Guidelines for Tuberculosis Control in New Zealand 2003

Published in December 2002 by the Ministry of Health
P O Box 5013, Wellington, New Zealand

ISBN: 0-478-25593-4 (Website)

This document is available on the Ministry of Health's website: http://www.moh.govt.nz
Chapter 1: The Epidemiology and Surveillance of Tuberculosis in New Zealand

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Summary

TB epidemiology

The current TB notification rate in New Zealand is 10 per 100,000. Incidence has increased slightly in recent years.

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

The highest rates of disease are seen in:
- urban areas, particularly Auckland and South Auckland
- older adults aged ≥70 years
- individuals of non-European ethnicity, particularly ‘Other’ and Pacific.

Contact with a known TB case is an important risk factor for the disease.

Outbreaks of TB occur.

Type, management and outcome of TB 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.

Mortality rates are highest among older individuals (≥70 years) but vary by ethnicity.

Information on directly observed therapy (DOT) is poorly recorded by most health districts, where the information is recorded.

Multi-drug resistance accounts for only 1% of all TB isolates.

Surveillance of TB

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

Any medical practitioner diagnosing or suspecting a case of new or relapsed TB is required, under the Tuberculosis Act 1948, to notify the case to the local medical officer of health.

EpiSurv data entry should ideally be done by the Public Health Service after liaison with the reporting clinician.

Although people receiving treatment for latent TB infection are not legally required to be notified, clinicians are requested to notify them to the medical officer of health for monitoring purposes.

Recent changes to surveillance include:
- alterations to the Tuberculosis Case Report Form (see Appendix 1.2)
- DNA fingerprinting of all isolates.

Suggested improvements to the current system include:
- developing methods to identify unnotified cases
- regular review of surveillance data to inform policy.
Introduction

In this chapter we:

- review the epidemiology of TB in New Zealand using EpiSurv notification data from 1995 to 2001
- describe the system of TB surveillance adopted in New Zealand from November 2002
- outline some recommendations for improving the current system of TB surveillance.

The most thorough recent review of TB epidemiology in New Zealand is provided by J Carr et al. The Epidemiology of TB in New Zealand, 1995–1999. The information in this chapter was obtained from that review and from ESR data.
1.1 Epidemiology of TB

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 159 per 100,000 (see Figure 1.1). After a peak in cases around the time of the Second World War there was a steady decline in disease incidence.

\textbf{Figure 1.1:} Tuberculosis notification rates, 1948–2001

TB incidence reached its lowest point in 1988, with 295 notified cases. Since this time between 300 and 500 cases have been notified annually, with some evidence that incidence is increasing slightly (see Figure 1.2). A similar trend has been observed in other developed countries and is related to HIV/AIDS, immigration from high-incidence countries, and the deterioration of control programmes.\textsuperscript{2}
The current average annual rate of TB in New Zealand of around 10 per 100,000 is comparable to that reported from the UK (10 per 100,000), but is higher than that reported from the US (6 per 100,000), Canada (7 per 100,000) and Australia (5 per 100,000).³

Although the validity of international comparisons is limited by variations in case detection and reporting practices, higher rates in this country 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 disease resurgence in New Zealand.⁴

1.1.2 Outbreaks

An estimated 10% of all notified 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. In 2001 there were five reported outbreaks of TB, with an average of 2.8 cases per outbreak. Large outbreaks involving between 12 and 61 cases have previously occurred in a church group, a prison and in schools.

1.1.3 Incidence by health district

Within New Zealand several health districts report consistently high rates of disease. Auckland (23.0 per 100,000) and South Auckland (19.0 per 100,000) report the highest rates, followed by Wellington (15.1 per 100,000) and the Hutt (13.6 per 100,000) (see Table 1.1 and Figure 1.3). High rates in these cities are consistent with overseas findings that disease tends to persist in urban areas⁵ and with the geographic distribution of ethnic groups most affected by the disease.
Several studies have examined the epidemiology of TB in the Auckland\textsuperscript{6,7,8} and Wellington regions.\textsuperscript{9,10} Clustering of cases in areas of socioeconomic deprivation within these health districts and the importance of immigration from countries with a high prevalence of TB has been noted in both areas.

