the Mantoux test

Practice point
When interpreting a person’s Mantoux test, there are three dimensions to consider:
- positive predictive value
- the person’s risk of developing active TB disease (see Table 8.2)
- the size of the Mantoux reaction.

Positive Mantoux result: predictive value for LTBI

The positive predictive value of a Mantoux test represents the percentage of those with any given Mantoux reading who truly have TB infection. The predictive value varies with different clinical situations. Where the expected prevalence of true infection is low, as in screening situations in a low risk country, the influence of factors other than TB (such as BCG and non-tuberculous mycobacteria) is significant, so lower readings have a low positive predictive value. Where the expected prevalence of TB infection is high, as in contacts of smear-positive cases or immigrants from high-incidence countries, the positive predictive value of lower readings is higher. Therefore, in these situations the effects of factors such as BCG and non-tuberculous mycobacteria carry less weight.

In other words, where there is a low likelihood of TB disease, as in a screening situation, a positive Mantoux test is less likely to be due to TB and more likely to be
caused by another factor. Where there is a higher likelihood of TB disease, as in a contact of a smear-positive case, a positive Mantoux is more likely to be due to TB.

**Whether size matters: significance of strongly positive Mantoux**

There is no correlation between size of reaction and likelihood of current active TB disease ie, the Mantoux test has a poor positive predictive value for current active TB disease. However, size of the Mantoux reaction is correlated with future risk of development of active TB disease.15,16,17,48

A large retrospective population-based cohort study into the risk of TB development among over 26,000 untreated contacts with a 12-year follow-up found that TB rates were high for all tuberculin skin test (TST) sizes in household contacts, 0–10 year old contacts and immunosuppressed contacts. For all types of contacts (household contacts, close non-household contacts and casual contacts), the risk of developing TB disease increased with larger TST sizes.49

Therefore, as the size of the Mantoux test result increases beyond the cutting point, the extent of increase should be taken into account as one of the risk factors for progression to disease. This is relevant when deciding whether to give treatment for LTBI.

**False-positive Mantoux test results**

False-positive Mantoux reactions can be caused by:

- previous BCG vaccination
- exposure to non-tuberculous mycobacteria
- factitious false positives, which may occur if the injection site is rubbed or scratched
- observer error
- recording error.

Post-BCG vaccination tuberculin reactions have been extensively studied, and the age at which BCG vaccination was performed affects subsequent Mantoux reactivity.50,51 Among people who received BCG in infancy, 3 to 5% have a subsequent positive Mantoux reaction, whereas 30 to 35% of people who received BCG at an older age may have a subsequent positive Mantoux reaction.38

A Mantoux reaction larger than 15 mm induration should not be attributed to BCG vaccination. No relationship exists between the post-BCG vaccination Mantoux result and protection against TB disease. Therefore routine post-BCG vaccination Mantoux testing serves no purpose and should not be done.

Non-tuberculous mycobacteria (NTM) are found in soil and water in the environment, especially in warm and moist climates.38 Therefore, particularly in tropical and subtropical climates but also to a lesser extent in cold and temperate climates, people may have been exposed and sensitized to NTM antigens. This may result in a false positive Mantoux reaction due to cross-reactivity, as many of the antigens from NTM and *M. tuberculosis* are similar.
IGRAs are not affected by previous BCG vaccination or by infection with most NTM.

**False-negative Mantoux test results**

A negative Mantoux test result usually signifies that the individual has never been exposed to *M. tuberculosis*. However, some factors may cause a false-negative result or diminished ability to respond to tuberculin.\(^1,46\) Therefore a negative Mantoux does not absolutely exclude either LTBI or TB disease.

People with HIV infection may have a false-negative Mantoux or IGRA test.

A negative Mantoux reaction in an infant under 12 weeks of age may reflect the fact that very young infants may not mount an immune response. The test will need to be repeated if the child has been exposed to an infectious TB case.

IGRAs may have a place in investigating an unexpectedly negative Mantoux test.

Anergy testing is not recommended as a method to discover whether a negative Mantoux result is true or false in either HIV-positive subjects\(^52\) or HIV-negative subjects.\(^53\)

Causes of false-negative Mantoux test results are factors related to:

- the person being tested, including:
  - viral infections (especially HIV, but also measles, mumps and chickenpox)
  - severe and overwhelming TB
  - other bacterial infections (such as typhoid, brucellosis, typhus, leprosy or pertussis)
  - metabolic disorders (especially renal failure and diabetes)
  - disorders of lymphoid organs (sarcoidosis, lymphoma or leukaemia)
  - corticosteroids or other immuno-suppressive drugs (including commonly used agents such as prednisone at 15 mg or more per day, cyclophosphamide, methotrexate and azathioprine, together with many drugs used to treat cancer)
  - age (infants under 12 weeks of age, and older people, in whom sensitivity wanes)
  - stress (surgery, burns or severe illness of any type)
- technical factors, including the tuberculin solution used, method of administration and reading of results.\(^37\)

### 8.1.6 Interferon-gamma release assays

Interferon-gamma release assays (IGRAs) have been developed for the diagnosis of TB infection, as an alternative to tuberculin skin tests (TSTs) such as the Mantoux test.

One type of IGRA is the QuantiFERON-TB Gold In-tube assay (QFT-G IT), which has been available in New Zealand since 2006. Another type of IGRA is the T-SPOT.TB test, which is available in Europe, but is not currently licensed for use in New Zealand.
Underlying principle of IGRAs

IGRAs work on the principle that if a person is infected with *M. tuberculosis*, T-lymphocytes circulating in their blood will produce interferon-gamma (IFN-gamma) if re-exposed to TB antigens in vitro. In the QFT-G IT, the amount of IFN-gamma released is quantified using an enzyme-linked immuno-sorbent assay (ELISA).

Administering the QFT-G IT test

The QFT-G IT is a blood test, and involves a small blood sample being collected into three specialised tubes (a ‘TB antigen tube’ that contain three synthetic TB antigens, a ‘nil control tube’ and a ‘positive control tube’ that contains mitogen).

Interpretation of QFT-G IT results

When interpreting a person’s QFT-G IT result, the person’s risk of developing active TB disease (see Table 8.2) should be taken into account in addition to the test result itself.

<table>
<thead>
<tr>
<th>Practice points</th>
</tr>
</thead>
<tbody>
<tr>
<td>A QFT-G IT can be positive (which means that infection with <em>M. tuberculosis</em> is likely), negative (infection is unlikely) or indeterminate (the test cannot be interpreted).</td>
</tr>
<tr>
<td>If a QFT-G IT is positive, the person should be investigated further (as for a positive Mantoux test).</td>
</tr>
<tr>
<td>If a QFT-G IT is negative or indeterminate and:</td>
</tr>
<tr>
<td>• the person is asymptomatic and not immuno-compromised, no further action is required</td>
</tr>
<tr>
<td>• the person is symptomatic or immuno-compromised, the person should be investigated further (as for a positive Mantoux test).</td>
</tr>
</tbody>
</table>

An indeterminate QFT-G IT result means that the test cannot be interpreted (‘test failure’). Indeterminate results may be due to laboratory error, a low mitogen response or a high background response. If a person has an indeterminate result, it may be worthwhile repeating the QFT-G IT once, or a Mantoux test can be done. Indeterminate QFT-G IT results are more common in immuno-compromised people. See Chapter 11 for further technical details regarding the interpretation of QFT-G IT.

Selected literature on IGRA

Cost-effectiveness studies

A number of studies looking at the cost-effectiveness of IGRAs (mostly looking at QuantiFERON-TB Gold or QFT-G) have been published. One Canadian study concluded that, as long as screening was targeted at people at high risk of TB disease, QFT-G was cost-effective when used to test TST-positive persons, while another study concluded that implementation of QFT-G as a confirmatory test for TST-positive individuals could significantly reduce the number of people given LTBI treatment in a low-incidence country such as Canada. A third Canadian study concluded that the
most cost-effective strategy was to use QFT-G in BCG-vaccinated contacts and to use TST for all others, although when the assumptions were altered to include a higher prevalence of recent infections and greater adherence to LTBI treatment, QFT-G became cost-effective in more subgroups. Studies from France and Germany concluded that the use of QFT-G alone was more effective in reducing the number of TB cases and more cost-effective than QFT-G followed by confirmatory TST.

Screening immigrants and asylum seekers

Several studies looked at IGRA use in screening immigrants and asylum seekers. Positive IGRA results in immigrants who were close contacts of smear-positive cases may have reflected TB exposure in their country of origin many years before, rather than infection due to recent exposure. A Norwegian study of asylum seekers found that 43% less asylum seekers needed referral for positive tests if QFT-G was used. A UK study in immigrants from high TB burden countries found that QFT-G testing followed by CXR was feasible, was cheaper than using the NICE guideline (which recommends IGRA following a positive Mantoux test) and identified more cases of LTBI.

Predicting the development of TB disease

A study of the prognostic value of IGRA.s looked at whether the QuantiFERON-TB Gold In-tube assay (QFT-G IT) was better than the TST at predicting the development of active TB disease in 601 recently exposed close contacts of infectious TB cases over a two-year follow-up period. Of the contacts, 40.4% were TST positive at a 5 mm cut-off, while only 11% were QFT-G IT positive. QFT-G IT positivity, but not TST, was associated with exposure time (p < 0.0001). The progression rate to TB disease within the two-year follow-up period amongst untreated contacts was only 2.3% (five of 219 contacts) of those who were TST-positive. This was a significantly lower progression rate compared with the 14.6% (6 of 41 contacts) of those who were QFT-G IT positive who progressed to TB disease (p < 0.003). The conclusion was that QFT-G IT appears to be a more accurate indicator of the presence of LTBI than the TST and is at least as sensitive for detecting those who will progress to active TB disease.

8.2 Treatment

LTBI is treated to prevent the future development of TB disease. Effective treatment is available for LTBI.

8.2.1 Who should be offered treatment for LTBI

Treatment should be offered to those people with LTBI who are at high risk of developing TB disease. Refer to sections 8.1.1 and 8.1.2 above, and see practice points and text below.

Practice points

The following groups of people should be offered treatment for LTBI:

- People likely to have been infected recently (see Table 8.1)
- People who have an increased risk of developing active TB disease (see Table 8.2)
Within the high risk groups in Tables 8.1 and 8.2, the following people with LTBI should be offered treatment as a priority:

- Mantoux- or IGRA-positive people living with HIV
- children under five years of age who are close contacts of any pulmonary or laryngeal TB case (commence treatment irrespective of initial Mantoux reaction; reassess eight weeks after last exposure)
- Mantoux- or IGRA-positive close contacts of pulmonary or laryngeal TB cases.

The Centers for Disease Control and Prevention’s Targeted tuberculin testing and treatment of latent tuberculosis infection is a useful reference document. It contains several useful tables, one showing the incidence of active TB in people with positive TST, by selected risk factors, and another showing relative risk for developing active TB, by selected clinical conditions, compared to a control population.1

HIV infection

See Chapter 6. HIV infection is the greatest single risk factor for developing TB disease. About 30% of people with HIV who have untreated LTBI will develop active TB disease at some stage during their life. Treatment of LTBI reduces the risk of active TB in HIV-positive individuals, especially in those with a positive TST.64

Children under five years of age

The risk of developing TB disease after infection is inversely associated with age. In children, the risk of developing TB disease after infection is as high as 40% in infants under one year of age,14 and disease can develop within weeks of infection.65,66

Therefore all children under five years of age who are close contacts of pulmonary or laryngeal TB cases, regardless of the child’s initial Mantoux reaction and the TB case’s smear status, should be referred promptly to a paediatrician.

If the first Mantoux test is positive, a child under five should receive treatment for LTBI.

If a child under five is Mantoux-negative, preventive treatment for possible LTBI should be given for eight weeks, when a second Mantoux test should be done. If the Mantoux converts (an increase of 10 mm or more), a repeat CXR should be considered at that time (to exclude the possibility of active TB disease) and treatment should be continued until complete. If the Mantoux reaction increases between tests by less than 10 mm (ie, does not meet the criteria for conversion), the paediatrician should consider continuing treatment until complete (especially in children under two years of age). If the Mantoux test remains negative, treatment should be stopped and a BCG vaccination should be offered.

If, during the eight weeks between the first and second Mantoux tests, pulmonary specimens from the presumed source case are found to be culture-negative, treatment may be discontinued immediately. The second Mantoux test should still be performed, but it is extremely unlikely that it will convert if the case is culture-negative.
Children aged under five who are not close contacts (ie, are casual contacts) of pulmonary or laryngeal cases should be referred to a specialist only if their Mantoux test is positive on either the first or the second test.

Close contacts of infectious pulmonary or laryngeal TB cases

If they become infected, close contacts of infectious (smear-positive or culture-positive) pulmonary or laryngeal TB cases are at increased risk for developing TB disease, especially within the first one to two years following infection. Therefore Mantoux- or IGRA-positive close contacts should be offered treatment for LTBI. Investigation and follow up of contacts of TB cases is the responsibility of the local public health service.

Medical conditions and immuno-suppressive treatments

Various medical conditions and immuno-suppressive treatments increase the risk for developing TB disease following infection (see Table 8.2). Specialists who test their high risk patients for LTBI should do so with the intention to treat, and should have a clear plan for follow up, monitoring adherence and monitoring for side effects (see sections 8.2.3 and 8.2.5).

Renal failure

People who are on renal dialysis or are recipients of a renal transplant are at increased risk of developing TB disease (10–25 times greater risk than the general population). Treatment for TB disease in these patients is usually curative, but a higher risk of mortality has been noted for patients on dialysis compared with other TB patients.

In New Zealand many people with renal failure belong to ethnic communities that also have relatively high rates of TB disease, such as Pacific peoples, Māori, and Asian peoples. Therefore, these groups are at risk of LTBI and subsequent TB disease.

Isoniazid treatment of LTBI is well tolerated by renal transplant recipients, but encephalopathy resulting in temporary confusion and convulsions has been documented in uraemic patients.

All patients with chronic renal failure should be tested for LTBI, preferably with an IGRA, and if the test is positive should be considered for treatment of LTBI. Treatment for Mantoux- or IGRA-negative people with renal failure is not recommended, because there is no evidence to support this. However, if the CXR of a Mantoux-negative renal failure patient shows evidence of past, presumably inactive, TB disease, then their clinician should:

- compare with old CXRs, if possible
- investigate for possible active TB disease
- discuss the need for treatment of LTBI or inactive TB disease with a clinical TB expert.
Diabetes

People with diabetes have a 2–4 times greater risk of developing TB disease, compared with non-diabetics, and the risk is probably greater in those who have poorly controlled or insulin-dependent diabetes. A systematic review and meta-analysis of 13 observational studies showed that diabetes was associated with an increased risk of TB (RR = 3.11, 95% CI 2.27-4.26). A large Hong Kong study looking at diabetic control in elderly people found that diabetic subjects with a baseline haemoglobin A1c of < 7% were not at increased risk of TB, but that a three times greater risk of TB was observed in subjects with a baseline haemoglobin A1c of ≥ 7%.84

Many people with diabetes in New Zealand are of Pacific, Māori, and Asian ethnicity. These communities also have relatively high rates of renal disease and TB disease. Therefore individuals from these groups may be at higher risk, due to an increased risk of exposure to TB cases, as well as multiple co-morbidities which increase their risk of subsequent TB disease.

Anti-TNF alpha treatment

Anti-tumour necrosis factor (anti-TNF) alpha treatment is used to treat various rheumatologic, skin and gastrointestinal conditions. People on these drugs are at around five times increased risk of developing TB disease. A higher incidence of TB disease has also been reported with other immunosuppressive and immunomodulatory treatments used in these diseases. Various guidelines are available, which all recommend screening for LTBI, and if an individual is Mantoux- or IGRA-positive, preferably starting treatment for LTBI at least one to two months prior to commencing anti-TNF alpha treatment, or completing LTBI treatment before commencing anti-TNF alpha treatment (although this is often not possible). People on anti-TNF alpha treatment, whether or not they are on LTBI treatment, should be monitored closely for development of TB disease.

Smoking

Several recent meta-analyses found that current smokers, compared with never smokers, have around a 1.8 times increased risk of infection (LTBI), and a 2.6 times increased risk of TB disease, while former smokers have around a 1.6 times increased risk of TB disease. Similar levels of increased risk were described for passive smoking, especially in studies of children and young adults in households of TB patients who smoke.

Situations where LTBI treatment may not be indicated

Mantoux test increases from negative to positive but the increase is less than 10 mm

If the Mantoux reaction increases between tests by less than 10 mm, the change in diameter of induration does not meet the criterion for conversion. There is no evidence to guide a decision in such a situation, but the Tuberculosis Advisory Group of the Ministry of Health recommends that:

- a CXR be done
treatment of LTBI should generally not be given unless there:
- are risk factors for TB infection progressing to disease (ie, a child aged under five, immune-suppressive treatment, or medical conditions associated with immune-suppression (see Table 8.2)
- has been close contact with a smear-positive pulmonary case.

Immigrants from high-incidence countries

See Chapter 10. Adult immigrants with a normal CXR and no known recent contact with an infectious TB case have probably been infected in the remote past, so are at lower risk of developing TB disease. However LTBI treatment may be considered if medical or other risk factors exist.

Management of previously treated people who are re-exposed

A person who has adhered to a course of treatment for LTBI or TB disease has a very low risk of later developing TB disease. Protection comes from the treatment and from innate and acquired resistance. However, it is possible to develop disease a second time following re-infection with TB. People who are re-infected cannot be distinguished by a Mantoux test or IGRA because these tests will be positive from their earlier episode of infection. Therefore repeat Mantoux or IGRA testing is not advised after re-exposure, and assessment must be with CXR. Re-treatment should be considered. Re-treatment is needed only for those who have been close contacts of a smear-positive case and have risk factors for progression to TB disease (see Table 8.2).

Deciding whether to treat LTBI

The decision to treat must be a joint one by the patient and the doctor (as well as the public health nurse, if the patient is a contact of a TB case).

Practice points

The decision to treat may be guided by the answers to the following four questions:
- How likely is the person to have been infected? (see Table 8.1)
- How likely is the person to progress to active TB disease? (see Table 8.2)
- What are the risks of an adverse reaction to treatment? (see section 8.2.2)
- How likely is the person to adhere to treatment? (see Chapter 4)

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 conversion, the risks of infection and progression to disease are high and a directly observed nine-month or even 12-month course of isoniazid is appropriate. It is much less likely that treatment would benefit a Mantoux-positive, foreign-born migrant with a normal CXR who has been in New Zealand for many years or a healthcare worker with
presumed LTBI discovered during routine pre-occupational Mantoux or IGRA screening. Prior BCG vaccination and its possible effect on Mantoux status should also be taken into account.45,94

Chest X-ray prior to starting treatment

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 (eg, a small scar or patch of calcium; see Table 2.1 in Chapter 2).