Table 1.1: TB notifications, by health district, 1995–2001

<table>
<thead>
<tr>
<th>Health district</th>
<th>Total number of cases (1995–2001)</th>
<th>Average annual notification rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Northland</td>
<td>90</td>
<td>9.4</td>
</tr>
<tr>
<td>Northwest Auckland</td>
<td>260</td>
<td>9.4</td>
</tr>
<tr>
<td>Auckland</td>
<td>557</td>
<td>23.0</td>
</tr>
<tr>
<td>South Auckland</td>
<td>454</td>
<td>19.0</td>
</tr>
<tr>
<td>Waikato</td>
<td>133</td>
<td>6.3</td>
</tr>
<tr>
<td>Tauranga</td>
<td>51</td>
<td>6.5</td>
</tr>
<tr>
<td>Eastern BOP</td>
<td>31</td>
<td>8.8</td>
</tr>
<tr>
<td>Rotorua</td>
<td>29</td>
<td>6.4</td>
</tr>
<tr>
<td>Gisborne</td>
<td>17</td>
<td>5.3</td>
</tr>
<tr>
<td>Taupo</td>
<td>22</td>
<td>10.2</td>
</tr>
<tr>
<td>Ruapehu</td>
<td>12</td>
<td>10.2</td>
</tr>
<tr>
<td>Taranaki</td>
<td>15</td>
<td>2.0</td>
</tr>
<tr>
<td>Hawke's Bay</td>
<td>81</td>
<td>8.1</td>
</tr>
<tr>
<td>Wanganui</td>
<td>31</td>
<td>7.2</td>
</tr>
<tr>
<td>Manawatu</td>
<td>71</td>
<td>6.7</td>
</tr>
<tr>
<td>Wairarapa</td>
<td>12</td>
<td>4.5</td>
</tr>
<tr>
<td>Wellington</td>
<td>257</td>
<td>15.1</td>
</tr>
<tr>
<td>Hutt</td>
<td>126</td>
<td>13.6</td>
</tr>
<tr>
<td>Nelson-Marlborough</td>
<td>18</td>
<td>2.2</td>
</tr>
<tr>
<td>West Coast</td>
<td>7</td>
<td>3.1</td>
</tr>
<tr>
<td>Canterbury</td>
<td>197</td>
<td>7.3</td>
</tr>
<tr>
<td>South Canterbury</td>
<td>19</td>
<td>3.4</td>
</tr>
<tr>
<td>Otago</td>
<td>58</td>
<td>4.8</td>
</tr>
<tr>
<td>Southland</td>
<td>32</td>
<td>4.1</td>
</tr>
</tbody>
</table>
1.1.4 Incidence by age

The majority of TB cases occur in adults, with the highest rates in those aged 70 years and above (see Table 1.2). Children aged under 15 years account for between 6% and 10% of all cases, but this proportion varies significantly by ethnicity (European 3%, Māori 15%, Pacific peoples 17%, Other 6%). Although the incidence of TB in children remains low, there has been no reduction in recent years.11
Table 1.2:  
TB notifications, by age group, 1995–2001

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Proportion of all cases (%)</th>
<th>Average annual age-specific rate per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>0.8</td>
<td>5.2</td>
</tr>
<tr>
<td>1–4</td>
<td>4.4</td>
<td>7.3</td>
</tr>
<tr>
<td>5–9</td>
<td>3.0</td>
<td>3.9</td>
</tr>
<tr>
<td>10–14</td>
<td>3.1</td>
<td>4.4</td>
</tr>
<tr>
<td>15–19</td>
<td>5.1</td>
<td>7.2</td>
</tr>
<tr>
<td>20–29</td>
<td>18.6</td>
<td>12.7</td>
</tr>
<tr>
<td>30–39</td>
<td>16.8</td>
<td>10.8</td>
</tr>
<tr>
<td>40–49</td>
<td>11.1</td>
<td>8.3</td>
</tr>
<tr>
<td>50–59</td>
<td>10.2</td>
<td>11.0</td>
</tr>
<tr>
<td>60–69</td>
<td>11.2</td>
<td>15.6</td>
</tr>
<tr>
<td>70+</td>
<td>15.6</td>
<td>20.1</td>
</tr>
</tbody>
</table>

1.1.5  Incidence by gender

There are no marked gender differences in the incidence of TB in New Zealand. Males account for 52% of cases.

1.1.6  Incidence by ethnicity

TB rates among Māori are five times those of Europeans, while Pacific peoples are 12 times and ‘Other’ ethnic groups 35 times greater (see Table 1.3). Ethnic disparities have increased in recent times, although differences in TB incidence by ethnic group are confounded by place of birth. When foreign-born cases are excluded, the highest number and proportion of cases are among Māori.

Table 1.3:  
Age-specific TB notifications, by ethnicity, 1995–2001

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>No. cases</th>
<th>Notification rate per 100,000</th>
<th>Relative rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>European</td>
<td>468</td>
<td>2.6</td>
<td>1.0</td>
</tr>
<tr>
<td>Māori</td>
<td>486</td>
<td>13.3</td>
<td>5.1</td>
</tr>
<tr>
<td>Pacific Island</td>
<td>375</td>
<td>30.9</td>
<td>11.8</td>
</tr>
<tr>
<td>Other</td>
<td>1126</td>
<td>91.8</td>
<td>35.3</td>
</tr>
</tbody>
</table>

* Notification rate relative to European.

The association between increasing age and disease rates applies to all ethnic groups (see Figure 1.4).
1.1.7 Incidence by place of birth

Immigration has been an important factor contributing to the TB incidence in New Zealand (see Chapter 7: ‘Tuberculosis Control in People from Countries with a High Incidence of Tuberculosis’). In 2001 60% of notified TB cases occurred in foreign-born individuals – the highest rate in recent years (see Table 1.4). There has been a small decrease in the proportion of cases notified within one year of arrival in New Zealand and a concomitant increase in the proportion notified more than one year after arrival, suggesting the possibility of more local transmission within immigrant populations (Figure 1.5). Other possible explanations for this trend include increased delay in diagnosis, or a longer interval between arrival and screening for asylum seekers.

Table 1.4: Foreign-born TB cases, 1995–2001

<table>
<thead>
<tr>
<th>Year</th>
<th>Total no. cases</th>
<th>No. (%) foreign-born cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>391</td>
<td>186 (47.5)</td>
</tr>
<tr>
<td>1996</td>
<td>352</td>
<td>197 (55.9)</td>
</tr>
<tr>
<td>1997</td>
<td>321</td>
<td>188 (58.5)</td>
</tr>
<tr>
<td>1998</td>
<td>365</td>
<td>203 (55.6)</td>
</tr>
<tr>
<td>1999</td>
<td>446</td>
<td>224 (50.2)</td>
</tr>
<tr>
<td>2000</td>
<td>354</td>
<td>197 (55.6)</td>
</tr>
<tr>
<td>2001</td>
<td>379</td>
<td>228 (60.1)</td>
</tr>
</tbody>
</table>
1.1.8 Social vulnerability as a risk factor for TB

TB has been described as a ‘barometer of social justice and equity’: although it affects people in all countries, it affects the poorest and the most vulnerable sectors of communities the most. Importantly, the effect of poverty 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). In Wellington, Naing et al. found that notification rates were associated with socioeconomic deprivation, with median household income and household crowding being independent risk factors.

1.1.9 Other risk factors

The following are the known risk factors for contacting TB.

- **Contact with a known case of TB** – this is the most common risk factor for disease. Around 42% of cases recorded this as a factor, reinforcing the importance of adequate contact tracing (see Chapter 6: ‘Contact Investigation’).

- **Institutional contact** – around 10% of notified cases have a current or recent history of institutionalisation. Listed institutions include refugee camps/immigration centres, prisons, rest homes and mental health facilities (see Chapter 10: ‘Tuberculosis Control in Non-Clinical Settings’).
Occupational contact – as a risk factor this is poorly documented. In 2000 6% of TB cases with a listed occupation were in health-related or hospital employment, but there is no information on how many of these were infected at work. An earlier study of Auckland medical students, residents and registrars found that the risk to medical staff of TB infection remains important. This study demonstrated significant differences in the prevalence of positive Mantoux tests between the three groups, indicating that infection rates increase with duration of training. Occupationally acquired TB has recently been documented in hospital and prison settings in Auckland.

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.

TB in certain high-incidence countries is increasing because of the 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 18: ‘Tuberculosis and HIV’).
1.2 Type, management and outcome of notified TB cases

1.2.1 Laboratory confirmation

The proportion of laboratory-confirmed cases has increased from 44% in 1988 to 81% in 2001 (Figure 1.6).