### Practice points

In a person with LTBI, the CXR is normal, or shows trivial and stable evidence of past TB (eg, a small scar or patch of calcium; see Table 2.1 in Chapter 2).

People with radiological evidence of active or inactive TB disease should not be treated for LTBI, and require further investigations (see section 8.2.2, and Table 2.1 in Chapter 2).

8.2.2 LTBI treatment contraindications and precautions

In LTBI, treatment is being given to a well, asymptomatic person, so a lower level of risk is acceptable.

### Practice points

People with clinical or radiological or laboratory evidence of active or inactive TB disease should not be treated for LTBI.

There is 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 the benefits of LTBI treatment need to be assessed carefully, when deciding whether or not to treat:

- a pregnant woman
- a person who has acute or chronic liver disease
- a person who is taking concurrent medications that can cause hepatotoxicity
- a person with a high alcohol intake or alcohol abuse, especially if they are not willing/able to stop or reduce their intake
- a person who is unlikely to adhere to treatment and/or to monitoring (clinical and/or laboratory)
- a person who has peripheral neuropathy, or risk factors for its development (eg, diabetes, chronic renal failure, alcohol abuse or malnutrition).
Clinical, radiological or laboratory evidence of tuberculosis disease

Treatment for LTBI is contraindicated if there is clinical, radiological or bacteriological evidence of active or inactive (old, healed) TB disease. Prompt investigation is needed to assess whether the disease is active or inactive (see Table 2.1 in Chapter 2 for radiological criteria for induced sputum testing or bronchoscopy), and if treatment is needed, full multi-drug treatment should be given.

Close contacts of MDR-TB cases

A 2006 Cochrane review (updated to 4 March 2009) of drugs for preventing TB in people at risk of MDR-TB found no randomised controlled trials (RCTs) that met the inclusion criteria. The conclusion was that the balance of benefits and harms associated with treatment of LTBI in people exposed to MDR-TB was far from clear. The World Health Organization (WHO) does not recommend the universal use of second-line drugs to treat LTBI in contacts of MDR-TB cases. One prospective cohort study found individualised tailored treatment to be effective in preventing active TB in children.

Outside the context of a well-designed RCT, drug treatments should only be offered to contacts of MDR-TB cases where they are informed of the current evidence on benefits and harms, along with the uncertainties.

It is important to note that those contacts of MDR-TB cases who have been assessed as requiring treatment with second-line drugs, as well as those contacts who are not treated but who are at high risk of progression to TB disease, should be managed by or co-case managed with a hospital specialist experienced in the treatment of MDR-TB cases and contacts of MDR-TB. Contacts started on drug treatment should be monitored very carefully for adverse effects, due to the toxicity of second-line TB drugs. All contacts should be educated about the need for lifelong awareness of the symptoms and signs of active TB disease, and should be monitored closely for at least two years.

Pregnancy and breastfeeding

Treatment of active TB disease is justified in pregnancy but treatment of LTBI is more controversial. Treatment of LTBI in pregnant women is usually delayed until after the birth of the baby, except in HIV-positive pregnant women or documented recent LTBI infection, where the risk of progression is high (eg, a documented conversion or Mantoux test of 15 mm or more after exposure to a smear- or culture-positive case). Isoniazid or rifampicin may be used for LTBI treatment in pregnant or breastfeeding women. Pregnant or breastfeeding women taking isoniazid should also receive pyridoxine (vitamin B6).
Acute and chronic liver disease

Treatment of LTBI is not contraindicated in hepatitis B surface antigen-positive carriers who have no evidence of active liver disease, or in people with hepatitis C. However, they may be more likely to develop hepatotoxicity, and hepatitis B e antigen positivity (HBeAg) represents an important risk factor for severe isoniazid hepatitis. Frequent monitoring of liver function is indicated (see Chapter 3).

Treatment of LTBI may need to be considered in a person who has acute liver disease and a high risk of TB infection progressing to disease after they have had close and prolonged contact with a highly infectious TB case; especially if the contact is receiving immuno-suppressive treatment.

Age

Isoniazid hepatotoxicity increases with age and underlying disease. However, United States and Canadian guidelines recommend no age limit for treatment of LTBI because the risk of severe or fatal hepatotoxicity is considered low, even in those aged over 35, and if testing and treatment are targeted at those at high risk, the risk-benefit ratio is acceptable. However, the elderly have fewer years left in which to benefit from treatment. The UK National Institute for Health and Clinical Excellence (NICE) TB guidelines do not recommend treatment for those aged over 35 years.

Rifampicin also carries a small risk of hepatotoxicity, but the risk does not appear to increase with age. See Chapter 3 for further details regarding adverse reactions associated with TB medications.

Age over 35 years should not be a contraindication to treatment for LTBI, if the clinical indications are strong, but closer monitoring of people over 35 years of age is probably advisable.

8.2.3 Who should prescribe treatment and follow up for LTBI

Prescribing

Treatment of LTBI is a specialised task. In New Zealand, TB medications may only be prescribed by specialist medical practitioners (eg, respiratory physicians, infectious diseases physicians, renal physicians, paediatricians, occupational health physicians). Specialists who treat LTBI should have knowledge and experience in this area. General practitioners (GPs) should consult with an appropriate specialist if they have identified a patient who has LTBI, is at high risk of developing TB disease (see Table 8.2) and who would therefore benefit from LTBI treatment.

Follow-up

Careful follow-up of people on LTBI treatment is essential, and is the responsibility of the prescribing clinician. See section 8.2.5 on practical considerations in treating LTBI, including patient education, recommended baseline laboratory tests, and ongoing monitoring of adherence and for adverse effects.
Most public health units do not have the capacity to offer follow-up for high risk patients diagnosed with LTBI who are not contacts of active TB disease cases. Follow-up of non-contacts prescribed LTBI treatment is therefore the responsibility of the prescribing clinician. Investigation and follow up of contacts of TB cases notified to the medical officer of health is the responsibility of the local public health service’s medical and public health nursing staff.

### 8.2.4 LTBI treatment regimens

Note re abbreviations in this section: the commonly accepted abbreviations for TB drugs are used ie, isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E). A number before a capital letter refers to the number of months of daily treatment in that regimen eg, 3RH means three months of daily rifampicin and isoniazid. The terms used to describe study types and results include randomised controlled trial (RCT), relative risk (RR) and confidence interval (CI).

#### Practice points

The choice of drug regimen for treatment of LTBI in an individual depends on:
- the presence or absence of risk factors for progression to TB disease (Table 8.2)
- assessment of the individual’s likely level of adherence to treatment
- whether there are time constraints (ie, need for a short course)
- the antibiotic susceptibility of the presumed source case (if known)
- whether the individual is likely to tolerate the drug(s).

Recommended drug regimens for treatment of LTBI are shown in Table 8.4.

Drug doses, pharmacological considerations and side effects are discussed in Chapter 3.
### Table 8.4: Recommended drug regimens for treatment of LTBI

<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>

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

* 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.95 One prospective cohort study found individually tailored regimens to be effective in preventing active TB in children.96

### Efficacy of LTBI treatment regimens in HIV-negative people

#### Isoniazid

A Cochrane review of treatment of LTBI in HIV-negative people included 11 randomised trials (with a total of 73, 375 participants) comparing isoniazid versus placebo.63 This review showed that in HIV-negative individuals, treatment of LTBI with isoniazid for six to 12 months prevents the development of TB disease (RR 0.40, 95% CI 0.31 to 0.52) and reduces deaths from TB disease, but does not reduce all-cause mortality. The number needed to treat (NNT) to prevent one case of TB disease was 100 overall. Efficacy and NNT vary, depending on an individual’s risk of progression to TB disease. In this review, durations of isoniazid of longer than six months (RR 0.38, 95% CI 0.28 to 0.50 for 12 months) had little additional benefit, compared with a duration of six months (RR 0.44, 95% CI 0.27 to 0.73).

The UK National Institute for Health and Clinical Excellence (NICE) TB guidelines recommend 6H (or 3RH) for HIV-negative adults and children.25

The recommended standard treatment regimen for LTBI in HIV-negative people in the USA and Canada is 9H.1,42

### Contacts of isoniazid-resistant cases

For contacts of isoniazid-resistant TB cases, rifampicin is usually used to treat LTBI.98 However, evidence is sparse in this area.
In the USA and Canada, the recommended regimen for contacts of isoniazid-resistant TB cases is 4R.\textsuperscript{1,42}

The NICE TB guidelines recommend 6R for contacts aged 35 years or younger of isoniazid-resistant TB cases.\textsuperscript{25}

A recent modelling study considered the rate of isoniazid resistance at which a rifampicin-containing regimen should be used for LTBI treatment in immigrant children originating from countries where isoniazid resistance is common.\textsuperscript{101} The study concluded that rifampicin should be considered for treatment of LTBI in children originating from countries which have > 11% isoniazid resistance.

**Short course regimens**

Overall, short course regimens using R or RH have better adherence, better completion rates, similar or fewer serious side effects, and are cost-effective.

However, large scale prospective studies of short course regimens are needed, with extended post-treatment follow up, to clarify the long-term rate of development of active TB disease following short course treatment of LTBI with R or RH, compared with standard isoniazid treatment.

The risk of development of acquired rifampicin resistance following LTBI treatment with rifampicin-containing regimens also requires study.\textsuperscript{98}

**Rifampicin plus isoniazid regimens (3RH and 4RH)**

The NICE TB guidelines recommend 3RH as an alternative to 6H for HIV-negative adults and children.\textsuperscript{25}

A meta-analysis of five trials comparing 3RH with H (for 6 to 12 months) included a total of 1926 adults with average duration of follow up between 13 to 37 months.\textsuperscript{102} The study concluded that 3RH and standard isoniazid regimens of 6 to 12 months duration were equivalent in terms of efficacy and safety.

A 1998 UK study conducted in one health district showed that no child notified with TB disease in the period 1987 to 1996 (the period during which shorter three and four month RH regimens were introduced) had received prior treatment for LTBI.\textsuperscript{103} No children needed to have treatment stopped due to adverse effects. A randomised controlled study of treatment of LTBI in children compared 9H with 4RH and also compared 3RH with 4RH.\textsuperscript{104} Follow-up was for a minimum of three years. The study concluded that 3RH and 4RH were as effective and safe as 9H, and were associated with much better adherence than 9H.

In tuberculin-positive people with silicosis in Hong Kong, treatment regimens 3RH, 3R and 6H were shown to have similar efficacy and were all effective compared with placebo.\textsuperscript{105}
Rifampicin regimen (4R)

In the USA and Canada, 4R is considered an acceptable alternative to isoniazid when a shorter regimen is needed, or for people who cannot tolerate isoniazid.\(^\text{1,42}\)

A recent meta-analysis of 4R versus 9H included four studies (including two RCTs and two non-randomised studies) with pooled data from a total of 3586 patients.\(^\text{106}\) Compared with 9H, treatment with 4R was associated with better compliance, showing a significant reduction in the risk of non-completion (RR 0.53, 95% CI 0.44 to 0.64). The 4R regimen was associated with significantly less hepatotoxicity than 9H (RR 0.12, 95% CI 0.05 to 0.30) and was more cost-effective. The authors noted that a large trial was needed to define the risks of TB disease among people who received 4R.

Rifampicin plus pyrazinamide (2RZ) is no longer recommended

The 2RZ regimen has been shown to be as effective as isoniazid in both HIV-negative and HIV-positive people,\(^\text{107}\) but is no longer generally recommended due to an unacceptably high rate of severe hepatotoxicity.\(^\text{108}\)

Efficacy of LTBI treatment regimens in HIV-positive people

Isoniazid

See the treatment of LTBI section in Chapter 6. A Cochrane review of LTBI treatment in HIV-infected people showed that treatment of LTBI with any regimen was associated with a reduced risk of developing active TB (RR 0.68, 95% CI 0.54 to 0.85).\(^\text{64}\) The benefit was more pronounced in Mantoux-positive individuals (RR 0.38, 95% CI 0.25 to 0.57). Efficacy was similar for all regimens, regardless of drug type, frequency or duration of treatment. However, compared to isoniazid monotherapy, short-course multi-drug regimens in HIV-positive people had more adverse effects requiring discontinuation of treatment. Isoniazid does not have any significant interactions with anti-retroviral therapy.

The recommended standard treatment regimen for LTBI in HIV-positive people in the USA and Canada is 9H.\(^\text{1,42}\)

The NICE TB guidelines\(^\text{25}\) recommend 6H (rather than 9H) for HIV-infected people of any age, based on the results of the Cochrane review.\(^\text{64}\)

Contacts of isoniazid-resistant cases

In the USA, for contacts of isoniazid-resistant TB cases (both HIV-positive and HIV-negative), the recommended regimen is 4R.\(^\text{1}\)

The NICE TB guidelines recommend 6R for contacts aged 35 years or younger of isoniazid-resistant TB cases.\(^\text{25}\)
Short course regimens

The 2RZ regimen has been shown to be effective in HIV-infected people, but as mentioned above, is no longer generally recommended due to an unacceptably high rate of severe hepatotoxicity.

Other short course regimens only appear to be recommended in HIV-positive people who are contacts of isoniazid-resistant TB cases (4R or 6R, see above).

Hepatotoxicity

The three TB drugs most likely to cause hepatotoxicity, which may result in drug-induced liver injury (DILI), are isoniazid, rifampicin and pyrazinamide.

Isoniazid hepatotoxicity is age related, occurring more frequently with increasing age. Elevated baseline transaminases and excessive alcohol consumption are other risk factors for hepatotoxicity. A literature review found limited data suggesting an association between chronic viral hepatitis infection (hepatitis B and hepatitis C) and isoniazid-associated hepatotoxicity during LTBI treatment (although there is substantial evidence suggesting an association in people treated for TB disease with isoniazid-containing multi-drug regimens).

The 2RZ regimen is no longer generally recommended due to an unacceptably high rate of severe hepatotoxicity.

Studies have found RH regimens to be as safe as isoniazid regimens in adults (3RH) and in children (3RH and 4RH).

A meta-analysis found that 4R was associated with significantly less hepatotoxicity than 9H.

Cost-effectiveness

The cost-effectiveness of treatment for LTBI, if treatment is targeted towards people at high risk of developing TB disease, compares favourably with that of other medical interventions.

Six months is probably the most cost-effective duration of treatment for isoniazid.

4R is more cost effective than 9H.

Impact of LTBI treatment on antibiotic susceptibility of tuberculosis

Concern that single drug treatment for LTBI might generate drug-resistant strains does not seem to have occurred, but this issue requires further study.

In New Zealand, isoniazid LTBI treatment regimens have been used for 30 years, but the rate of isoniazid resistance among New Zealand-born TB cases has not increased (see Chapter 1).
8.2.5 Practical considerations in treating LTBI

Baseline investigations including HIV status

All adults (and children who are considered at risk of HIV) should be tested for their HIV status when being considered for LTBI treatment, since HIV-positive people require a longer course of treatment (9H) and more treatment supervision than HIV-negative people.

Other recommended pre-treatment baseline tests in adults include haematology, creatinine, alanine amino-transferase (ALT) followed by full liver function tests (LFTs) if elevated, hepatitis B and hepatitis C serology. Children have a lower risk of hepatotoxicity from TB drugs than adults, therefore baseline tests may not always be needed.

Education

Patient education (using interpreters and written translations if needed) should include:
- the difference between TB disease and LTBI
- that LTBI is not infectious to others
- the possible adverse effects of treatment (including written information about the symptoms of hepatotoxicity and other adverse effects)
- timing for monitoring visits and blood tests
- the contact person/contact details if the patient needs further advice.

Alcohol and smoking

Patients should be advised that drinking alcohol is an important risk factor for hepatotoxicity, and that they should abstain from alcohol while taking drugs for LTBI.

Smokers should receive advice and be supported to stop smoking, as per the Ministry of Health’s New Zealand Smoking Cessation Guidelines.115

Communication with the patient’s usual doctor

When prescribing treatment for LTBI, the prescribing clinician should advise the patient’s doctor (usually the GP) in writing of the indications, drug(s), dosage and duration of treatment, and the management of adverse reactions and potential drug interactions, including the potential for hepatotoxicity. See Chapter 3 for further details regarding adverse reactions associated with TB medications.

Follow-up and monitoring for adverse effects and for adherence

Follow-up should be face to face, and at monthly intervals (or more frequently if necessary, for example if there are adverse effects). Monthly follow-up of contacts with LTBI being treated by public health services is usually done by public health nurses. Follow up of non-contacts prescribed LTBI treatment is the responsibility of the prescribing clinician.
Prescriptions should be issued for one month at a time to ensure monthly face to face follow-up.

To prevent symptoms and signs of peripheral neuropathy in patients on isoniazid or isoniazid-containing LTBI regimens, 25 mg of pyridoxine daily should be prescribed for all adults, including pregnant women and mothers of fully breastfed infants. Breastfeeding infants who are on isoniazid should be prescribed pyridoxine, even if their mother is also taking it. The following groups of children may also need to take pyridoxine: older (ie, adult-sized) children and adolescents, those who develop paraesthesia, those with poor nutritional status and those with co-morbidities that may increase the risk of pyridoxine deficiency (seizure disorders, diabetes, uraemia, HIV).

At each follow-up visit patients should be asked about symptoms and signs of adverse effects and reminded to abstain from alcohol.

Patients should be reminded that it is essential to stop their LTBI drug(s) at the first symptom or sign of a possible adverse effect, and then to contact their prescribing clinician or GP immediately for further advice, as urgent LFTs are indicated. Severe liver injury may occur if LTBI treatment is continued in the presence of symptoms, and patients must not wait for signs such as jaundice to occur before stopping their drugs.

Symptoms and signs of possible hepatotoxicity for which patients should be alert include loss of appetite, nausea, vomiting, abdominal discomfort or pain, and unexplained fatigue or feeling generally unwell (symptoms), jaundice and dark urine (signs).

In people being treated for LTBI, monitoring of LFTs should generally be done at baseline, one month after starting treatment, and then every second month in people without risk factors for hepatotoxicity. In people with risk factors for hepatotoxicity, LFTs should be done monthly (or more frequently if necessary). See Chapter 3.

Efficacy of LTBI treatment is affected by both duration of treatment and adherence to the treatment regimen. Chapter 4 discusses how to improve adherence.

**Threshold for stopping LTBI treatment due to hepatotoxicity**

If AST or ALT reach three times the upper limit of normal consult with a clinical TB expert. If the patient has no symptoms, treatment can usually be continued, but the patient should be closely monitored. Re-check for symptoms and repeat LFTs three to four days later. In an asymptomatic person, with very close monitoring, AST or ALT may be allowed to rise up to five times the upper limit of normal.

If AST or ALT reach three times the upper limit of normal, and the patient has symptoms, treatment should be stopped. When LFTs have normalised, treatment with a different drug can be considered, with very close monitoring.

If ALP or GGT exceed twice the upper limit of normal, treatment should be stopped. When LFTs have normalised, treatment with a different drug can be considered, with very close monitoring.
Antibiotic susceptibility of source case

The antibiotic susceptibility of the presumed source case must be established (where possible). If the person with LTBI has been started on treatment before the antibiotic susceptibility of the source case is known, their regimen may need to be changed.

If the regimen needs to be changed, it should be started from scratch (ie, the period during which the contact took the ineffective drug should not be counted).

The most common scenario necessitating a change in the LTBI regimen is a source case who is found to be isoniazid-resistant, in which case isoniazid should be stopped and 4RH should be started.

Search for a source case

When a child is diagnosed with LTBI, there must be an urgent search for the presumed source case, if they have not already been identified. The child’s immediate family or household should be assessed for symptoms and signs of active TB disease.

Changing regimens because of adverse effects

If a patient’s regimen is changed because of side effects or adverse effects from the first agent given, the whole period of treatment on the first agent counts toward the eradication of LTBI and a lesser period is needed on the second regimen.

Ending treatment

Treatment should be extended for the appropriate length of time to compensate for all missed doses/missed weeks on treatment.

For adults, an end-of-treatment CXR is needed only if the pre-treatment CXR was abnormal. Most children will need an end-of-treatment CXR because subtle radiological changes are more often seen in children and they are at higher risk of undetected progression to TB disease than adults.

The patient should be given a written record of their Mantoux test or IGRA result, the LTBI treatment they received, and a reminder of the need for lifelong awareness of the symptoms and signs of TB.

If treatment is not given

If treatment is contraindicated, declined or considered inappropriate (eg, because of likely non-adherence), the patient and their GP should be alerted to the risk of future TB disease.

Routine CXR monitoring of people with LTBI who are not treated is not recommended.
Monitoring with CXRs over two years is recommended for some untreated IGRA- or Mantoux-positive people, including:

- children aged under five who are close contacts of smear- or culture-positive cases
- HIV-positive contacts
- contacts of MDR-TB source cases
- people with inactive fibrotic scars on the CXR.

Reporting LTBI under treatment to the medical officer of health

Although LTBI is not notifiable, if a clinical decision is made to offer treatment to a person with LTBI, the treating clinician should seek the person’s consent to report them as a case of ‘LTBI under treatment’ to the local medical officer of health. No public health action is required, but the case details are entered into the national surveillance database so that LTBI trends can be monitored.

References


29 Voss L. 2010. Personal communication.


Guidelines for Tuberculosis Control in New Zealand 2010

Chapter 8: Diagnosis and Treatment of Latent Tuberculosis Infection


Chapter 9: Tuberculosis Control in Correctional Facilities

Summary

Correctional facilities or prisons are an important reservoir of tuberculosis (TB) infection in most parts of the world. In many countries, including New Zealand, there are reports of disproportionately high rates of TB disease in prisons. These guidelines recommend that all inmates be screened for active TB disease on entry into a correctional facility. Identification and treatment of cases of latent TB infection (LTBI) could be applied as a TB strategy in correctional facilities. Directly observed therapy is essential for all treatment of LTBI or TB disease in correctional facilities.

9.1 Tuberculosis rates and risk factors

Correctional facilities or prisons are an important reservoir of TB infection in most parts of the world, but particularly in countries that have a high incidence of TB.

Overcrowding, poor hygiene and inadequate ventilation may contribute to the spread of infection.

Factors common to the inmates of correctional facilities may predispose this population to TB infection and disease. These factors include:

- high representation of people from low socioeconomic backgrounds
- high rates of substance abuse
- underlying poor health or nutrition
- an over-representation of Māori and Pacific peoples, who have higher rates of TB.¹

Prison incarceration was linked to an outbreak of TB in the North Island in 1999.² The outbreak highlights the public health consequences of TB in this setting. Cases of MDR-TB from correctional facilities have not been reported in this country, but contribute a large proportion of cases in other countries.³⁴

9.2 Screening of inmates in correctional facilities

The purpose of screening is to identify people who have active TB disease, and sometimes also latent TB infection (LTBI). CDC and WHO guidelines recommend that all inmates be screened on entry into a correctional facility.⁵⁶
9.2.1 Recommended minimum process

Figure 9.1 shows a recommended minimum process for TB screening of inmates on their entry into correctional facilities, based on current practice in New Zealand, which is screening by symptom questionnaire, history and examination, looking for active TB disease cases only.

![Figure 9.1: Recommended minimum TB screening of inmates on entry into correctional facilities](image)

* Cough for more than three weeks, haemoptysis, fever, sweats.
** History, physical examination and chest X-ray.

9.2.2 Symptom and history inquiry

Inmates should be asked for symptoms of active tuberculosis including cough, fever and weight loss. Chronic cough is common in the prison population due to high rates of smoking.

History should include: active TB disease, family history of TB and other contact history. Any previous investigations of treatment for TB disease or LTBI should be documented.

9.2.3 Physical examination

A thorough medical examination should be undertaken if the history suggests possible TB disease.

9.2.4 Chest X-ray

A CXR should be requested, if the symptom inquiry is suspicious for possible TB disease or for those with a positive Mantoux test or IGRA. CXRs suggesting the possibility of TB should be discussed promptly with an appropriate hospital specialist, without awaiting results of sputum culture for TB.

9.2.5 Mantoux test or interferon gamma release assay (IGRA)

In the USA, all prison inmates with previously negative Mantoux or IGRA tests are screened for LTBI on entry to correctional facilities and then re-screened periodically, usually on an annual basis. Inmates with LTBI who are at high risk for development of active TB disease are offered LTBI treatment.
In New Zealand, prison inmates are not currently screened for LTBI, either on entry into correctional facilities or periodically. However, if screening for LTBI in inmates is considered in future, either a baseline two-step Mantoux test or IGRA (see Chapter 8) should be undertaken for all inmates entering long-term correctional facilities who do not have a documented history of a positive test. Testing may not be possible for short-stay inmates.

Mantoux or IGRA test results should be recorded in the inmate’s medical records and be accessible on any transfer. Positive tests should be highlighted in the inmate’s medical records, so that a high index of suspicion is always maintained for the development of active TB disease. If resources allow, inmates with LTBI who are at high risk for development of active TB disease should be offered LTBI treatment (see Chapter 8).

9.3 Treatment of TB cases in correctional facilities

There is a higher rate of treatment failure in TB cases in correctional facilities.\(^7\) Short duration of incarceration and a high turnover rate in institutions are major factors.

Refer to the Ministry of Health’s *Tuberculosis Case Management in Prisoners*, which is a joint protocol for corrections facilities and TB treatment supervising services (usually the public health service in most regions of New Zealand, but occasionally the clinical TB service).\(^8\)

Successful treatment requires:
- directly observed therapy for all cases of TB
- close liaison between prison medical staff, specialists and public health authorities
- completion of treatment.

When prisoners are released into the community, appropriate transfer of responsibility must be made to the medical officer of health and District Health Board in the area where the patient will be residing.

The involvement of a probation officer or social worker may assist follow-up and completion of treatment.

9.4 Treatment of LTBI in correctional facilities

The identification and treatment of cases of LTBI is an important TB control strategy, see Chapter 8. However, adherence rates to courses of isoniazid are low in prisoners with LTBI and a minority continue with treatment after discharge.\(^9\) Adherence within a month of discharge has been as low as 3%.\(^10\) Regular education and incentives can improve follow-up rates when cases leave prison on isoniazid, although only regular education has been shown to improve the rate of completion of therapy.\(^11\)

However, for long-term inmates with LTBI who are at risk of developing TB disease, there is a good opportunity for effective treatment. It is recommended that directly observed therapy (DOT) be used for treating LTBI in prisons (see Chapter 4).
If screening for LTBI in inmates is considered in future, prisoners with LTBI who are at high risk of developing TB disease should be considered for treatment of LTBI. In this case, additional resources will probably be necessary for prison services to effectively screen for LTBI and to administer LTBI treatment.

The prison-related groups who should be targeted for treatment of LTBI are:
- the contacts of prisoners with sputum smear-positive pulmonary TB
- HIV-infected prisoners
- infants of imprisoned mothers with pulmonary TB.

9.5 Infection control in correctional facilities

See Chapter 12, section 12.7, and the Ministry of Health’s *Tuberculosis Case Management in Prisoners.* An infectious TB case should immediately be transferred to a hospital with a negative-pressure isolation room (an airborne infection isolation room) until they have completed at least two weeks of appropriate anti-TB treatment.

All staff in correctional facilities should be familiar with the infection control policy for that institution. This policy should include how to access N95 particulate respirators should infectious TB be suspected in an inmate.

9.6 Occupational health in correctional facilities

Healthcare workers (HCW) working in correctional facilities should undergo the same screening processes as HCW in healthcare settings (see Chapter 12, section 12.6 and section 12.7).

9.7 Contact investigation in correctional facilities

The prison medical service should seek early guidance from the local public health office if a case of TB disease is diagnosed. Contact investigation is a specialised task (see Chapter 7), and contacts within the correctional facility will often be released before their investigation and definitive management is complete.

9.8 Tuberculosis protocols

Protocols for screening and managing TB, including educating prison medical officers and other staff about TB, should be produced for all correctional facilities. If screening for LTBI in inmates is considered in future (see section 9.2.5), a suitable screening protocol should be produced.
References


Chapter 10: Tuberculosis Control in People from Countries with a High Incidence of Tuberculosis

Summary

Tuberculosis is a global problem. In New Zealand, as in other countries with a low-incidence, tuberculosis rates are strongly influenced by migration from high-incidence countries. About 65% of TB cases in New Zealand are foreign-born, and most cases occur in the first five years after arrival. While this may place costs on the New Zealand healthcare system, it does not act as an important source of TB for most New Zealand-born populations.

This chapter summarises the:

- current rates of TB in people from high incidence countries
- immigration screening requirements for TB disease
- current screening and management recommendations for people from high incidence countries with LTBI
- initial steps in investigation of an abnormal immigration CXR
- considerations when deporting people with who may have TB
- recommendations for travellers planning to spend extended time in high-incidence countries.

Finally, the importance of early detection of TB disease is emphasised. General practitioners, particularly those with patients from high-incidence countries, are aware of the need for early detection of tuberculosis, to improve clinical outcomes and limit the spread to others. They should inform new patients from high incidence countries about:

- the need for early investigation of signs and symptoms of TB
- TB is a treatable disease
- treatment of TB in New Zealand is free.

This chapter is intended as a reference for clinicians, public health practitioners and immigration officials who work with people from high-incidence countries.

Introduction

Internationally, migration has a huge impact on the global distribution of tuberculosis. In many low-incidence countries, TB among the foreign-born contributes a substantial proportion of the total number of cases.\(^1\)\(^2\) This chapter briefly summarises the effect of migration on TB in New Zealand and summarises the measures that are used to minimise the impact on New Zealand’s health care system. New Zealand also has a responsibility to contribute to global TB control but this is not covered in this chapter.
10.1  Influence of immigration on tuberculosis in New Zealand

10.1.1  Tuberculosis in foreign-born people in New Zealand

A review of TB notification data from 1995 to 2004 found that TB incidence is not decreasing in New Zealand mainly due to infection of TB infected people from high-incidence countries. During this time, of cases for whom country of birth was known, 64% were born overseas. The numbers of TB notifications were highest within the first year of arrival and decreased substantially in the subsequent years.

Between 2000 and 2004, incidence of TB in New Zealand were over 100 per 100,000 in people born in:
- Ethiopia, Somalia, Zimbabwe
- Afghanistan, Pakistan, India, Cambodia, Laos, Vietnam, Philippines
- Tuvalu.

While this may place costs on the New Zealand healthcare system, it does not act as an important source of TB for most New Zealand-born populations.

10.1.2  Tuberculosis rates in the Pacific region

From 2000–2004, TB incidence in the people born in the Pacific Islands was 42.2 (per 100,000). This compares with the rate in New Zealand born people of 3.9.

New Zealand has a strong interest in the control of TB in Pacific nations because of the increasing Pacific population in New Zealand as well as our proximity, social and economic links, and commitment to development in the region.

10.1.3  Multi-drug resistant tuberculosis (MDR-TB)

From 1995–2004 there were 19 cases recorded of MDR-TB. Eighteen of the 19 cases identified were in people born overseas who were presumed to have acquired the MDR-TB overseas. Although the incidence of MDR-TB is currently low in New Zealand, increasing numbers of MDR-TB cases are likely to be diagnosed in the future, as many migrants to New Zealand come from countries where MDR-TB is much more prevalent than in New Zealand. See Chapters 1 and 3 for more information.

10.2  Immigration screening for TB

10.2.1  Purpose of tuberculosis screening

People intending to travel to New Zealand and stay for a period of more than 6 – 12 months and people wishing to extend their stay (to more than 6 - 12 months) in New Zealand are screened to detect active TB disease, so early, effective medical intervention can be offered. This provides a public health benefit of improved TB control. The application for a temporary visa or residence provides a unique opportunity for screening and may represent one of the few reliable points of contacts for new arrivals.
10.2.2 Immigration New Zealand tuberculosis requirements

Immigration New Zealand requires people intending to stay in New Zealand for more than 12 months to have a medical examination and a chest X-ray (CXR) before they arrive in New Zealand (see Table 10.1). If they are already in New Zealand when they decide to extend their stay, this process is done in New Zealand.

A doctor in New Zealand or, if the examination is conducted in another country, an approved Immigration New Zealand panel doctor must complete the medical and CXR certificate. Completed forms must not be more than three months old when the person lodges their application for entry. If the certificate is more than three months old, the applicant is usually required to submit another examination and CXR. However, once an application for temporary entry has been lodged, the certificate can be used for any entry within two years. A physician in New Zealand examines abnormal CXRs and provides comment on whether or not the person has an acceptable standard of health for entry into New Zealand.

If they are intending to stay more than six months but less than 12 months, people assessed as having risk factors for TB must have a CXR and have a temporary X-ray certificate completed by a radiologist. Risk factors for TB are:

- holding a passport of a country not on the list of low TB prevalence countries
- having spent a total of three months or more in the past five years in a country which is not on the list of low TB prevalence countries.6

Immigration New Zealand cannot require TB screening in:

- people with New Zealand or Australian passports
- people from the Cook Islands, Tokelau and Niue (who hold New Zealand passports)
- children involved in overseas adoptions (who have been granted New Zealand citizenship before arrival).

This is because people travelling on New Zealand passports have an unfettered right of entry to New Zealand and cannot be subjected to immigration screening or controls. People travelling on Australian passports are not subject to normal immigration controls, as they have the right to travel to New Zealand without a visa and remain in New Zealand indefinitely.

Immigration New Zealand does not require TB screening in:

- people who hold Australian permanent residence (who are treated for immigration purposes as though they have New Zealand permanent residence)
- asylum seekers (who are however strongly encouraged to undertake (free) screening, through information provided with the letter sent advising that their asylum claim has been received)
- children under 11 years of age, and pregnant women (unless a CXR is requested by Immigration New Zealand).

Quota refugees are screened for TB offshore and again after arrival in New Zealand (see section 10.2.4).
Table 10.1: Questions in the Immigration New Zealand Medical and Chest X-ray Certificate (INZ 1007), May 2010

<table>
<thead>
<tr>
<th>Section</th>
<th>Question asked</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section B: Medical history of person having</td>
<td>B10: Do you have or have you ever had tuberculosis (TB), an abnormal chest X-ray, chronic cough, coughed up blood, or had close contact with a person with TB?</td>
</tr>
<tr>
<td>the medical examination</td>
<td></td>
</tr>
<tr>
<td>Section D: Medical examination and findings</td>
<td>D6: Are there any abnormalities in the respiratory system (including nose and lungs)?</td>
</tr>
<tr>
<td></td>
<td>D11: Are there any abnormalities in the lymph nodes?</td>
</tr>
<tr>
<td>Section F: Medical examiner’s summary of</td>
<td>Please provide your comments on the history and health of this applicant, especially any areas where you consider follow-up is required. Please note any further tests or investigations that you would recommend.</td>
</tr>
<tr>
<td>findings</td>
<td></td>
</tr>
<tr>
<td>Section K: Results of chest X-ray examination</td>
<td>K4: Hilar and lymphatic glands Normal Abnormal</td>
</tr>
<tr>
<td></td>
<td>K6: Lung fields Normal Abnormal</td>
</tr>
<tr>
<td></td>
<td>K7: Evidence of TB No Yes</td>
</tr>
<tr>
<td></td>
<td>K8: Evidence of old, healed TB No Yes</td>
</tr>
<tr>
<td></td>
<td>K9: Evidence suspicious of active TB No Yes</td>
</tr>
</tbody>
</table>

Source: Immigration New Zealand (2010).7

10.2.3 New Zealand entry requirements

Table 10.2 summarises the medical requirements for the various visas and permits for people entering New Zealand. Immigration New Zealand also reserves the right to ask any person applying for a visa to enter New Zealand to undertake a medical examination and CXR before the visa is issued, even if their stay is for less than 12 months.
Table 10.2: Current Immigration New Zealand visas and medical requirements

<table>
<thead>
<tr>
<th>Visa type</th>
<th>Description</th>
<th>Permitted length of stay</th>
<th>Medical exam and X-ray*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visitor visa</td>
<td>Required for visits to New Zealand unless from a visa waiver country</td>
<td>Nine months in an 18-month period (may be extended for three extra months)</td>
<td>Required if applicant is intending to stay in New Zealand longer than 12 months (medical exam and X-ray), or is intending to stay between 6–12 months if the applicant has risk factors for TB (X-ray)†</td>
</tr>
<tr>
<td>Work visa</td>
<td>Required for those offered employment in New Zealand</td>
<td>Up to three years</td>
<td></td>
</tr>
<tr>
<td>Student visa</td>
<td>Required for study in New Zealand of over three months’ duration</td>
<td>Three months or longer</td>
<td></td>
</tr>
<tr>
<td>Limited purpose visa</td>
<td>Required if entering New Zealand for a specific purpose</td>
<td>No maximum applied – depends on the purpose of visit but is usually brief</td>
<td></td>
</tr>
<tr>
<td>Recognised seasonal employer limited purpose visa</td>
<td>Required if entering New Zealand under the recognised seasonal employer scheme</td>
<td>Up to nine months</td>
<td>Required, regardless of intended length of stay in New Zealand, if the applicant has risk factors for TB (X-ray)†</td>
</tr>
<tr>
<td>Residence visa</td>
<td>Required if wanting to live in New Zealand indefinitely</td>
<td>Indefinite</td>
<td>Required†</td>
</tr>
<tr>
<td>Asylum seeker</td>
<td></td>
<td></td>
<td>Required on application for residence (encouraged beforehand)</td>
</tr>
<tr>
<td>Quota refugee (residence)</td>
<td></td>
<td></td>
<td>Screened before travel and on arrival</td>
</tr>
<tr>
<td>Samoan Quota (residence)</td>
<td></td>
<td></td>
<td>Required before arrival†</td>
</tr>
</tbody>
</table>

* Must be completed before arriving in New Zealand if stay is intended to be at least 12 months, and must be completed in New Zealand if stay is extended to longer than 12 months.
† Applicants must:
- not be likely to be a danger to public health
- not be likely to cause excessive demand on health or special education services
- be fit for the purposes of entry.