**Figure 1.6:** Laboratory-confirmed cases of TB, 1988–2001

1.2.2 Site of infection

Of the notified cases for which site of infection is recorded, two-thirds (66.7%) are pulmonary. The remaining cases are a combination of pulmonary and extra-pulmonary (5.0%), and extra-pulmonary alone (28.3%). A breakdown of extra-pulmonary cases by site of infection is shown in Table 1.5.
Table 1.5: Extra-pulmonary TB cases, by site, 1995–2001

<table>
<thead>
<tr>
<th>Site of extra-pulmonary TB</th>
<th>No.</th>
<th>Proportion of extra-pulmonary cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Node (excluding abdominal)</td>
<td>319</td>
<td>36.7</td>
</tr>
<tr>
<td>Intra-abdominal (excluding renal)</td>
<td>87</td>
<td>10.0</td>
</tr>
<tr>
<td>Pleural</td>
<td>98</td>
<td>11.3</td>
</tr>
<tr>
<td>Renal/urinary tract</td>
<td>69</td>
<td>8.0</td>
</tr>
<tr>
<td>Tuberculous meningitis</td>
<td>40</td>
<td>4.6</td>
</tr>
<tr>
<td>Miliary TB</td>
<td>22</td>
<td>2.5</td>
</tr>
<tr>
<td>Bone/joint</td>
<td>23</td>
<td>2.6</td>
</tr>
<tr>
<td>Other*</td>
<td>147</td>
<td>17.0</td>
</tr>
<tr>
<td>Not stated</td>
<td>62</td>
<td>7.0</td>
</tr>
<tr>
<td>Total</td>
<td>867</td>
<td>100</td>
</tr>
</tbody>
</table>

* Other includes TB of skin.

1.2.3 Morbidity and mortality

Although the incidence of disease has increased slightly over recent years, the proportion of all cases hospitalised or dying (the case fatality rate) as a result of TB declined between 1995 and 2001 (Figure 1.7).
Nearly two-thirds (65%) of TB hospitalisations are in adults. Hospitalisation and mortality rates are highest for older adults aged (> 70 years). In this group the mortality rate (2.0 per 100,000) is more than six times the overall mortality rate for all ages (0.3 per 100,000). Case fatality rates (CFRs) among those aged > 70 years vary by ethnicity:

- European: 31 deaths, CFR 20%
- Māori: seven deaths, CFR 17.1%
- Pacific peoples: four deaths, CFR 13.3%
- ‘Other’: three deaths, CFR 7%.

1.2.4 Directly observed therapy (DOT)

Information on the administration of directly observed therapy (DOT) has been collected on EpiSurv since the beginning of 1999. Between 1999 and 2001, DOT information was recorded for 31% (864 out of 2775) of all types of notified cases. Of these 864 cases, 419 (48%) received DOT (Table 1.6). Although the recording of DOT improved slightly from 30% to 32% of all cases over this time period, the proportion of those recorded who received DOT decreased from 63% in 1999 to 43% in 2001 (see Chapter 5: ‘Directly Observed Therapy’).

<table>
<thead>
<tr>
<th>Type of case</th>
<th>Receiving DOT</th>
<th>Total cases</th>
<th>% of total cases on DOT</th>
<th>% of total cases with DOT information recorded</th>
<th>% of cases, with DOT information recorded who received DOT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
<td>% of total cases on DOT</td>
<td>% of total cases with DOT information recorded</td>
</tr>
<tr>
<td>TB disease (new case)</td>
<td>262</td>
<td>199</td>
<td>624</td>
<td>24.1</td>
<td>42.5</td>
</tr>
<tr>
<td>TB disease (reactivation)</td>
<td>16</td>
<td>15</td>
<td>63</td>
<td>17.0</td>
<td>33.0</td>
</tr>
<tr>
<td>TB infection (on chemoprophylaxis)</td>
<td>134</td>
<td>210</td>
<td>1196</td>
<td>8.7</td>
<td>22.3</td>
</tr>
<tr>
<td>TB infection (on preventive treatment)</td>
<td>7</td>
<td>21</td>
<td>28</td>
<td>12.5</td>
<td>50.0</td>
</tr>
<tr>
<td>All cases</td>
<td>419</td>
<td>445</td>
<td>1191</td>
<td>2775</td>
<td>15.1</td>
</tr>
</tbody>
</table>

There is wide variation in the reporting of DOT information by health district (Table 1.7).
### Table 1.7: DOT information, by health district, all notified types of TB, 1999–2001

<table>
<thead>
<tr>
<th>Health district</th>
<th>Receiving DOT</th>
<th>Total</th>
<th>% with DOT information recorded</th>
<th>% of total on DOT</th>
<th>% with DOT information recorded who received DOT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Northland</td>
<td>12</td>
<td>0</td>
<td>34</td>
<td>46</td>
<td>26.1</td>
</tr>
<tr>
<td>Northwest Auckland</td>
<td>62</td>
<td>74</td>
<td>241</td>
<td>377</td>
<td>36.1</td>
</tr>
<tr>
<td>Auckland</td>
<td>129</td>
<td>121</td>
<td>570</td>
<td>820</td>
<td>30.5</td>
</tr>
<tr>
<td>South Auckland</td>
<td>150</td>
<td>72</td>
<td>310</td>
<td>532</td>
<td>41.7</td>
</tr>
<tr>
<td>Waikato</td>
<td>9</td>
<td>3</td>
<td>229</td>
<td>241</td>
<td>5.0</td>
</tr>
<tr>
<td>Tauranga</td>
<td>0</td>
<td>1</td>
<td>32</td>
<td>33</td>
<td>3.0</td>
</tr>
<tr>
<td>Eastern Bay of Plenty</td>
<td>0</td>
<td>4</td>
<td>12</td>
<td>16</td>
<td>25.0</td>
</tr>
<tr>
<td>Rotorua</td>
<td>0</td>
<td>0</td>
<td>12</td>
<td>12</td>
<td>0.0</td>
</tr>
<tr>
<td>Gisborne</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>7</td>
<td>0.0</td>
</tr>
<tr>
<td>Taupo</td>
<td>0</td>
<td>1</td>
<td>9</td>
<td>10</td>
<td>10.0</td>
</tr>
<tr>
<td>Ruapehu</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
<td>0.0</td>
</tr>
<tr>
<td>Taranaki</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0.0</td>
</tr>
<tr>
<td>Hawke’s Bay</td>
<td>11</td>
<td>8</td>
<td>30</td>
<td>49</td>
<td>38.8</td>
</tr>
<tr>
<td>Wanganui</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>15</td>
<td>26.7</td>
</tr>
<tr>
<td>Manawatu</td>
<td>4</td>
<td>9</td>
<td>31</td>
<td>44</td>
<td>29.5</td>
</tr>
<tr>
<td>Wairarapa</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>60.0</td>
</tr>
<tr>
<td>Wellington</td>
<td>26</td>
<td>84</td>
<td>186</td>
<td>296</td>
<td>37.2</td>
</tr>
<tr>
<td>Hutt</td>
<td>9</td>
<td>34</td>
<td>71</td>
<td>114</td>
<td>37.7</td>
</tr>
<tr>
<td>Nelson–Marlborough</td>
<td>0</td>
<td>3</td>
<td>11</td>
<td>14</td>
<td>21.4</td>
</tr>
<tr>
<td>West Coast</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
<td>0.0</td>
</tr>
<tr>
<td>Canterbury</td>
<td>1</td>
<td>15</td>
<td>80</td>
<td>96</td>
<td>16.7</td>
</tr>
<tr>
<td>South Canterbury</td>
<td>1</td>
<td>3</td>
<td>7</td>
<td>11</td>
<td>36.4</td>
</tr>
<tr>
<td>Otago</td>
<td>1</td>
<td>7</td>
<td>10</td>
<td>18</td>
<td>44.4</td>
</tr>
<tr>
<td>Southland</td>
<td>0</td>
<td>3</td>
<td>9</td>
<td>12</td>
<td>25.0</td>
</tr>
</tbody>
</table>

#### 1.2.5 Antibiotic resistance

Despite the high proportion of imported cases of TB in New Zealand, multi-drug resistance (resistance to at least isoniazid and rifampicin) is not yet a major problem in this country. Between 1989 and 1992 10% of cases showed resistance to one or more anti-tuberculous drugs, while 1% showed multi-drug resistance. Since data collection on drug resistance began in 1995, all multi-drug-resistant isolates have been from people born outside New Zealand. Current drug resistance data are shown in Table 1.8.
**Table 1.8:** Resistance patterns among culture-positive cases of TB notified in 2000 and 2001

<table>
<thead>
<tr>
<th>Resistance pattern</th>
<th>No. (%)</th>
<th>No. (%) of isolates with each pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully susceptible</td>
<td>456 (84.8)</td>
<td></td>
</tr>
<tr>
<td>Resistant to 1 agent</td>
<td>63 (11.7)</td>
<td>H 25 (5.5) S 24 (5.3) Z 13 (2.9) E 1 (0.2)</td>
</tr>
<tr>
<td>Resistant to 2 agents</td>
<td>15 (2.8)</td>
<td>HS 12 (2.6) HZ 2 (0.4) RE 1 (0.2)</td>
</tr>
<tr>
<td>Resistant to 3 agents</td>
<td>2 (0.4)</td>
<td>HSE 1 (0.2) HZS 1 (0.2)</td>
</tr>
<tr>
<td>Resistant to 4 agents</td>
<td>1 (0.2)</td>
<td>HZSE 1 (0.2)</td>
</tr>
<tr>
<td>Resistant to 5 agents</td>
<td>1 (0.2)</td>
<td>HRZSE 1 (0.2)</td>
</tr>
</tbody>
</table>