Source: Immigration New Zealand (2010).§

10.2.4 Offshore screening of quota refugees

The goal of offshore screening is to diagnose and treat refugees before their travel to and resettlement in another country. An annual quota of refugees is accepted for permanent resettlement in New Zealand, mandated by the United Nations High Commissioner for Refugees (UNHCR). Since 2005, Immigration New Zealand has screened quota refugees for TB and human immunodeficiency virus (HIV) in approved offshore facilities. If found to have infectious TB, entry to New Zealand is delayed while they receive treatment. Quota refugees must still undergo medical examination (including a further CXR) on arrival, at the National Refugee Health Screening Centre, Mangere Refugee Reception Centre.
10.2.5 Communication between countries

Communication between national health authorities and between healthcare providers in different countries is important in the international control of TB.

Under the International Health Regulations 2005, the Ministry of Health in each participating country has a nominated ‘national focal point’. Information on people with tuberculosis who are travelling between countries, or about international contact tracing for people exposed to tuberculosis, should be transferred through this mechanism. In addition it may be necessary for clinicians to communicate directly with treating clinicians in other countries around case management.

10.2.6 TB in people being removed or deported

People who are not entitled to stay in New Zealand may be removed or deported at short notice. Immigration New Zealand officials involved in this process should check whether the person is under investigation or receiving treatment for TB, and should liaise early with the person’s doctor and the local medical officer of health if this is a possibility.

This is for two reasons:
- People with tuberculosis must not travel if they are infectious.
- Arrangements will need to be made between the clinicians and public health services locally and at the destination to ensure continuity of treatment for TB.

10.3 Investigation of abnormal immigration CXRs

Physicians are often asked to investigate a person in whom TB is suspected as a result of a CXR taken for immigration purposes.

10.3.1 ‘Immigration clearance’ for tuberculosis

An ‘immigration clearance’ is often requested for non-New Zealand residents after an abnormality is found on a CXR when a person applies for residence or a temporary entry visa. If the person has had previous multi-drug resistant TB, they should be reviewed by a specialist TB clinician.

Non-residents who are currently in New Zealand and elect to undergo private medical assessment for CXR abnormalities must pay for the ensuing costs, including TB-related costs. However, if the medical officer of health considers the health care services to be compulsory (as defined in the Minister of Health’s gazetted notice 2003 Direction of the Minister of Health regarding eligibility for publicly-funded health and disability services in New Zealand), the cost of investigating and treating TB disease in non-residents is borne by the New Zealand taxpayer.9

‘Compulsory’ services are defined as services the medical officer of health requires a person to undergo under section 9 of the Tuberculosis Act 1948 (for example, if a non-resident with an abnormal CXR suggestive of active TB disease refused to undergo medical assessment and/or further investigations due to inability to pay).
10.3.2 Role of the clinician in an immigration medical

The clinician needs to exclude or diagnose active TB disease, and must also decide if treatment is required for latent TB infection (LTBI) or inactive disease (requiring full preventive treatment).

The clinician must also consider other possible diagnoses (eg, lung cancer, chronic obstructive pulmonary disease or bronchiectasis).

In addition to obtaining the applicant’s history, a recent CXR and physical examination, the investigation may include:
- a Mantoux test or IGRA
- mycobacterial sputum testing
- mycobacterial tests on bronchial specimens.
- other investigations such as a CT scan of the chest.

See Chapter 2 for the more details on investigation of active and inactive TB disease.

10.3.3 Notifying the medical officer of health of cases of active TB

Under the Tuberculosis Act 1948, section 3(1), every medical practitioner is required to notify the medical officer of health if they have reason to believe that a person consulting them may have (or has been confirmed to have) active TB. Therefore if active TB is suspected, for example because the person has symptoms of TB and/or the CXR shows evidence suggestive of active TB, the medical practitioner concerned must notify the medical officer of health at the local Public Health Unit. This applies to all medical practitioners, including radiologists reporting CXR results for X-ray certificates for temporary entry, as well as physicians undertaking immigration medical examinations or examining people referred for further investigation because of an abnormal temporary entry CXR. A list of contact details for all Public Health Units is available on the Ministry of Health website.10

10.4 Screening and management of LTBI in people from high-incidence countries

At a population level, the treatment of people recently infected with LTBI is more effective than treatment of people infected in the remote past.

Currently, screening and treatment for LTBI in people from high incidence countries is limited to refugee children aged under 16 years.

Adults who are recent immigrants from high-incidence countries should be screened and considered for LTBI treatment if they have:
- a known history of exposure to an infectious case within the preceding two years
- immune-suppression or a predisposing medical condition
- a fibrotic lesion on CXR and disease requiring full multi-drug treatment has been excluded.
Management of treatment for LTBI should be under the supervision of an appropriate medical, occupational health or public health specialist.

In view of advances in the diagnosis and treatment regimes for LTBI, it is timely to consider extending LTBI screening programmes for other children and adults from high-incidence countries. However any new programme needs to be adequately planned and resourced, to ensure adequate follow-up of medication side effects and adherence.

10.5 Travel to high-incidence countries

The risk for travellers to high-incidence countries will relate to the length of stay, activity while overseas and prevalence of TB within the country visited.

BCG vaccination (if not previously administered) should be offered to children aged under five if travel to a high prevalence country is likely to exceed three months.

BCG vaccination is unnecessary in most adult travellers.

A two-step Mantoux or IGRA (see Chapter 8) should be done before visits of more than three months to a high-prevalence country, if there has not been a previous positive test.

Those travelling to undertake healthcare work and other high-risk activities should have pre-travel testing even if they are travelling for shorter durations. The test should be repeated eight weeks after return. If conversion has occurred, investigations for TB disease should be undertaken. If these are negative, but risk factors exist, treatment of LTBI should be considered.

A high index of suspicion and early investigation are required, if a returning traveller presents with symptoms suggestive of active TB.

10.6 The importance of early detection

It is important that general practitioners with patients from high-incidence countries, are aware of the increased rate of TB in these patients and the importance of early detection. They should inform new patients from high incidence countries about tuberculosis, including:

- the need for early investigation of signs and symptoms of TB
- TB is most likely in the first year after arrival in New Zealand, but can also occur many years later
- TB is a treatable disease
- treatment of TB in New Zealand is free.
References


Summary

Mycobacteria

Mycobacteria are aerobic bacilli. Their cell walls have a high lipid content, which includes waxes with characteristic mycolic acids with long, branched chains. Their resistance to decolourisation by acid is termed ‘acid fastness’. Isolation of species of mycobacteria other than *Mycobacterium tuberculosis* (TB) from a patient may reflect colonisation, contamination or clinical infection whereas isolation of TB always indicates clinical infection.

Diagnostic testing for tuberculosis

Specimen collection and transport

All relevant clinical details need to be written on the request form. Request forms need to clearly state all the tests required on the specimen (eg, routine culture, cytology).

Sterile body fluids should be collected aseptically to avoid contamination with commensal flora. Volumes should be sufficient for culture and NAAT testing if required. For both NAAT testing and culture, the chances of recovering TB are higher when larger volumes are used.

Sputum specimens

An early morning specimen from deep productive cough is preferred. Samples produced later in the day are acceptable.

Send three consecutive specimens collected at 8–24 hour intervals.

Specimen processing

Specimens from non-sterile sites require decontamination to kill contaminating commensal flora and maximise chances of recovering mycobacteria. Tissues or aseptically collected body fluids do not usually require the digestion and decontamination procedures that are used for contaminated specimens.

Smear microscopy and staining

The detection of AFB in a stained smear is the quickest procedure to confirm the diagnosis of mycobacterial infection.

For uniform reporting of smear results, it is recommended that an internationally standardised reporting system be used (eg, the Centers for Disease Control (CDC)).

The predictive value of a positive smear result for tuberculosis (TB), rather than infection with non-tuberculous mycobacteria (NTM), depends on the pre-test probability of TB in that patient.

Culture methods

Liquid (broth) media reduce the time to detect the growth of mycobacteria by about seven days, and all mycobacterial cultures must include a liquid culture medium.

At least one solid medium must also be used for each specimen cultured for mycobacteria.
Mycobacterial identification

Nucleic-acid identification systems allow same-day identification of referred cultures of *M. tuberculosis* complex. Probes are specific mycobacterial DNA or RNA sequences that detect complementary target sequences through nucleic acid hybridisation. Immunochromatographic tests are also available that detect antigens specific to TB. The sensitivity and specificity of both commercial probe assays and antigen tests are close to 100% when used on isolates obtained from broth culture.

Nucleic acid amplification tests (NAATs)

Most (about 95%) smear-positive specimens have positive NAAT results, but only about 50% of smear-negative specimens are NAAT-positive. Because of their cost, as well as sensitivity and specificity issues, NAATs should be reserved for situations where a rapid result will have a significant bearing on management decisions. The routine use of NAATs for all respiratory specimens is not justified.

Interferon-gamma release assays

Interferon-gamma release assays (IGRAs) involve incubation of TB-specific antigens with lymphocytes in blood samples from patients with known or suspected TB infection (either latent or active). If the lymphocytes recognise the antigens, they produce interferon-γ which is then measured by enzyme immunoassay. Commercially available IGRAs have comparable sensitivity to tuberculin skin tests (TSTs) but have greater specificity, particularly in patients who have been previously vaccinated with BCG.

Molecular typing (fingerprinting) of *Mycobacterium tuberculosis*

The routine typing of *M. tuberculosis* isolates in New Zealand began in July 2002 in order to do the following:

- support epidemiological information on the likely source and spread of *M. tuberculosis* in New Zealand
- identify TB outbreaks
- identify false-positive cultures due to cross-contamination of specimens during collection, processing or culture
- identify mislabelled specimens
- assist contact investigations and management of contacts.

Drug susceptibility testing (DST)

All initial isolates from patients with culture-proven TB should have DST performed against first line drugs. Rapid DST using molecular methods may be indicated for patients at high risk of multi-drug resistant TB (MDR-TB) or for infected patients who are critically unwell.

Other laboratory issues

Both Australia and the United States have developed ‘level of service’ guidelines for the delivery of a diagnostic laboratory mycobacteriology service.

Levels of service: recommendations

- Level I service – microscopy only.
• Level II service – microscopy and culture: a broth medium included in all mycobacterial cultures.
• Level III service – microscopy, culture, identification to species level, and susceptibility testing.

Laboratory safety
TB is hazardous to laboratory workers. Stringent safety precautions are required at all stages in the processing of samples and handling of cultures. All sputum specimens should be handled as if they contain TB.

Cross-contamination and false-positive cultures
False-positive cultures due to cross contamination are not uncommon. Laboratory and clinical staff should be aware of this possibility.
Clinicians should have a high index of suspicion of contamination as an explanation for unexpected culture results. They should contact the clinical microbiologist to discuss positive TB cultures that do not align with the clinical scenario.

Internal quality control
Quality standards for the laboratory diagnosis of TB should cover all aspects of the service, from the labelling and transportation of samples to the laboratory through to the issuing of reports and collation of data.

Air flow and biological safety cabinet performance
Mycobacteriology laboratories require regular checks and maintenance of laboratory airflow systems and biological safety cabinets to minimise risk to staff through faulty equipment or air-handling.

Reporting guidelines
Laboratories should review their turnaround times for reporting smear, culture or identification results to ensure they are meeting the reporting guidelines.

External quality control (proficiency testing)
In addition to normal internal quality control protocols, laboratories should take part in a quality control programme covering smear testing and processing (e.g., the Royal College of Pathologists of Australasia programme).
Level III laboratories should participate in the College of American Pathologists’ programme, which covers identification and susceptibility testing.

Introduction
Clinical mycobacteriology laboratories play a pivotal role in the control of Mycobacterium tuberculosis (TB) by ensuring that TB is isolated; identified; and tested against appropriate drugs in a timely manner.1–6 Laboratories must maintain close communication with both clinicians and public health services responsible for TB control (for example, medical officers of health and the Institute of Environmental Science and Research (ESR)).
This chapter provides an overview of the laboratory diagnosis of TB, and updates the issues relating to quality, performance and safety in mycobacteriology laboratories. Although many mycobacterial species other than TB are accepted as true human pathogens, the focus of this chapter is TB.7

11.1 Classification of mycobacteria

11.1.1 Description of mycobacteria

Mycobacteria are aerobic, slightly curved or straight bacilli (ie, rod shaped), 0.2–0.6 by 1.0–10 \( \mu \text{m} \) in size. The cell walls of mycobacteria have high lipid content due to the presence of characteristic mycolic acids with long, branched chains. Although the unusual composition of the mycobacterial cell wall means that mycobacteria are not readily stained by the Gram stain method, they are, however, considered gram-positive. Special staining methods must be used to promote the uptake of dye and, once stained, mycobacteria are not easily decolourised; that is, they retain the stain even when washed with acid-alcohol solutions. Their resistance to decolourisation is termed ‘acid fastness’, hence the term ‘acid-fast bacilli’ (AFB).

Growth rates for mycobacteria are slow compared to most other bacteria (16–18 hours to undergo one cycle of replication compared to 20 minutes for most bacteria).

11.1.2 Classification

Mycobacterium tuberculosis complex (MTB complex)

The Mycobacterium genus is divided into the M. tuberculosis complex and ‘non-tuberculous mycobacteria’. The M. tuberculosis complex includes M. tuberculosis, M. bovis (M. bovis subsp. bovis, M. bovis subsp caprae and M. bovis BCG), M. microti, M. canettii, M. africanum and M. pinnipedii.1 M. bovis is the name given to the bovine tubercle bacillus in 1896. The bacillus Calmette-Guérin (BCG) is derived from M. bovis that has attenuated pathogenicity and is used as a vaccine against TB. M. africanum and M. microti occupy positions along the phenotypic continuum between M. tuberculosis and M. bovis. M. pinnipedii is associated with granulomatous lesions in pinnipeds (seals, seal lions, etc).8 M. canettii is probably the source species of the M. tuberculosis complex and is associated with lymphadenitis and pulmonary disease in Africa.

Mycobacterium other than MTB complex

A variety of terms have been used to describe the rest of the Mycobacterium genus, including mycobacteria other than tuberculosis (MOTT), environmental mycobacteria, atypical mycobacteria (ATM), and non-tuberculous mycobacteria (NTM).7 The term ATM was first used because when these organisms were grouped together they were not typical of M. tuberculosis. However, the term NTM is now preferred7 and is used in this chapter to refer to these species as a group.
11.2 Diagnostic testing for tuberculosis

Several publications cover the topic of diagnostic testing for TB.1–6

11.2.1 Smear and culture testing

Specimen collection

- Relevant clinical details must be written on the request form as well as a clear statement regarding the tests requested (eg, routine culture, cytology).
- Sterile, leak-proof disposable plastic containers must be used to send specimens to the laboratory.
- Containers must be clearly labelled with the patient’s name, the specimen type, and the time and date of collection.
- Specimens should be collected aseptically in order to minimise contamination with commensal flora.
- Sufficient material must be collected for all the tests required. Do not use fixatives or preservatives for culture specimens.
- Swabs are not recommended for the isolation of mycobacteria.

Specimen transport to laboratory

- Specimens should be transported to the laboratory in as short a time as possible to avoid overgrowth by contaminating commensal flora.
- Specimens should be refrigerated if transport is delayed.
- Although sputum specimens can be stored for up to seven days at 4°C without a decrease in the viability of M. tuberculosis or a decrease in the sensitivity of smear results, delays in transport to the laboratory should be avoided if possible.

Sputum specimens

Early morning specimens from deep productive cough are preferred, although samples produced later in the day are acceptable. Three consecutive specimens should be collected at 8–24 hour intervals. For additional comments, see Chapter 2.

Specimens should not be pooled. Pooling specimens that have been collected over several days delays the turnaround time and increases the chance of overgrowth by contaminating respiratory flora.

While a patient is on treatment for TB, specimens should be sent for smear and culture so the efficacy of treatment can be followed. Patients, who are still producing sputum that is smear-positive during treatment, should have specimens sent for quantitative smear reporting and culture approximately every four weeks (see also Chapter 3).
Other respiratory specimens
Bronchial washings, lavages and induced sputum specimens should be sent in separate sterile containers. For information on the role of sputum induction in the diagnosis of TB, see Chapter 2.

Early morning urines
The entire volume of early morning urine should be collected into a clean container. The minimum volume required is 40 ml. Send one specimen on three consecutive mornings.

Unacceptable specimens for mycobacterial culture include pooled urine from catheters; urine from 24-hour collect specimens, and volumes less than 40 ml. Indications for early morning urine tests are discussed in Chapter 2.

Tissues, curettings, bone and aspirates
Tissues, curettings, bone and aspirates should be collected into sterile containers. The request for mycobacterial culture should be clearly noted on the request form. If histopathology is also required, the specimens should first be processed for microbiology and then sent on to histopathology. The biopsy must not be sent in formalin.

Blood and bone marrow
Specimens of blood and bone marrow must be inoculated immediately into the mycobacterial blood culture system used by the receiving laboratory. This must be done at the bedside. The minimum volume of blood for culture is 5 mL for adults and 1 mL for children.

Wound swabs
The rate of recovery of mycobacteria from swabs is poor. For this reason, swabs are only acceptable if a biopsy or aspirate cannot be obtained. Under these circumstances, the swab should be placed in a transport medium before transporting to the laboratory.