Source: ESR: Health

Notes:

a) H = isoniazid; S = streptomycin; Z = pyrazinamide; E = ethambutol; R = rifampicin.
b) Includes 11 *M. bovis* isolates.
c) Both were *M. bovis* isolates.
d) Multidrug-resistant isolate (ie, resistant to at least isoniazid and rifampicin).
1.3 Surveillance of TB

1.3.1 Objectives

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

The specific objectives of surveillance are to:

- support local management of identified cases, contacts and screening programmes
- monitor the incidence and distribution of disease and infection, at both the local and national level
- identify risk factors to support interventions aimed at the prevention of TB
- monitor the process and outcome of disease control and screening programmes so that improvements can be introduced
- monitor antibiotic susceptibility of \( M. tuberculosis \) and \( M. bovis \) to guide the appropriate use of antibiotics.

An overview of TB surveillance is shown in Appendix 1.3.

1.3.2 Definitions of terms used in surveillance

Accurate classification of cases is essential to good-quality surveillance. ESR has produced a *Public Health Surveillance in New Zealand Manual*, which provides details of how to complete the Tuberculosis Case Report Form. (See Appendix 1.1 for the pages pertaining to TB in this manual.)

*Tuberculosis disease – new cases*

A new case is defined as:

- bacteriological confirmation by a positive culture for \( M. tuberculosis \) or \( M. bovis \), or a positive microscopic examination for acid-fast bacilli when a culture has not been or cannot be obtained; *or*
- histology strongly suggestive of TB; *or*
- demonstration of \( M. tuberculosis \) nucleic acid (PCR or LCR only); *or*
- in the absence of bacteriological or histological confirmation:
  - there are symptoms or signs compatible with active TB, such as compatible radiology or clinical evidence of current disease; *and*
  - full anti-TB treatment has been started by a clinician.

*Tuberculosis disease – relapse or reactivation*

Relapse or reactivation refers to a case of active TB disease in a person whose TB has previously been non-infectious and quiescent. This definition includes people who reactivate:
early – during the course of current treatment; or
late – some time after completing full or partial treatment; or
after spontaneous resolution without treatment.

Tuberculosis – treatment of latent infection (formerly called chemoprophylaxis)
Treatment given to a person with all of the following:
positive Mantoux result or Mantoux conversion
no evidence of active disease
placed on treatment with one or more drugs (including child contacts under five years of age on three months’ interim treatment (chemoprophylaxis) for presumptive TB infection).

Tuberculosis infection – old disease on preventive treatment
Preventive treatment is defined as anti-tuberculous treatment with multiple drugs, given with the aim of curing TB in patients in whom:
active disease is suspected but remains unproven (ie, smear-negative, culture-negative disease); or
reactivation is likely to occur.

Clinicians may prescribe two or more drugs as ‘preventive treatment’ for a person with chest X-ray evidence of ‘old disease’. This should be classified as TB infection, not disease. On the Tuberculosis Case Report Form (Appendix 1.2) this is recorded as ‘tuberculosis infection – old disease on preventive treatment’.

TB contact
This is a person who has had contact with a case of active TB disease. (See Chapter 6: ‘Contact Investigation’ for information on risk assessment and management of contacts.)

TB outbreak
A TB outbreak is 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 to be an outbreak.

1.3.3 Notification and data collection

Tuberculosis disease – new cases
Any medical practitioner diagnosing or suspecting a case of new or relapsed TB is required, under the Tuberculosis Act 1948, to notify the case to the local medical officer of health. Notification should be made by telephone or fax, and the public health service will liaise with the diagnosing clinician. The Tuberculosis Case Report Form (Appendix 1.2) must be completed. Public health services will enter details of a suspected case on to the national TB computerised database (EpiSurv).
These details will only be provisional, since laboratory results and some other surveillance data are not usually available until some time after the initial diagnosis is made. Once further results are obtained, the database can be amended to record them. When a presumptive case is subsequently shown not to meet the case definition, the medical officer of health must be notified so that the record can be de-notified (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 Tuberculosis Case Report Form allows such cases to be clearly distinguished from new cases of disease. Information on previous diagnosis and treatment should be recorded on the relevant sections of the form. Importantly, cases must be renotified if treatment is started, the patient is rendered non-infectious and then becomes infectious again (as a result of treatment failure or non-adherence).

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

These cases are not legally required to be notified. However, clinicians are requested to notify every case to the medical officer of health for surveillance and control purposes (eg, adherence monitoring).

**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 6: ‘Contact Investigation’). These data should be computerised to allow periodic analysis. Provision to record this information is contained in EpiSurv.

Contacts who are subsequently identified as cases of TB disease or infection should have a Tuberculosis Case Report Form completed and should be entered onto the database. Responsibility for record keeping, where contacts reside in more than one health district, is discussed in Chapter 6: ‘Contact Investigation’.

**TB/HIV co-infection**

Surveillance of TB/HIV co-infection, including recommendations for improvements to the current system, is discussed in Chapter 18: ‘Tuberculosis and HIV’.

1.3.4 Completeness of notification

There has been no published national audit of the completeness of notification of TB in New Zealand. Auckland routinely compares laboratory isolates with EpiSurv to detect un-notified cases (which are few). An audit of prescriptions in Auckland in 1995 detected no un-notified infectious TB and found that the EpiSurv was 96% complete. The audit method used was expensive, due to a lack of computerised prescription records, but was found to have 86% sensitivity, 99% specificity, positive predictive value of 90% and negative predictive value of 99%.18
The extent of under-notification of TB diagnosed post-mortem in New Zealand is unknown. An Auckland study found that 22 previously undiagnosed cases were discovered on autopsy during 1975–92. Six of these had chronic respiratory disease.

1.3.5 Population surveillance

Tuberculin surveys

Population-based tuberculin surveys can:

- describe the extent of the TB problem in a population (periodic surveys provide information on recent changes in transmission)
- provide data with which to assess the value of continued screening
- identify people who would benefit from prophylactic or curative therapy.

Population-based tuberculin surveys also help to increase awareness about TB in the population being tested. However, they have limitations, including the following:

- Tuberculin surveys are resource intensive and may divert funding from activities that have more health gain in TB control.
- Large samples are needed in populations with a low prevalence (eg, a sample size of at least 864 13-year-old children is required to detect a 50% increase in tuberculin reactivity from 1% to 1.5% in a population of 2000 13-year-old children).
- The validity of tuberculin tests is reduced in populations where a proportion of people tested have received BCG vaccinations in the past.
- The predictive value of screening tests declines with decreasing prevalence.
- Screening populations in order to identify people who would benefit from prophylactic or curative therapy has limited cost-effectiveness in populations with a low prevalence.
- It is difficult to design studies that are acceptable to the populations being tested. The problem of ensuring a high level of compliance makes this type of surveillance less cost-effective than in the past, when compliance levels often reached 100%.

Population-based tuberculin surveys require significant resources in terms of workforce and budget and must be carefully planned to provide useful information. Community input is required at an early stage in the planning. Other forms of TB disease control are likely to provide more health gain in most populations in New Zealand.

Population-based tuberculin surveys can, however, provide useful information in populations with high levels of endemic TB. Regular surveys in these populations can provide timely information on changes in transmission, and valuable feedback about the success of TB control programmes.

1.4 Recommendations and future developments

Recent reviews of TB in New Zealand have identified some deficiencies in the current surveillance and monitoring systems. These include:
significant variability in the quality and completeness of information (eg, incomplete or poorly collected ethnicity and occupational data, incomplete treatment and outcome data, and a lack of match between the TB outbreak reporting system and notifications)

lack of timeliness of notification and recording on EpiSurv in some regions

inadequate annual reporting of TB and use of this information to guide evidence-based policy-making and designing effective interventions

under-use of DNA fingerprinting and inadequate recognition of its importance in identification, investigation and confirmation of outbreaks (this has now been addressed with DNA testing of all isolates from 2002)
lack of data on completeness of notification of TB.