Gastric aspirate (lavage)
If possible, Gastric aspirate (lavage) specimens should be processed within four hours of collection. When transportation is expected to be delayed, the specimen should be collected into 10% sodium carbonate. Early morning specimens should be sent on three consecutive days. The role of gastric aspirate testing is discussed in Chapter 2.

Processing and decontamination
Sputum specimens
Sputum specimens contain oropharyngeal flora, which, unless eliminated, will overgrow TB cultures. Optimal recovery of mycobacteria from clinical specimens requires special
laboratory decontamination procedures designed to eliminate contaminating bacteria while releasing mycobacteria trapped in organic material (mucus, cells, serum and other proteinaceous material).\(^1\)

Most laboratories decontaminate and liquefy sputum samples using sodium hydroxide which also serves as a mucolytic agent. Other decontamination / mucolytic agents include dithiothreitol (sputolysin) and N acetyl-L-cysteine (NALC). The stronger the decontamination agent used, the higher its temperature and the longer it is in contact with the specimen, the greater the killing action will be on both contaminants and mycobacteria.

Following decontamination, the decontaminant must be neutralised and the sample centrifuged to concentrate the mycobacteria.

All decontaminating methods are to some extent toxic to mycobacteria. The best yield of mycobacteria from cultures will be obtained when the mildest decontamination procedure is used that sufficiently reduces contamination. However, even under optimal conditions decontamination kills all but 10–20% of mycobacteria in a specimen.\(^1\) Decontamination is generally considered to be inadequate for sputum specimens when rates of contamination with oropharyngeal flora are greater than 5%.

**Practice point**

During processing there are many opportunities for generating splashes and aerosols that can lead to cross-contamination of specimens. All handling should be done using techniques that minimise the risk of cross-contamination.

**Other specimens**

Non-sterile specimens other than sputum also require decontamination to eliminate contaminating bacterial flora\(^1\) whereas ‘sterile specimens’ such as tissues and aseptically collected body fluids do not usually require decontamination. Body fluids infected with TB usually contain only few mycobacteria and should be concentrated by centrifugation to maximise recovery. Tissues can be ground and inoculated directly to both solid and liquid media.

**Smear staining and microscopy**

The detection of AFB in a stained smear is the quickest and easiest procedure to provide preliminary laboratory confirmation of the diagnosis of mycobacterial infection.\(^1–3\) All specimens, except urine and cerebrospinal fluid (where the volume provided for analysis is low) should have a stained smear read to detect the presence of AFB. Smears of urine are rarely positive and are usually not cost-effective. For cerebrospinal fluid (CSF) it is important to culture as large a volume as possible. For low volume samples, culture should be performed in preference to stained smears. The preferred minimum volume of CSF for culture is 2–3 mL.\(^9\)
Smears should be fixed by placing the prepared slides on a heated surface. The use of heat to fix smears does not kill mycobacteria and all slides must be handled as if infectious.

Three staining techniques are commonly used to detect AFB: two carbolfuchsin-based stains (Ziehl-Neelsen and Kinyoun) and fluorochrome stains. The classic Ziehl-Neelsen stain involves heating the slide during staining for better penetration of the dye. The Kinyoun acid-fast stain is a similar method but without heat where dye penetration is aided by using a higher concentration of phenol in the stain. Both carbolfuchsin methods stain the mycobacterial cells red against a methylene blue counter-stain. Both are examined under oil immersion at 1000 times magnification. At least 300 fields should be examined a slide is reported as ‘negative’.

A fluorochrome stain (auramine O or auramine-rhodamine) is the screening method recommended for laboratories with a fluorescent (ultraviolet) microscope. These stains bind to mycobacterial cell walls and fluoresce under ultraviolet illumination, so that mycobacteria appear bright yellow against a dark background. For this reason fluorochrome stained smears can be read at lower magnification, and in less time than carbolfuchsin based smears. Fluorescence microscopy is more sensitive than conventional microscopy and has similar specificity. If necessary, positive fluorochrome stains can also be ‘over-stained’ with a carbolfuchsin dye in order to further confirm the presence of AFB.

If too few AFB are present to call a smear ‘positive’ (see Table 11.1), another smear should be made from the same specimen (if possible) and a repeat specimen requested. For a sputum specimen to be smear-positive, it must contain approximately $10^5$ AFB/ml. Positive cultures can be expected when the sputum specimen contains 10–100 AFB/ml.

Acid-fast smears have high specificity but some other organisms may also stain acid-fast, including *Nocardia* species, *Rhodococcus* species, and *Legionella micdadei* as well as cysts from *Cryptosporidium*, *Isospora*, *Cyclospora* and *Microsporidium* spores.

Direct microscopy for AFB remains the most rapid and economical means of detecting infectious cases of pulmonary TB. The predictive value of a positive smear for TB as opposed to infection with NTM, will depend on host factors such as age, immune competence and underlying disease.1,3,7

**Reporting smear results**

The number of fields that need to be examined and the number of AFB seen in a microscopic field will vary depending on the type of stain and the magnification being used. For standardised reporting of smear results, it is recommended that either the reporting system of the Centers for Disease Control and Prevention (CDC)11 or the reporting system of the International Union against Tuberculosis and Lung Disease / World Health Organization be used.12 The wording of reports and the corresponding number of AFB present in the smear for both systems are summarised in Table 11.1. It is also recommended that laboratories report, the numerical result in brackets alongside the 1+ to 4+ result (eg, 2+ AFB seen (1–9 AFB/10 fields)).
Laboratories using carbolfuchsin-stained smears simply report as indicated in Table 11.1. Laboratories using a fluorochrome stain need to convert the number of AFB seen to the corresponding number seen on a carbolfuchsin-stained smear.

### Table 11.1: Acid-fast smear evaluation and reporting

<table>
<thead>
<tr>
<th>Report</th>
<th>Carbfuchsin stain x 1000</th>
<th>Fluorochrome stain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>x 250</td>
</tr>
<tr>
<td>CDC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No AFB seen</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Doubtful; repeat</td>
<td>1–2/300 F (3 sweeps)†</td>
<td>1–2/30 F (1 sweep)</td>
</tr>
<tr>
<td>1+</td>
<td>1–9/100 F (1 sweep)</td>
<td>1–9/10 F</td>
</tr>
<tr>
<td>2+</td>
<td>1–9/10 F</td>
<td>1–9/F</td>
</tr>
<tr>
<td>3+</td>
<td>1–9/F</td>
<td>10–90/F</td>
</tr>
<tr>
<td>4+</td>
<td>&gt; 9/F</td>
<td>&gt; 90/F</td>
</tr>
<tr>
<td>IUATLD/WHO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No AFB in at least 100 fields</td>
<td>0/negative</td>
<td></td>
</tr>
<tr>
<td>Actual AFB count</td>
<td>1 to 9 AFB in 100 fields††</td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>10 to 99 AFB in 100 fields</td>
<td></td>
</tr>
<tr>
<td>++</td>
<td>1 to 10 AFB per field in at least 50 fields</td>
<td></td>
</tr>
<tr>
<td>+++</td>
<td>&gt;10 AFB per field in at least 20 fields</td>
<td></td>
</tr>
</tbody>
</table>

Notes: AFB = acid-fast bacilli; CDC = Centers for Disease Control and Prevention; F = microscope fields; IUATLD = International Union against Tuberculosis and Lung Disease; WHO = World Health Organization.

† In all cases, one full sweep refers to scanning the full length (2 cm) of a smear 1 cm wide by 2 cm long.

†† A finding of 1–3 bacilli in 100 fields does not correlate well with culture positivity.

Source: Adapted from Kent and Kubican (1985).11

### Culture methods

A variety of media are available to use for recovering mycobacteria, including solid and liquid (broth) media.1,3 Several liquid media are available for recovering and sub-culturing mycobacteria. Liquid media reduce the time to detect the growth of mycobacteria by about seven days and have been a significant advance in the laboratory diagnosis of TB. Liquid media also recover more isolates than solid media and also detect mixed mycobacterial cultures more frequently. All mycobacterial cultures must include a liquid-culture medium.1–3

### Commercial broth-based culture systems

Early broth based systems detected mycobacterial growth using radioisotope labelled carbon dioxide. The classic example of such a system is the BACTEC 460TB system.
Some laboratories still use this system although it has the disadvantage of requiring repeated sampling of vials using syringes.

Most modern mycobacteriology laboratories use automated, continuously monitored systems to culture mycobacteria in liquid media. These systems use specialised vials/tubes into which processed specimens are inoculated. Several mechanisms are used to detect the growth of mycobacteria. For example, the MGIT 960 system detects bacterial growth using a fluorescence-quenching based oxygen sensor within each tube. As mycobacteria multiply within the tube, oxygen is consumed and fluorescence is detected by the system. The contents of the tube can then be stained to look for the presence of mycobacteria and tested for the presence of TB using molecular probe-based assays or TB antigen tests. Examples of different continuously automated systems include the BACTEC MGIT 960 (BD), the BACTEC 9000 MB (BD), the MB/BacT Alert 3D (Biomerieux).

**Solid media**

Solid media may be egg-based or agar-based. Egg-based media, of which Löwenstein-Jensen (LJ) is the most commonly used, support the growth of *M. tuberculosis* well and have a long shelf life. Agar-based media have the advantage of being transparent, allowing earlier detection of mycobacterial colonies (Middlebrooks agar). They are more expensive than LJ, have a shorter shelf life and are not commonly used in New Zealand.

Solid media should be inspected regularly and kept for eight weeks. Cultures from smear-positive specimens that have no growth at eight weeks should be kept for a further six to eight weeks. Detection of colonies on solid media offers several advantages over growth in broth. Colonial morphology may provide clues for identification and mixed cultures can be detected.

At least one solid medium must be used for each mycobacterial culture.

**Mycobacterial identification**

**Nucleic acid probes**

Nucleic-acid probes allow same-day identification of *M. tuberculosis* recovered from liquid culture medium. Specific probes are commercially available for several mycobacterial species including: *M. tuberculosis* complex; *M. avium* complex; *M. kansasii* and *M. gordonae* (AccuProbe, Gen-Probe Inc, San Diego, California). These probes produce a fluorescent signal on binding to their specific target nucleic acid sequence.

Although the specificity of nucleic acid probes is generally close to 100%, the uncommon NTM, *M. celatum* can cross-react with the *M. tuberculosis* probe if present. The sensitivity of the Accuprobe varies according to the species targeted. For example, the sensitivity of the M-TB AccuProbe is 100% whereas the sensitivity of the *M. avium* complex AccuProbe is 95–97%. Despite the high sensitivity and specificity of these probes.
tests, as with all laboratory tests, additional testing should be performed if the results do not correlate with clinical or epidemiological risk factors.

Two 'line probe' assays have been developed; LiPA Mycobacterial kit, (Innogenetics) and GenoType® Mycobacteria (Hain Lifescience). These kits can be used to identify isolates recovered from either solid or liquid media. In contrast to the AccuProbe, line probe assays allow testing for several mycobacterial species at once because more than one probe can be immobilised onto a plastic membrane strip. Line-probe assays have the advantage of allowing several species to be identified from a single PCR reaction and thus do not require pre-selection of the appropriate probe.

**Antigen tests**

Antigen testing using a commercially available immunochromatographic kit can be used to identify MTB complex in positive broth cultures. Such assays use the *Mycobacterium tuberculosis* protein 64 as a target antigen (MPT-64). This is an antigen specific to MTB-complex which is secreted during bacterial growth. The sensitivity and specificity of these assays compared to the Accuprobe molecular assay are approximately 97% and 100% respectively. The kit requires a 15-minute assay time, is easy to perform and is relatively cheap.\(^{14}\)

**11.2.2 Nucleic acid amplification tests**

Nucleic acid amplification tests (NAATs) utilise a variety of molecular techniques to amplify target DNA sequences and thus detect and identify mycobacteria in specimens or cultures. Both commercial and 'in-house', amplification assays can usually provide results within a single working day. Despite the faster turnaround time for NAATs compared to culture methods, culture should always be performed alongside NAATs for two reasons:

1) culture methods tend to be more sensitive and
2) culture of *M. tuberculosis* allows susceptibility testing to be performed.\(^5,6\)

If there is insufficient specimen to process for both culture and NAAT, culture must be performed in preference.

Laboratories undertaking NAATs for mycobacteria must participate in quality assurance programmes. Positive and negative control tubes should be included with each NAAT reaction to rule out inhibition of amplification and cross-contamination respectively.

NAATs are a useful adjunct to culture methods but because of their cost and suboptimal sensitivity, NAATs should be reserved for clinical situations where an expedited positive result will have an impact on management decisions. (See also the section 'Recommendations for NAAT testing', below.)

**Sensitivity and specificity**

The analytical sensitivity of NAATs for TB can be as low as 10 mycobacteria, as judged by serial dilutions of a suspension of known colony count. Many 'in-house' PCR assays target the insertion sequence IS6110. Therefore, both *M. tuberculosis* and *M. bovis* are
detected by such assays. Additional molecular targets, such as the region of difference (RD) gene can be utilised to distinguish species within the *M. tuberculosis* complex. Rare strains of *M. tuberculosis* lacking IS6110 have been reported from China and Vietnam. Strains such as these will be missed in this assay, but none has yet been encountered in New Zealand. Around 82–100% of smear-positive specimens have positive NAAT results but only about 50% of smear-negative specimens are NAAT positive. Thus a negative NAAT test on a sputum specimen should not be used to rule out TB, particularly when the patient is smear negative.

When amplicons (the products of NAAT reactions) are sequenced to confirm identity, the specificity of NAATs for TB is 100%. However, as with all PCR assays contamination with exogenous target DNA can cause false-positive results. Specimens that contain inhibitors of *Taq* polymerase (the enzyme used in the PCR reaction) cannot be assayed by PCR.

**Applicable specimens**

NAATs are an alternative way to make the diagnosis of TB:
- as an adjunct to culture, where speed of diagnosis is desired (eg, TB meningitis)
- where fresh tissue is not available (eg, retrospective analysis of fixed tissues that are histologically suggestive of TB); however, formalin fixation does affect the molecular arrangement of DNA and may lead to a decrease in the efficacy of amplification – the sensitivity of the assay decreases, the longer the tissue has been fixed.

NAATs generally have low sensitivity when used on pauci-bacillary specimens such as pleural and peritoneal fluids. For this reason it is preferred that all the fluid is cultured. Fine-needle biopsy may be suitable for NAAT testing, but if the specimen comprises only the washings from a biopsy needle (after histology and other culture aliquots have been taken) the likelihood of detecting TB is extremely low.

Sputum samples should be sent for culture and may not be accepted for PCR by all laboratories although the Cepheid GeneXpert® platform can be used directly on sputum specimens (see below).

**How to request**

The laboratory may decline to assay inadequate or inappropriate material. Pertinent clinical details including CSF results in suspected meningitis must accompany the request. Ideally, the need for PCR should be discussed with a clinical microbiologist. Results should be available within three working days after the specimen is received in the laboratory.

Auckland, Waikato, Wellington and Christchurch Hospital laboratories offer PCR testing for appropriate clinical specimens.

**Commercially available NAATs validated for use on respiratory specimens**

Available assays for TB include:
- Gen-Probe Amplified *M. tuberculosis* Direct Test (MTD II)
- Becton Dickinson ProbeTec Direct (SDA) system
- Roche Cobas® Amplicor® *M. tuberculosis* test
- Roche Cobas® TagMan® MTB Test
- Loop-mediated isothermal amplification (LAMP), Eiken Chemical Co Ltd
- Hain Lifescience Genotype® Mycobacterium Direct (RNA)
- Cepheid Xpert MTB/RIF assay.

**Recommendations for nucleic-acid amplification tests**

The routine use of NAATs for respiratory specimens is not justified. These tests should be used only when diagnostic, therapeutic or infection control issues require a rapid result. Requests for NAAT testing for TB should be discussed with the clinical microbiologist.

Settings in which NAATs should be considered include the following:

- smear-positive cultures of clinical and public health importance (eg, where a non-tuberculous mycobacterium is likely and a major public health investigation could be prevented by rapid diagnosis)
- respiratory smear-negative specimens in someone with a high probability of TB, when there are significant risks to starting TB treatment inappropriately
- non-respiratory specimens where prompt management decisions are necessary
- immuno-compromised patients at high risk of TB, where delay in diagnosis may compromise the prognosis or make empirical treatment of other conditions necessary
- when culture is not possible (eg, paraffin embedded tissue)
- when a patient who has been treated for TB previously presents with signs and symptoms of TB and a rapid diagnosis of infection and testing for rifampicin resistance is essential.

NAATs should *not* be considered for:

- smear-negative specimens with low probability of TB
- smear-positive patients with high probability of TB but of no public health concern
- paucibacillary non-respiratory specimens (eg, pleural fluid; pleural biopsy is the preferred specimen)
- testing for cure, because it may be falsely positive (mycobacterial DNA may persist for a time despite the organisms being killed by treatment).

**11.2.3 Immunological tests for tuberculosis infection (see also chapter 8)**

The traditional test for latent TB infection is the tuberculin skin test (TST). Problems with the TST include the need for return visits, subjectivity in reading results and cross-reactivity with the BCG vaccine. Several immunological methods to diagnose TB infection have been evaluated as alternatives to the TST
Immunological tests for TB measure some aspect of the immune response to TB (humoral or cellular) in order to infer the presence of TB infection. TB infection may be latent or active. Unlike culture and NAATs, immunological tests do not differentiate between active and latent TB infection.

**Interferon gamma release assays – underlying principle**

Interferon gamma release assays (IGRAs) involve incubation of peripheral blood lymphocytes with mycobacterial antigens. The underlying principle of IGRAs is that specific lymphocytes that have been previously exposed to mycobacterial antigens will release interferon-\(\gamma\) (IFN-\(\gamma\)) on re-exposure. IFN-\(\gamma\) is then measured using either an enzyme immunoassay or elispot technique. The currently available commercial assays use antigens that are present in TB but absent from BCG (for example; CFP-10, ESAT-6 and TB7.7). These antigens are encoded by genes located within the region of difference 1 (RD1) of the *M. tuberculosis* genome. This is a region of the genome that is absent in BCG and most NTM. Only a few other NTM contain the genes for these antigens (*M. kansasaii, M. marinum* and *M. szulgai*).

**Interferon gamma release assays – performance characteristics (see also Chapter 8)**

Two commercial IGRAs are available: The QuantiFERON-TB Gold assay (QFN) (Cellestis Limited, Carnegie, Victoria, Australia) and the T.SPOT TB assay (Oxford Immunotec, Oxford, United Kingdom). The QFN assay is available in two formats; a 24-well culture plate and an ‘in-tube’ method. The ‘in-tube’ method is used by all labs in NZ offering IGRA (see Appendix 1). The QFN assay uses an EIA method to measure the amount of IFN-\(\gamma\) released whereas the T.SPOT TB assay uses an enzyme-linked immunospot assay to quantify the number of cells producing IFN-\(\gamma\) per unit volume.

Commercially available IGRAs are more specific than the TST, particularly among BCG vaccinated populations. Furthermore when culture proven TB is used as a gold standard, IGRA also appear to have similar sensitivity to the TST (approximately 80%).

However, despite the sensitivity of IGRA for active TB being similar to the TST, the sensitivity of IGRA for latent TB infection (LTBI) is more difficult to assess because no reliable gold standard exists. It is possible, for example, that some discordant results observed between the TST and IGRAs represent remote, cleared infection rather than true latent TB. Ideally, large prospective studies are needed to determine rates of progression to active TB among patients with discordant TST / IGRA results.

Several recent reviews have compared the performance of IGRA in comparison to the TST in a variety of clinical settings. Studies using either or both of the two commercially available IGRAs have evaluated their performance in the diagnosis of both LTBI and active tuberculosis. The utility of IGRAs in specific groups has also been examined: including patients with HIV, healthcare workers, injecting drug users, patients with inflammatory arthropathies, contacts of smear-positive cases, and paediatric populations.
More recently several studies have looked at the cost-effectiveness of using the IGRA instead of the Mantoux in various settings. In high-income countries such as Canada and Germany, IGRA have been shown to be more cost effective when used to test TST-positive patients.34,35

Interpretation of IGRA results (see also Appendix 2)

- A positive result suggests TB infection, but will not differentiate between LTBI and active TB.
- A negative result should not be used to definitively exclude TB in someone who has clinical features of TB because the sensitivity of IGRA for active TB is only approximately 80%.
- An indeterminate result may indicate immune-compromise or reflect poor processing (for example inadequate mixing of tubes after inoculation for the QFN in-tube test).

Serological tests

Serological tests for TB do not correlate well with the presence of active or latent TB infection. For this reason they are not recommended for use in the diagnosis of infection (either latent or active) in New Zealand.

11.3 Molecular typing (DNA fingerprinting) of Mycobacterium tuberculosis

The routine typing of M. tuberculosis isolates in New Zealand started in July 2002. Applications for molecular typing for TB control were proposed in 2003. The applications are:

- detection of cross-contamination of clinical specimens and isolates
- differentiation between relapse and exogenous re-infection
- identification of outbreaks
- reinforcing (or disproving) epidemiological links
- evaluating contact investigation and management
- providing a basis for the study of TB epidemiology.

All isolates of M. tuberculosis look similar on culture plates. Earlier typing methods relied on antibiotic susceptibility profiles, an unusual biochemical reaction, or susceptibility to viruses capable of infecting M. tuberculosis. The latter two are not used in contemporary mycobacteriology. Comparing susceptibility profiles is of limited value because the majority of isolates in New Zealand (88% in 2008) are fully susceptible.36

The only adequate way to show the uniqueness, or otherwise, of an isolate of M. tuberculosis is to use molecular typing methods.

Restriction fragment length polymorphism

Restriction fragment length polymorphism (RFLP) is a method for fingerprinting isolates of M. tuberculosis.37 Most strains of M. tuberculosis contain 6–20 copies of a particular
insertion sequence called IS6110. The location and number of copies of IS6110 varies between strains. After cutting up the genome with restriction enzymes and separating different-sized fragments by gel electrophoresis, the fragments are detected using a fluorescent labelled ‘probe’ for IS6110 (that is a fluorescent labelled complementary DNA sequence for IS6110). Strains of TB are characterised by the position and number of bands, called the strain’s ‘fingerprint’. Strains with identical or closely related fingerprints are considered ‘clonal’ while isolates with unique patterns are considered unrelated. Patients who are found to share the same clonal strain by RFLP are likely to be linked epidemiologically and to share a common chain of transmission. Strains with no or low copies of IS6110 require alternative typing methods to test their relatedness.

**Spoligotyping and variable number tandem repeat – mycobacterial interspersed repetitive units typing (VNTR-MIRU typing)**

Alternative typing methods include ‘spacer oligonucleotide typing’ (spoligotyping) and ‘variable-number tandem repeat typing’ (VNTR). Spoligotyping is a PCR-based technique that detects the presence or absence of spacers in the direct-repeat locus of *M. tuberculosis*. VNTR utilises genetic elements called ‘mycobacterial interspersed repetitive units’ (MIRU). MIRU-VNTR genotyping involves PCR amplification of at least 12 target MIRU loci followed by determination of the size of each of the PCR products. Each PCR product is assigned a numerical value based on its size, so that for 12 loci MIRU, a 12 digit profile is obtained. The size of each product is determined by the number of ‘repeats’ at each locus. The numerical profile generated for any given isolate can be used to make comparisons with MIRU profiles obtained from isolates processed at other laboratories. A recent large comparison of IS6110, spoligotyping and MIRU-VNTR for typing isolates with low copy numbers of IS6110 showed that for these isolates, MIRU-VNTR had resolution surpassing both other methods. MIRU-VNTR is in common use in Australia.

**Molecular typing of *M. tuberculosis* in New Zealand**

Until recently, RFLP was the method used for the genotyping of all strains nationally. However, although, electronic storage of all RFLP profiles did allow for comparison between isolates over time, as the database increased in size, analysis of strain relatedness became more time consuming and technically difficult. In addition, unlike VNTR-MIRU profiles, RFLP profiles are not directly comparable between laboratories. Because of these issues a recent review of the molecular typing process has led to a change from routine use of RFLP to VNTR-MIRU.

Genotyping has general applications in New Zealand. For example, typing information confirmed transmission of a single strain of *M. tuberculosis* in an Auckland school and community outbreak, as it did in a large chain of transmission within an Auckland church group. Typing has also been of pivotal importance in determining the duration and extent of a prolonged outbreak in the North Island. Thus, establishing a link between patients in geographically diverse places would not have been possible without routine typing of TB in New Zealand.

A review of universal genotyping of TB isolates after the first five years (July 2002 to June 2007) was recently undertaken. Over this period, 1411 culture-confirmed cases of
TB were notified and 1368 (97%) isolates were matched with the notification. Over one-third of the typed cases could be assigned to a cluster. There were 472 cluster cases distributed between 130 different clusters. The mean number of cases per cluster group was 3.6 and the median 2.0. Four clusters had more than 20 associated cases, comprising 22, 23, 27 and 55 cases respectively. Cluster cases were more likely to be Māori or of Pacific ethnicity and less likely to be Asian. 43

11.4 Drug susceptibility testing (DST)

11.4.1 When to perform DST

Multi-drug resistant TB is becoming increasingly common worldwide (MDR-TB, defined as resistance to both rifampicin and isoniazid). All initial isolates from patients with culture-proven TB must have DST performed against “first line drugs” (isoniazid, rifampicin, pyrazinamide and ethambutol +/- streptomycin). 2, 44, 45

The need for repeat DST to first line agents on isolates recovered from patients during TB treatment depends on the patient’s clinical progress, and the risk of resistance developing. Patients who have received a “partial regimen” at any stage of their treatment are at increased risk of developing resistance to first line drugs (see also Chapter 3).

11.4.2 Phenotypic DST methods

All phenotypic DST methods for M. tuberculosis use specific ‘critical concentrations’ (or ‘breakpoints’) for each anti-tuberculous drug. Although the ‘agar proportion’ method using solid agar is the traditional method for performing DST, most laboratories now use broth-based DST using either the BACTEC 460 or the MGIT960 system. Critical concentrations for the MGIT 960 system have recently been published by the WHO. 46 These concentrations represent the lowest drug concentration that inhibits 95% of ‘wild TB strains’ (ie, strains that have never been exposed to the drugs), without inhibiting growth of resistant strains.

An isolate is considered to be ‘resistant’ to a drug when growth in the presence of a critical drug concentration exceeds growth of the same isolate diluted 1:100 in drug-free media.

The BACTEC 460 or the MGIT960 systems can be used to test rifampicin, isoniazid, ethambutol and streptomycin, however DST for pyrazinamide using the MGIT 960 is technically difficult and consequently, many labs use the “Wayne’s test” to test for pyrazinamide resistance. Pyrazinamidase activity is required to convert pyrazinamide into its active form. 8 Therefore, failure to detect pyrazinamidase activity by the Wayne’s test indicates pyrazinamide resistance. M. bovis is intrinsically resistant to pyrazinamide. M. tuberculosis complex isolates resistant only to pyrazinamide should be suspected of being M. bovis. They should have appropriate biochemical tests or molecular tests performed to fully speciate the isolate.

DST to isoniazid should be performed using two critical concentrations: low and high level. Isolates resistant to the low-level critical concentration but susceptible to the high-
level critical concentration should be reported as having low level resistance to isoniazid.47

11.4.3 Rapid DST methods

Rapid DST methods use molecular techniques to detect resistance, usually within 1–2 days of a positive TB culture. The Cepheid GeneXpert system is also validated to detect rifampicin resistance directly from respiratory specimens within several hours.

Rifampicin resistance occurs due to mutations in a particular ‘hotspot’ of the rpoB gene. ‘In-house’ PCR of this region, followed by sequencing can identify these mutations. Rifampicin resistance usually occurs in combination with isoniazid resistance (85–95% of the time) and so identification of mutations in the rpoB gene usually indicates that the isolate is also resistant to isoniazid.48 Commercial assays that detect mutations in the rpoB gene include:

- Hain Lifescience Genotype® Mycobacterium Direct (RNA)
- Cepheid Xpert MTB/RIF assay.

Patients with disseminated disease due to TB and patients at high risk of having multi-drug resistant TB (MDR-TB) in particular, may benefit from rapid DST. Patients at high risk of MDR-TB include patients with relapsed TB after previous treatment and patients from areas of high MDR-TB prevalence.

11.4.4 DST to ‘second line drugs’

DST to second line drugs should be performed on all isolates of MDR-TB. Critical concentrations for second line agents and testing methods for the MGIT 960 have been published by the World Health Organization (WHO) and in the literature.46,49

Currently LabPlus, Auckland Hospital is the only laboratory in New Zealand that performs second line DST. The second line drugs that can be tested in New Zealand include amikacin, capreomycin, ofloxacin, ethionamide, rifabutin, and streptomycin (ofloxacin is generally considered a proxy for moxifloxacin and other fluoroquinolones).

Unfortunately, reliable testing methods for other second line drugs such as cycloserine and PAS have not been developed for the MGIT 960.

Isolates of MDR-TB that are also resistant to fluoroquinolones and one or more second line injectable drugs (such as amikacin, kanamycin and capreomycin) are defined as ‘extensively drug resistant TB’ (X-DR TB).

11.4.5 Quality control for first and second line DST

Because a diagnosis of MDR TB or X-DR TB has profound implications for the patient and for public health investigations, laboratories that perform DST for TB must have rigorous quality controls in place to ensure that results are reliable. Results that are unusual or unexpected should be carefully cross-checked to eliminate the possibility of contamination with NTM or another organism before a final report is issued. All broth cultures used for DST must be routinely sub-cultured onto blood agar once growth is
detected in order to rule out the possibility that the culture is contaminated with bacteria other than TB.

11.5 Other laboratory issues

11.5.1 Levels of service

The Centers for Disease Control and prevention (CDC), American Thoracic Society (ATS), and the College of American Pathologists (CAP) have developed a classification system that defines levels of service capability for laboratories within the USA that process clinical specimens for mycobacteria. Levels of service are defined according to specimen workload, personnel expertise and cost-effectiveness.\(^9\)

In Australia, the National Tuberculosis Advisory Committee has published *Guidelines for Australian Mycobacteriology Laboratories* (2006).\(^{50}\) These guidelines provide a framework for maintaining high-quality laboratory testing for TB. This framework is based on the premise that mycobacteriology laboratories must process adequate numbers of clinical specimens in order to maintain proficiency.

USA Guidelines

The three levels of service (I, II, III) are summarised in Table 11.2.

**Level I service: microscopy only**

Level I laboratories collect and transport specimens to referral laboratories for culture, identification and susceptibility testing. These laboratories can examine direct smears. When preparing direct smears, the laboratory should concentrate the sputum before preparing the stained film and render the mycobacteria non-viable before staining. To maintain proficiency at Level 1 status, a laboratory must prepare at least 15 specimens per week and examine them for AFB.

**Level II service: microscopy and culture**

Level II laboratories, in addition to level I services, culture and identify *M. tuberculosis* complex. The laboratory may also perform susceptibility testing. A Level II laboratory must process and culture at least 20 specimens per week.

**Level III service: microscopy, culture, identification to species level, and susceptibility testing**

Level III laboratories, in addition to performing Level I and II services, identify mycobacterial species and perform susceptibility testing when indicated.

Three laboratories offer services for identification and susceptibility testing for mycobacteria in New Zealand (Auckland, Waikato and Wellington Hospital laboratories). A reference service for identification and susceptibility testing should be supported by specialised clinical advice.
Table 11.2: Levels of service

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I</td>
</tr>
<tr>
<td>Acid-fast smears</td>
<td>Yes</td>
</tr>
<tr>
<td>Culture</td>
<td>No</td>
</tr>
<tr>
<td>Identification of <em>Mycobacterium tuberculosis</em> complex</td>
<td>No</td>
</tr>
<tr>
<td>Identification of all mycobacteria</td>
<td>No</td>
</tr>
<tr>
<td>Drug susceptibility of <em>Mycobacterium tuberculosis</em> complex</td>
<td>No</td>
</tr>
<tr>
<td>Drug susceptibility of non-tuberculous mycobacteria</td>
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</tr>
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</table>

Australian guidelines (see table 11.3)

The Australian guidelines are divided into three areas.
- Laboratories performing smear microscopy (CDC/ATS/CAP level I).
- Laboratories performing mycobacterial culture (CDC/ATS/CAP levels II and III).
- Laboratories performing susceptibility tests (CDC/ATS/CAP levels II and III).

The guidelines reaffirm and reiterate the biosafety requirements for Australian mycobacteriology laboratories as outlined in the Australian/New Zealand Standard Safety in Laboratories. Part 3: Microbiological aspects and containment facilities (A/NZS 2243.3:2002).  

Any laboratory in New Zealand performing mycobacterial staining or culture should be IANZ accredited to the Australian/New Zealand Standard in full.

Table 11.3: Biosafety and quality assurance recommendations

<table>
<thead>
<tr>
<th>Laboratory capability</th>
<th>Physical containment level</th>
<th>Quality assurance recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smear only</td>
<td>PC2</td>
<td>Yes, Royal College of Pathologists of Australasia smear Quality Assurance Programme (QAP)</td>
</tr>
<tr>
<td>Culture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 &lt; 5000 cultures per year</td>
<td>PC2</td>
<td>Yes, Royal College of Pathologists of Australasia smear and culture QAP or equivalent</td>
</tr>
<tr>
<td>2 ≥ 5000 cultures per year</td>
<td>PC3</td>
<td></td>
</tr>
<tr>
<td>3 Knowingly handling MDRTB</td>
<td>PC3</td>
<td></td>
</tr>
<tr>
<td>Susceptibility testing</td>
<td>PC3</td>
<td>Yes, as above and other external programmes which include DST such as the Centers for Disease Control and Prevention QAP or World Health Organization QAP</td>
</tr>
</tbody>
</table>

11.5.2 Timely reporting of results

Improvements in technology are of little use if the results do not reach their destination promptly. Positive smears should be reported by telephone to the clinician at once, and followed up immediately with a hard copy. Reference laboratories have a particular responsibility to keep their referring laboratories informed at all stages of identification and susceptibility testing. Preferably this should be done by fax or email. If email is
used, there must be a system so the messages are cleared daily. Culture and identification results should be reported within 14 days for smear-positive specimens. Susceptibility results should be reported within 15–30 days of specimen collection for smear-positive specimens.52

11.5.3 Laboratory safety

TB is hazardous to laboratory workers. Stringent safety precautions are required at all stages in the processing of samples and handling of cultures. All sputum specimens should be handled as if they contain TB.

The Australian/New Zealand Standard Safety in Laboratories Part 3: Microbiological aspects and containment facilities sets out requirements, responsibilities and general guidelines relating to safety in laboratories and containment of micro-organisms.51

The standard covers the following areas:
- organisation and responsibility
- degree of hazard from micro-organisms
- classification of laboratories, practices and procedures
- laboratory spills
- general precautions and special equipment
- work areas
- laboratory cleaning
- waste disposal
- transport of infectious and other biological materials.

This standard is being reviewed (2010).

11.5.4 Cross-contamination and false-positive cultures

A positive culture of *M. tuberculosis* is usually considered to be definitive evidence for disease. However, false-positive cultures are not rare.53–59 Almost all studies that have evaluated more than 100 isolates have identified false-positive cultures, many of which were not recognised as such by laboratory and clinical personnel.54

False-positive cultures can adversely affect patients, their contacts, hospitals and the public health system. Examples of these effects include psychological stress, social stigmatisation of patients and their families, unnecessary and costly medical treatment, eg, additional medical visits, chest X-rays, additional specimen collection and culturing, and adverse side effects resulting from unnecessary anti-TB treatment. Contact investigations lead to unnecessary Mantoux tests, chest X-rays, and many hours of wasted time.

The process of culturing mycobacteria is inherently prone to cross-contamination for several reasons, including the following:
- multiple steps are involved in processing mycobacterial cultures
- viability of *M. tuberculosis* for long periods in laboratory environments
large number of mycobacteria present in some specimens.

The potential for error underscores the need to recognise false positive cultures promptly.

Two mechanisms can potentially result in contamination and laboratory error.
- Mislabelling or switching of specimens during handling.
- Instrument or reagent contamination, resulting in carry-over of mycobacteria from one sample to another. This may occur during initial processing, processing for susceptibility testing and by airborne contamination by aerosols in the biological safety cabinet.53–59

Primary prevention of laboratory error requires use of standardised laboratory procedures designed to minimise the potential for errors.

Indicators of potential false-positive *M. tuberculosis* cultures include the following:
- all specimens but one from a patient are AFB smear-negative, and the single smear-positive specimen is *M. tuberculosis* culture-positive
- the patient’s signs, symptoms and clinical course are inconsistent with TB
- an *M. tuberculosis* culture-positive specimen, also likely to be strongly AFB smear-positive, was processed the same day as the suspected specimen
- the DNA fingerprint pattern of the suspected isolate is identical to that of the putative contaminating source isolate
- there are no known epidemiological links between the patient with the suspected isolate and the patient with the putative contaminating source isolate
- the duration of time for detection of growth in culture suspected of being contaminated was prolonged or only sparse colonies were detected on solid medium.

False-positive cultures may also occur following the use of contaminated clinical equipment, eg, bronchoscopes, or from the mislabelling of specimens when they are collected.

**Practice points**
Timely recognition and investigation of false-positive cultures of *M. tuberculosis* requires close co-operation and communication between clinicians, laboratories and public health. When culture results are inconsistent with the patient’s signs and symptoms or clinical course, the clinician must discuss the result with the laboratory and local public health.

If false-positive cultures and/or contamination are suspected, laboratory staff should notify the patient’s doctor and should have genotyping performed on the isolates from the putative source and the potentially contaminated specimen.

Laboratory staff should record the date and order of processing to enable easy identification of clusters of positive cultures. Simple procedural changes have been shown to decrease the rate of cross-contamination.60 These changes include:
- reducing the number of smear-positive specimens processed from a patient
handling high-risk specimens, eg, proficiency test samples, separately
- having only one tube uncapped at a time in the biological safety cabinet
- using aliquots of buffer and other reagents and not larger multi-use volumes
- waiting after the specimen centrifugation step to allow time for aerosol settling in the test tube.

11.5.5 Quality control

Quality standards for the laboratory diagnosis of TB should cover all aspects of the service, from the transportation of samples to the laboratory to the issuing of reports and collation of data.1-3 This section provides guidelines that laboratories should follow. Not all of the following guidelines are directly covered by the International Accreditation New Zealand (IANZ) laboratory accreditation system.

Internal quality control

Contamination rate with commensal flora

If the method used to decontaminate specimens for mycobacterial culture is too harsh, mycobacteria in the specimens will be killed. If the process is too mild, cultures will become overgrown with contaminating commensal bacteria. Laboratories should monitor to ensure that essentially all smear-positive specimens grow a mycobacterium and that the bacterial and fungal contamination rate for sputum specimens is within the range generally considered to be acceptable (3–5%).8 If contamination rates lie outside of this range then a review of decontamination methodology may be required.

Cross-contamination

All smear-negative single isolate positive cases should have their DNA fingerprint profiles compared with concurrent isolates that the laboratory has recovered to ensure that the result is not due to laboratory cross-contamination or mislabelling of specimens.56,57

Air-flow and biological safety cabinet performance

Regular maintenance and checks of the performance of the airflow system that serves the mycobacterial lab and the biological safety cabinet are required to ensure the safety of laboratory staff. An adequately performing biological safety cabinet is also required to reduce the risk of specimen cross-contamination.

Meeting reporting guidelines

Laboratories should review their turnaround times for reporting smear, culture or identification results in order to ensure they are meeting the reporting guidelines.
External quality control proficiency testing

In addition to normal internal laboratory controls, laboratories undertaking processing and smear examination should take part in a quality assurance programme (QAP) covering these procedures (e.g., the Royal College of Pathologists of Australasia’s programme). Level III laboratories should participate in a programme that covers identification and susceptibility testing (e.g., the College of American Pathologists’ programme).

The Australian Society for Microbiology Special Interest Group for Mycobacteria undertakes an annual survey, which also gives excellent coverage of identification and susceptibility testing. Recent surveys have included PCR and fingerprinting assessments. This activity is voluntary for participating laboratories.

Appendix 1: The QuantiFeron Gold in-tube assay®

One millilitre of blood is collected into each of three specialised blood collection tubes:

- a ‘TB antigen tube’ that contain the three synthetic TB antigens (ESAT-6, CFP-10, TB7.7)
- a ‘nil control tube’ (measures the background concentration of IFN-γ in the patient’s blood)
- a ‘positive control tube’ that contains mitogen (a non-specific stimulator of IFN-γ release from lymphocytes).

The concentration of IFN-γ in each tube is measured after 16–24 hours incubation. The final test result is defined as the concentration of IFN-γ in the TB antigen tube minus the concentration of IFN-γ in the nil control tube (that is, background IFN-γ). The test manufacturer has set a positive result to be equal to or greater than 0.35 international units per mL (IU/mL).

The mitogen tube should stimulate release of IFN-γ from the lymphocytes of immunocompetent individuals. Patients with low concentrations of IFN-γ (i.e., less than 0.5 IU per mL) in the mitogen tube following incubation are considered to have an ‘indeterminate’ result.

Indeterminate results may occur either due to immune compromise or due to technical factors such as inadequate mixing of the mitogen tube following addition of blood. Repeat testing of patients with indeterminate results may yield either a positive or negative in a proportion of patients, particularly when technical factors are suspected as being the cause of an indeterminate result.
Appendix 2: Interpretation of the QuantiFERON Gold in-tube assay®

Results interpretation guide
References


Guidelines for Tuberculosis Control in New Zealand 2010
Chapter 11: Mycobacteriology: Laboratory Methods and Standards


Chapter 12: Infection Control and Occupational Health in Tuberculosis Disease

Summary

Exposure to tuberculosis in the healthcare setting

Tuberculosis (TB) is a communicable disease that is a risk to healthcare workers.

The greatest risk to healthcare workers is from a patient who is not suspected of having TB. Patients receiving treatment for TB may continue to be smear-positive for prolonged periods but have significantly reduced infectivity.

Infectivity of children

Children aged under 12 years are rarely infectious. However, if children are sputum smear-positive, they need to be treated with the same precautions with which adults are treated.

Isolation of patients with infectious tuberculosis

Isolation of patients with infectious TB is an important public health intervention and may take place in hospital or the community.

If infectious patients are sufficiently unwell to require hospital admission or cannot comply with community infection control precautions, they should be isolated in hospital.

For infectious patients who are not acutely ill, home isolation and treatment is often preferred. Patients with smear-positive pulmonary TB may be removed from isolation, if:

- they have had a minimum of two weeks’ effective chemotherapy
- their cough has resolved
- at least two sputum specimens have been smear-negative.

Many patients will have ceased to produce sputum after two weeks’ treatment. They are unlikely to be infectious.

Infection control within healthcare settings

Administrative controls

- All healthcare facilities should have in place administrative measures to reduce the exposure to patients with TB.
- Infection control policies and procedures.
- Laboratory diagnostic capabilities.
- Proper cleaning and sterilisation or disinfection of medical equipment.
- Staff education and training programmes to ensure prompt detection, airborne precautions, and treatment of persons who have suspected or confirmed TB.
- Linkage with public health services.

Hospital engineering controls

People should be isolated in airborne infection isolation rooms if pulmonary TB has been diagnosed or is suspected.
Personal protective equipment

Healthcare workers providing care for adult patients with known or suspected infectious pulmonary TB must wear particulate respirators (N95) that have been approved by the National Institute for Occupational Safety and Health, USA.

Staff screening

Pre-employment screening

Healthcare staff and students should be screened for TB infection using a risk-assessment questionnaire and either a Mantoux test or interferon gamma release assay (IGRA) before they start employment. If the test is positive or the person is at very high risk of TB infection, a chest X-ray (CXR) is indicated. A CXR is also indicated for healthcare workers with previous positive test results.

Universal use of the Bacille Calmette-Guérin (BCG) vaccination for staff and students is not advised in New Zealand for three reasons:

- The risk of occupationally acquired TB for most workers is relatively low.
- BCG has low efficacy in adults.
- BCG affects Mantoux reactions, so causes problems when the Mantoux test is subsequently used as a diagnostic tool. This is less of a concern if HCW screening is performed using IGRA.

Surveillance during employment

Staff at high risk of TB exposure should complete an annual questionnaire about TB symptoms and exposure, and a Mantoux test or IGRA (if they previously tested negative).

Conversion of the Mantoux test or IGRA is an indication for a CXR. People with abnormal CXRs should be investigated by a respiratory physician. If the CXR is normal, treatment of latent TB infection should be considered.

Staff working in lower-risk areas should complete periodic questionnaires during their employment and be asked to report symptoms consistent with TB, especially if they are working with immune-suppressed patients.

Routine, periodic CXR screening is not recommended for healthcare workers.

Infection control in non-healthcare facilities

Correctional facilities

Higher rates of TB occur among current or recent prisoners. The key activities required to prevent transmission of TB in correctional facilities are:

- screening to find persons with active disease
- containment to prevent transmission of TB
- supervision of the persons treatment
- maintenance of uninterrupted care prior to release into the community.

Other occupational group

The risk is difficult to define in other non-health-related occupational groups but does not appear to pose a significant risk for occupational acquisition.
Introduction

Healthcare workers face unavoidable hazards, including exposure to patients with infectious tuberculosis (TB). The risks posed by this hazard cannot be eliminated, but they can be reduced.

An infection control programme should formalise and document the policies, procedures and practices necessary to minimise the risk of acquiring TB from the work environment. The policy and procedures for infection control and prevention should take into account the particular characteristics and infection risks of the individual facility. The Health and Safety in Employment Act 1992 and the Health and Safety in Employment Regulations 1995 outline the legislative requirements for both employers and employees to minimise harm in the work place.

The employer responsibilities are to provide all staff in the healthcare facility with adequate protection against acquiring TB and to provide a safe working environment. Safe work procedures should be developed within the framework of hazards identification, assessment and control. These include screening at baseline for previous exposure, staff access to appropriate testing, vaccination and counselling programmes, procedures for monitoring employee health, a procedure for employees to report exposures and staff education and training in the principles, polices and procedures of infection control.

The employee has the responsibility to take all practicable steps to protect their health and the health of others by following the policies and procedures of the infection control and prevention programme at the facility.

The infection control aspects of tuberculosis in the healthcare setting include:

- administrative controls:
  - infection prevention and control policy and procedures, including staff screening for active tuberculosis, and latent tuberculosis
  - strengthen diagnostic capabilities of the laboratory
  - proper cleaning and sterilisation or disinfection of medical equipment
  - training and education of HCW regarding TB to ensure prompt identification of people with TB symptoms and adherence to policies for the prevention of transmission of TB
  - close liaison with public health services
- engineering controls
- use of protective personal equipment.

Although there are occupational TB screening programmes in hospitals, there are few published accounts of the epidemiology of latent TB infection and TB disease among New Zealand healthcare workers.¹
Information for this chapter was obtained from the following international guidelines:

- NICE (2006) Clinical diagnosis and management of tuberculosis, and measures for its prevention and control.²
- Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in healthcare settings (2005) Centers for Disease Control and Prevention.³
- Guidelines for Australian Mycobacteriology Laboratories (2006) National Tuberculosis Advisory Committee.⁴
- The BCG vaccine: information and recommendations for use in Australia (2006) National Tuberculosis Advisory Committee.⁵

### 12.1 Infectivity of patients with tuberculosis

#### 12.1.1 Change in sputum status with treatment

Analysis of smear and culture results from the mycobacteriology laboratory at Auckland Hospital showed that:

- at least 95% of (pre-treatment) specimens with \( \geq 0–1 \) acid-fast bacilli (AFB) per high-power field (HPF) on microscopy were culture-positive
- cultures from patients with smear-negative pulmonary TB take an average 14 days to become culture-positive
- cultures from patients with 10 or more AFB/HPF before TB treatment take an average four days to become culture-positive
- cultures from patients with 10 or more AFB/HPF who have received at least 14 days’ treatment take an average 10 days to become culture-positive.

The Auckland data⁵⁹ suggest that the time it takes for sputum specimens to become culture-positive may have potential as an indicator of the quantity of viable organisms, and therefore of patient infectivity. It may prove to be a more valid predictor of infectivity than the sputum smear result alone. This finding will need to be confirmed by others before it can be included in practical guidelines for the release of smear-positive patients from isolation.

Studies have also been conducted overseas.⁷,⁸ Telzak et al identified cavitatory disease, numerous AFB on the initial smear and no prior history of tuberculosis as independent predictors of a longer time to sputum smear and culture conversion.⁷ Al-Moamary et al looked at patients who remained smear positive 20 weeks after starting treatment.⁸ Only seven out of 30 patients (23%) remained culture-positive. This group of patients was more likely to have localised disease on a chest X-ray (CXR), had less radiologic improvement on follow-up, had a higher prevalence of drug resistance, and was less compliant with medication than patients with persistently positive smear results and negative culture results.
For compliant patients with fully susceptible TB, it is likely that they are rendered non-infectious in a matter of weeks, see section 12.3.3.

12.1.2 Infectivity of patients who remain smear-positive on treatment

Patients on treatment may continue to be smear-positive for prolonged periods. The infectivity of these patients is unclear. Most evidence suggests patients have significantly reduced infectivity on appropriate treatment, even if they continue to be smear-positive.9,10

Experimental exposure of guinea pigs to sputum smear-positive patients has demonstrated that the infectiousness of untreated patients was much greater than that of patients on chemotherapy. Some patients were markedly more infectious than others. Patients became non-infectious for guinea pigs after two weeks' chemotherapy.11,12

12.1.3 Infectivity of children

Children under 12 years are rarely infectious. They usually have primary rather than post-primary TB and do not usually have laryngeal or bronchial disease. Generally, they do not have a cough of adequate strength to expel significant numbers of TB bacilli. However, some children such as those with endobronchial disease and older children whose disease may more closely resemble adult TB may be infectious. Sputum smear-positive children need to be managed with the same precautions as adults.

12.2 Isolation of patients with infectious tuberculosis (sputum smear-positive tuberculosis)

Isolation of infectious TB is an important public health protection measure and may occur in hospital or the community.

12.2.1 Isolation of infectious cases in hospital

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

- sufficiently unwell to require admission to hospital
- unable to comply with the community infection control precautions.

Patients should be cared for using Airborne Precautions, in addition to Standard Precautions, which are designed to reduce the risk of airborne transmission of infectious agents. The patient should be placed in an airborne infection isolation (AII) room. An AII room is required to have monitored negative air pressure in relation to the surrounding areas, six to 12 air changes per hour and appropriate discharge of air outdoors or monitored high-efficiency filtration of room air before the air is circulated to other areas in the hospital. All individuals entering the room must wear respiratory protection (N95 respirator) when entering the room.
12.2.2 Isolation of infectious cases at home

It is possible to initiate anti-TB therapy at home. If the patient is not acutely ill, home isolation and treatment is often the preferred option. Home isolation and treatment minimises the possibility of previously unexposed people being exposed to TB, which might happen in a hospital. The management of these patients will be shared by the District Health Board Respiratory Service and Regional Public Health Communicable Team.

A public health nurse experienced in TB control should visit the home of the isolated patient within 24 hours of diagnosis and discuss isolation requirements with the patient and their family. The nurse must explain that:

- the patient should stay at home and not go to places where there will be previously unexposed or casually exposed people
- 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 be strongly discouraged 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 public health nurses) visit the house
- the patient must cover their mouth when sneezing or coughing
- the patient needs to adhere to the schedule of medication and side-effect monitoring.

The nurse must also educate the family about disease transmission and disease control.

12.2.3 Criteria for ending isolation

Patients with smear-positive pulmonary TB may be considered for removal from isolation, if all of the following have been met.

- The patient has had a minimum of two weeks’ effective chemotherapy.
- The patient has stopped coughing.
- The patient is infected with a fully susceptible strain of *Mycobacterium tuberculosis*.
- The patient is responding well to treatment.
- At least two of the patient’s sputum specimens are smear-negative or the patient remains smear-positive but is culture-negative.\(^\text{13}\)

Many patients will have ceased to produce sputum after two weeks’ treatment and are unlikely to be infectious. If spontaneous sputum specimens cannot be obtained, supervising nursing staff must be sure the patient is no longer coughing before the decision is made to end isolation.
12.3 Administrative measures for infection control

All healthcare facilities should have in place administrative measures to reduce the exposure to patients with TB.

12.3.1 Infection control policy

Important measures must be implemented when a person with suspected or confirmed infectious TB is admitted to hospital. These measures should be clearly documented in a written Infection Control Policy. The purpose of this policy is to ensure prompt detection of infectious cases and the proper placement of patients in Airborne Precautions.

- In addition to Standard Precautions, Airborne Precautions must be used when providing clinical care for patients if pulmonary TB is suspected or has been diagnosed.
- The patient should be placed in an airborne infection isolation (AII) room which must have modern, negative-pressure ventilation systems (see section 12.5.2).
- Aerosol-generating procedures such as bronchoscopy and sputum induction on patients with TB (and some other infections) should be carried out in respiratory isolation conditions even when TB is only remotely possible; particulate respirators must be worn.
- Patients with human immunodeficiency virus (HIV), regardless of whether they have TB or not, should be nursed in separate wards from non-HIV infected TB patients. Nosocomial TB outbreaks have been documented overseas in HIV-infected people.
- Infectious TB patients must wear surgical masks when they leave the isolation room for investigations in other parts of the hospital.
- Standard Precautions will protect against the unlikely possibility of cutaneous transmission of TB from body substances containing *M. tuberculosis*.
- Particulate respirators and gloves are required for TB wound care.

12.3.2 Laboratory diagnostics

The results of smear examinations for AFB on respiratory specimens should be available within 24 hours (see Chapter 11, so people in whom infectious TB is not confirmed can be considered for removal from isolation.

There should be processes in place to ensure that the results are promptly reported to the requesting Doctor or Medical Unit and to the Infection Control Service.

12.3.3 Proper cleaning and sterilising or disinfection of medical equipment

Instruments such as bronchoscopes and nebulisers used for patients with TB and other mycobacterial diseases become contaminated. If the cleaning and sterilisation or disinfection of the equipment is inadequate, organisms may be transferred from one patient to another. Contaminated equipment may also transfer viable organisms to specimens from patients who do not have TB disease, giving false-positive smears or cultures (see Chapter 11).
Each District Health Board should have a policy for the microbiological surveillance of endoscopes that is supervised by an infection control committee.

Standards New Zealand has published advice on the cleaning and sterilisation of instruments. The 3rd edition’s GENCA ‘Infection Control in Endoscopy’ guideline has recently been released in draft form. It recommends monthly testing for routine bacteria and mycobacterial cultures (culturing for rapid growing mycobacteria not M. tuberculosis) from all bronchoscopes. The water from the automatic endoscope processes should also be cultured for rapid growing mycobacteria.

12.3.4 Training and education of HCW regarding tuberculosis
All HCW should receive education about the symptoms of tuberculosis, the appropriate isolation precautions to be applied when caring for patients suspected or proven to have tuberculosis.

12.3.5 Close liaison with public health services
Tuberculosis disease is notifiable. Early liaison between the public health service and the infection control and occupational health services in the facility is necessary to avoid confusion of roles and responsibilities when inadvertent HCW exposure necessitating contact tracing occurs.

12.4 Hospital engineering controls
12.4.1 Background
Isolation areas require adequate ventilation with direct engineering controls that dilute airborne droplet nuclei containing TB bacilli.

The physical isolation of a patient in a well-ventilated room does not reliably prevent airborne transmission unless the room has negative pressure. An open window will change the direction of airflow and may contaminate areas outside the isolation room.

Engineering controls can be thought of as different ways of achieving ‘dilution’ of airborne droplet nuclei that contain TB bacilli. It is expensive for facility designers and maintenance staff to fully implement all the guidelines, and little empirical evidence shows what provides the best results for a certain level of investment. Some systems, unless very carefully designed and maintained, will not provide the necessary protection. Equipment such as fans deteriorate in performance with age and may be affected by structural alterations to the building or inappropriate maintenance. There are reports of facilities where the design intention was good, but the function was poor. The system’s performance must be regularly checked, using techniques such as smoke testing.
12.4.2 Negative-pressure rooms

Negative-pressure ventilation extracts air and lowers the pressure in the isolation room. This ensures contaminated air does not flow from the isolation room to clean areas. However, negative-pressure ventilation does not protect healthcare workers who enter the room; they must wear appropriate face masks. An anteroom outside the isolation room further reduces the risk of the isolation room contaminating air in the rest of the ward. Air is extracted from the anteroom at a lesser rate than from the isolation room.

In hospitals with air conditioning systems, the ventilation engineer needs to design a system to change the air more than the recommended number of times per hour. The Centers for Disease Control and Prevention recommends more than six air changes per hour in general patient areas such as waiting rooms and over 12 air changes per hour in areas used to nurse TB patients.3

It takes a long time to completely clear a room from the aerosol generated by a cough. As shown in Table 12.1, even at the recommended air change rate (12 air changes per hour) the room will not be completely clear (99.9% clean) for 35 minutes.3

Thus, dilution takes time and further demonstrates the need for personal respiratory protection. The information in Table 12.1 also assumes perfect mixing, which is rare in practice.

<table>
<thead>
<tr>
<th>Air change rate per hour</th>
<th>Percentage aerosol removed</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>90%</td>
</tr>
<tr>
<td>6</td>
<td>28 minutes</td>
</tr>
<tr>
<td>12</td>
<td>12 minutes</td>
</tr>
</tbody>
</table>

Table 12.1: Time required to remove the aerosol produced by a cough

12.4.3 Filtration

A TB isolation room does not need special inlet filtration to improve the incoming air quality since the contaminant is introduced within the room. However, filtration of re-circulated air within the room can be viewed as a method of increasing the effective dilution without increasing the number of air changes per hour. If air in a TB isolation room is re-circulated, filtration by high-efficiency particulate attenuation (HEPA) filters built into the ceiling space is required.

Self-contained portable HEPA filtration units are available and claim cost-effective performance, but they are prone to short-circuiting the air flow and are not recommended if built-in systems are available.22
12.4.4 Ultra-violet germicidal irradiation

There is increasing evidence about the effectiveness of ultra-violet germicidal irradiation (UVGI) on the TB aerosol. Upper-room UVGI systems are have evaluated to see how effective they are at killing or inactivating airborne mycobacteria. Currently it has been established that appropriately designed and maintained upper-room UVGI systems may kill or inactivate airborne mycobacteria and increase the protection afforded to HCW while maintaining a safe level of UVGI in the occupied lower portion of the room. Additional research needs to be done to better plan effective upper-room UVGI fixture installations in the healthcare setting taking into account variables such as air mixing and measurement of UV fluence levels in the upper room.

12.4.5 Monitoring the effectiveness of engineering controls

A programme of regular testing is required to ensure engineering controls of air quality are effective. Testing should include:
- monthly smoke tests to ensure air-flow direction is as intended
- checks that negative-pressure gauges are functioning correctly
- regular review and replacement of HEPA filters.

12.5 Personal protective equipment

Healthcare workers providing care for adult patients with known or suspected infectious pulmonary TB must wear particulate respirators (N95) that have been approved by the National Institute for Occupational Safety and Health, USA.

There are a number of approved particulate respirators available in New Zealand; the most commonly used ones in healthcare are the 3M n95 1860, 1860s and1870.

The following are important requirements.
- Training should be given in the use of particulate respirators and the need to check for satisfactory facial fit; periodic fit checks should be made.
- N95 particulate respirators are intended to be disposable or single use. The manufacturers advise that they be discarded when the user leaves the isolation room. Some New Zealand facilities re-use these respirators because of their high cost. If re-use occurs, careful labelling of the mask and placement of it in a suitable container, such as a biohazard bag used for clinical specimens, between uses is needed. The respirator should be discarded at the end of a working shift.
- Reusable or multi-use particulate respirators must be labelled for a single staff member’s use and maintained according to the manufacturer’s instructions.
- Some staff, such as those with beards, may need alternative protection. Obtain advice from the Infection Control Service.
12.6 Staff screening

The magnitude of the risk of occupational transmission of tuberculosis in any healthcare setting varies by setting, occupational group, prevalence of TB in the community, patient population and effectiveness of infection control procedures. In general the risk of TB is elevated in HCW who work in wards with patients with TB, nurses in hospitals in general, nurses attending HIV-infected or drug-addicted patients, pathology and laboratory workers, respiratory therapists and physiotherapists, physicians in internal medicine, anaesthetists, surgeons and psychiatrists. It is also elevated in non-clinical staff such as cleaners and orderlies.24

A recent review of the prevalence and incidence of TB infection and disease among HCW in countries categorised by income reported that the median prevalence of latent TB infection in HCW from low–median income countries (LMIC) was 63% (range 33–79%) compared to 24% (range 4-46%) in HCW from high income countries (HIC).25 Among HCW from LMIC latent TB infection was consistently associated with markers of occupational exposure but in HIC it was associated with non-occupational factors. The median annual incidence of TB infection attributable to health care work was 5.8% (range 0–11%) in LMIC and 1.1% (range 0.2–12%) in HIC. Rates of active TB in HCW were consistently higher than the general population in all countries. Administrative controls were identified as important in all countries for controlling occupationally-acquired TB. Administrative controls were also seen as the cheapest and easiest measure to implement.25

Internationally recommendations about staff screening are similar. Baseline screening in the form of a risk assessment questionnaire and either a Mantoux test or interferon gamma release assay (IGRA) are recommended. The purpose of the baseline screening is to provide a basis for comparison in the event of a potential or known exposure to tuberculosis and to facilitate the detection and treatment of new employees with latent or active TB infection. However, the response to screening outcomes (Mantoux or IGRA results) differs. The difference mainly relates to BCG vaccination being recommended by some guidelines for those employees found to have negative results.

In the UK2 it is recommended that all staff new to the National Health Service (NHS) who will be working with patients or clinical specimens undergo a TB check. This includes completing a questionnaire that assesses personal and family history of Tb, determines the presence of signs and symptoms suggestive of active TB infection and provides evidence for previous assessment for TB risk by screening with a Mantoux or IGRA in the last five years. Employees new to the NHS from a country of high TB incidence, or who have contact with patients in settings with a high TB prevalence, should have a Mantoux or IGRA.2 If the result is negative they should be risk assessed for HIV infection and offered BCG vaccination. If positive they should be referred to a TB clinical service. If a new employee is from a low incidence setting without prior BCG vaccination and has a positive Mantoux or IGRA then they should have a medical assessment and a chest X-ray.2 They should be referred to a TB clinical service for further consideration of TB treatment if the chest X-ray is abnormal, or for consideration of treatment for latent TB if the chest X-ray is normal.
In the USA all paid and unpaid persons working in healthcare settings who have the potential for exposure to TB through air space shared with persons with infectious TB disease should be included in a TB screening programme. The screening programme involves a questionnaire to assess risk factors and baseline testing for TB infection. If a Mantoux or IGRA has not been performed in the last 12 months then testing should be performed. If the result of the TST in the last 12 months was negative another Mantoux should be done.

For all employees with negative Mantoux or IGRA it is up to the institution to decide whether to perform serial testing or not. This decision will be based on a risk assessment for the setting. Serial screening for signs and symptoms of TB infection may be performed in high risk settings such as staff involved in aerosol-generating or aerosol-producing procedures (bronchoscopy, sputum induction and administration of aerosolised medications) and those participating in suspected or confirmed \textit{M. tuberculosis} specimen processing and culturing of \textit{M. tuberculosis}. TB training and education is also recognised as an important aspect of new staff induction.

In Australia the BCG strategy is no longer recommended as the primary means of HCW protection. The preferred strategy is appropriate infection control measures including staff education and Mantoux testing program that identifies and treats the at-risk infected HCW. The Australian guidelines for screening of personnel working in a mycobacteriology laboratory require all new staff to have a two-step Mantoux perform. Any positive results should be followed up by a CXR and medical assessment. Staff with negative TST should have an annual test and any staff with TST conversion will need further assessment.

12.6.1 Pre-employment screening

In New Zealand healthcare staff who have contact with patients or infectious materials must undergo pre-employment screening. This screening aims to:

- detect applicants who may have TB disease, and hence avoid the possibility that this may be transmitted to patients
- identify those with latent TB infection so that they can be counselled and offered treatment where appropriate
- obtain baseline data about Mantoux or IGRA status for comparison with data obtained during routine surveillance or after exposure to TB.

Similar screening by educational institutions is required for students of nursing, medicine and allied health. This screening must be included in the agreements between hospitals and educational institutions (universities and polytechnics). When hospitals employ agency (bureau) staff, the contract must specify similar screening for the agency workers. Larger hospitals should have an in-house occupational health unit to facilitate co-operation with other services such as infection control and public health.
Pre-employment screening to prevent staff exposure to patients with tuberculosis infection in rest homes is unnecessary. Among 288 cases aged over 70 years who were notified in 1995–99, only 15 (9%) were recorded as residing in a rest home or retirement village. This approximates the proportion of the elderly population living in such settings and indicates no excess risk. However, if the new staff member is from a country of high TB incidence, or has had contact with patients in settings with a high TB prevalence, then consideration should be given to have the new staff member undergo pre-employment screening. Advice should be sought from the local District Health Board Infection Control Service or Public Health Unit.

Pre-employment screening consists of:
- pre-employment questionnaire
- IGRA (recommended) or two-step Manotux
- CXR, if appropriate.

Pre-employment questionnaire
The pre-employment questionnaire should cover:
- birth, residence, and extended travel in countries of high TB prevalence
- previous TB
- previous Mantoux or IGRA results
- known TB exposure from family or work
- previous occupations
- proposed new occupation
- health problems that would increase the risk of developing TB disease.

Two-step TST or interferon gamma release assay
A number of District Health Boards are shifting away from using the Mantoux due the logistics of delivering the test and are now using the QuantiFERON Gold assay for pre-employment screening.

If the Mantoux is used for pre-employment screening then the two-step Mantoux is essential, if the person is not known to be positive. Failure to use the two-step test may later lead to an incorrect diagnosis of a Mantoux conversion and to unnecessary investigation or treatment. If a Mantoux has been done in the last 12 months and was negative then only a single Mantoux needs to be performed.

A full discussion of the two-step Mantoux test is in Chapter 8.

Chest X-ray
A CXR should be offered to those with a positive Mantoux reaction or IGRA or if concerns have been raised as a result of the questionnaire or there has been a previously positive Mantoux or IGRA.
Abnormal CXRs should be discussed with a respiratory physician, who may need to examine the person.

Pre-employment Bacille Calmette-Guérin vaccination
The place of Bacille Calmette-Guérin (BCG) vaccination for healthcare workers is controversial.2,3 Universal use of BCG for staff and students is not indicated in New Zealand or Australia, because most workers are at comparatively low risk of occupationally acquired TB. BCG has been shown to reduce the occurrence of severe forms of TB disease in children and overall might reduce the risk of progression from latent TB to TB disease but it is not thought to prevent TB infection. It has a low efficacy in adults and makes the further use of the Mantoux as a diagnostic tool more difficult.

12.6.2 Surveillance during employment
Surveillance during employment is a controversial issue and different countries have taken different approaches. The United States requires individual institutions to perform risk assessment in their setting to determine if serial screening is required.3 In the UK serial screening is not recommended.2 In New Zealand it is up to individual District Health Boards to determine the need for serial surveillance.

Surveillance can include regular:
- TB symptom questionnaires
- Mantoux or IGRA
- CXR, if applicable.

In general staff working in TB, or general respiratory wards, are at high risk of TB exposure, as are staff in bronchoscopy or induced-sputum rooms, TB laboratories, and post-mortem examination rooms. These staff should complete an annual questionnaire about TB symptoms and recent exposure and have a Mantoux or IGRA (if they previously tested negative).

Staff working in areas of lower risk should be informed of their duty to report signs and symptoms suggestive of TB as part of responsibility to protect patients. Serial screening is not required.

Staff with Mantoux or IGRA conversion should have a CXR, and those with abnormal CXRs should be examined by a respiratory physician. If TB disease is excluded by a normal CXR, treatment of latent TB infection may be considered.

12.6.3 Staff exposed to patients with infectious tuberculosis
Staff exposed to an infectious TB case are managed in the same way as other contacts are managed (see Chapter 7).
12.7 Infection control in non-healthcare settings

12.7.1 Infection control in correctional facilities

High rates of TB occur in correctional and detention facilities. In New Zealand, from 1997 to 2001 the TB rate among current or recent prisoners was approximately six times higher than the average national TB rate. Incarcerated persons are at high risk for TB for many reasons; most come from groups at higher risk of TB within the community. They may not have had access to primary care before incarceration and standards of healthcare within correctional facilities do not match those available in the community. The physical structure of the facilities contributes to disease transmission, as facilities often provide close living quarters with inadequate ventilation and are often overcrowded. Further compounding this is the movement of inmates into and out of overcrowded and inadequately ventilated facilities making transmission of TB more likely and hindering TB-control measures.

The key activities required to prevent transmission of TB in correctional facilities are:

- screening – finding persons with active disease
- containment – preventing transmission of TB and treating the person with TB
- supervision of the persons TB treatment
- maintenance of uninterrupted care by liaising with public health services before release into the community.

New prisoners may, during their screening process on admission to a correctional facility, give a history of being on current treatment for active TB disease (diagnosed in the community), past treatment for active TB disease or treatment for LTBI, or past diagnosis of LTBI without treatment. Infectious TB may also be suspected and diagnosed for the first time in a prisoner already being held in a correctional facility. It is important to raise awareness of signs and symptoms in prisoners, prison staff and healthcare workers working in these settings.

An infectious case should be immediately transferred to a hospital and placed in an airborne infection isolation room until they have completed at least two weeks of appropriate anti-TB treatment.

All staff in correctional facilities should be familiar with the infection control policy for that institution. This policy should include how to access N95 particulate respirators if the possibility of infectious TB in an inmate arises.

When an infectious TB case is discovered or managed in prison:

- the clinician should alert Department of Corrections and public health teams about the infectious potential and treatment
- written communication should continue throughout the period of treatment and follow-up
• public health staff must be available to conduct education and contact investigation among prison staff
• liaison between prison services and public health will allow identification and education of families at risk for TB exposure.

The management of inmates with TB should be in accordance with *Tuberculosis Case Management in Prisoners: Joint Protocol for Corrections Facilities and TB Treatment Supervising Services (Regional Public Health Services and/or Clinical TB Services) in New Zealand* (date of publication (online): April 2010).

**12.7.2 Screening for healthcare workers in correctional facilities**

The high incidence of TB cases in correctional facilities is associated with an increased rate of TB transmission to prison workers as well as other inmates in some studies. However, a recent study looking at the risk factors for occupational infection among healthcare workers in correctional facilities in the USA reported that the risk factors were predominantly demographic rather than occupational.

Healthcare workers working in correctional facilities should undergo the same screening processes as HCW in healthcare settings (see section 12.7).

**12.8 Occupational risk for persons working in occupations with risk of exposure to tuberculosis**

**Silica workers**

Silica workers have a high incidence of TB, particularly when silicosis has developed, but this is rarely an issue in New Zealand.

**Abattoir workers**

In New Zealand, bovine TB (*M. bovis*) is an important disease of livestock and has been documented in cattle, deer, sheep, pigs and goats. A high incidence of TB has been noted in New Zealand abattoir and freezing workers, with 21 cases notified from 1995 to 2000. However, in at least 12 of these cases the organism was identified as *M. tuberculosis*, implying that the source of infection was not the animal carcasses.

**Veterinarians**

Because of their exposure to livestock and domestic animals, veterinarians are at risk of infection by zoonotic pathogens. As well as farm animals, domestic pets, including cats and dogs, may be infected by *M. bovis*. Surprisingly, there has been no report of TB transmitted from a diseased animal to a veterinarian in New Zealand.

**Farm and animal workers**

Farm and animal workers have the potential for extensive contact with zoonotic pathogens.
Possum hunters

In New Zealand, possums are reservoir hosts for *M. bovis* and are responsible for the spread of infection in wild animals and domestic stock.\(^{34}\) It is estimated that around 15–20% of possums in an endemic area become infected. Transmission from possums to cattle and deer is probably also by the respiratory route, although some ingestion also occurs when domestic stock are attracted to terminally ill possums.\(^{34}\)

There has been no recorded case of human infection with *M. bovis* occurring in possum hunters, but there is a theoretical risk of this. Infection might occur by the respiratory route from live possums or when gutting infected lymph glands and other organs.

Armed forces

There is no recent evidence of increased risk of TB in the New Zealand armed forces. Recommendations for armed forces personnel working in high-incidence countries are the same as for travellers to these countries.

Miscellaneous occupations

Analysis of data from the United States National Occupational Mortality Surveillance database identified disproportionately high numbers of deaths from TB in funeral directors, food service and preparation workers, and machine operators, as well as healthcare workers and occupations with silica exposure.\(^{35,36}\) TB in food service and preparation workers and machine operators may be ascribed to confounding risk factors associated with their low socioeconomic status, but funeral directors may have a true risk of exposure from cadavers.\(^{37,38}\) This would also be consistent with the findings of higher rates in pathologists and mortuary workers.

There is no evidence of increased risk of TB in New Zealand for teachers; despite the fact about 167 children of school age were identified with TB between 1996 and 2000. Children have a low risk of transmission of TB.

There is no evidence of increased risk of TB in New Zealand for early childhood workers, police, and conservation or ambulance workers.

References


Further reading