Suggested improvements include:

establishing surveillance of BCG administration to neonates and adverse events following BCG (see Chapter 8: ‘BCG vaccination’)

more comprehensive annual analysis of TB epidemiology and treatment outcomes, and dissemination of this information to policy-makers and programme managers

audit and improvement of data completeness in EpiSurv

audit of the extent of under-notification of cases diagnosed post-mortem

ensuring routine comparison of laboratory culture results to EpiSurv to detect unnotified cases in every district

developing the capability to match prescription records of anti-TB drugs with EpiSurv to detect unnotified cases

collection of co-infection (TB/HIV) information (see Chapter 18: ‘Tuberculosis and HIV’).

Neonatal BCG surveillance should be incorporated in functions of the National Immunisation Register (project under way). Improvements to annual reporting, dissemination of this information for policy-making and programme enhancement, and raising awareness of TB among health services and in the community are key elements that remain to be addressed.
### Appendix 1.1: Excerpt from Public Health Surveillance in New Zealand Manual

#### Tuberculosis

**Disease name**

<table>
<thead>
<tr>
<th>Disease name</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tuberculosis disease - new case</strong></td>
<td>Active TB in a person who has never been treated for TB before.</td>
</tr>
<tr>
<td><strong>Tuberculosis disease – relapse or reactivation</strong></td>
<td>Active TB in a person whose tuberculosis has been non-infectious or quiescent following full, partial, or no treatment.</td>
</tr>
<tr>
<td><strong>Tuberculosis – treatment of latent infection</strong></td>
<td>A person with all of the following:</td>
</tr>
<tr>
<td></td>
<td>- positive Mantoux test or Mantoux conversion</td>
</tr>
<tr>
<td></td>
<td>- no evidence of active disease</td>
</tr>
<tr>
<td></td>
<td>- placed on chemoprophylaxis with one or more drugs</td>
</tr>
<tr>
<td></td>
<td>This includes child contacts &lt;5 years of age on three months interim treatment (“chemoprophylaxis”) for presumptive TB infection.</td>
</tr>
<tr>
<td><strong>Tuberculosis infection – old disease on preventive treatment</strong></td>
<td>A person on anti-tuberculosis treatment with multiple drugs in whom:</td>
</tr>
<tr>
<td></td>
<td>- active disease is suspected but remains unproven (ie, smear negative, culture negative)</td>
</tr>
<tr>
<td></td>
<td>OR</td>
</tr>
<tr>
<td></td>
<td>- reactivation is likely to occur.</td>
</tr>
</tbody>
</table>

**Reporting authority**

<table>
<thead>
<tr>
<th>Name of public health officer responsible for case</th>
<th>Basis of diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Indicate the name of the public health officer in charge at the recipient Public Health Unit.</td>
</tr>
</tbody>
</table>

**Laboratory criteria**

<table>
<thead>
<tr>
<th>Laboratory confirmation status</th>
<th>Laboratory confirmation method</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Demonstration of <em>M. tuberculosis</em> nucleic acid:</td>
</tr>
<tr>
<td></td>
<td>- This does not include positive DNA “probe”. (This identifies nucleic acid from a mycobacterial culture and therefore by definition confirmation has already been made).</td>
</tr>
<tr>
<td></td>
<td>- It does include positive PCR or LCR, where the clinician accepts these as presumptive evidence of TB. In body fluids positive PCR or LCR do not show whether the organisms are dead or alive.</td>
</tr>
</tbody>
</table>
### Mantoux status

**Mantoux tests**

Indicate whether Mantoux tests were carried out. If “Yes”, provide the date and induration measurement for each test. If the results are not yet available, tick “Awaiting results.” If not known or unavailable then tick the “Unknown” box. Tick the most appropriate result from the Mantoux tests. Refer to Chapter 2 of the *Guidelines for tuberculosis control in New Zealand (2002)* for the definition of Mantoux status. (The cutting point may be 5, 10 or 15 mm, depending on an individual’s circumstances.)

### Other criteria

| Treatment for presumptive TB | Full anti-tuberculous treatment has been started by the clinician. |
| Interim treatment for presumptive tuberculosis infection in children <5 years of age | The child has been placed on interim treatment for possible latent TB infection pending further Mantoux testing. |
| Status (complete only for TB disease which is active or presumed to be active: do not complete this section for old, inactive disease on preventive treatment) | **Under investigation** - A case which has been notified, but information is not yet available to classify it as confirmed. **Probable – presumptive** (without laboratory confirmation) - There is no laboratory confirmation but:
(a) there are symptoms or signs compatible with active tuberculosis, such as compatible radiology or clinical evidence of current disease, and
(b) full anti-tuberculous treatment has been started by a clinician
**Confirmed** (with laboratory confirmation) - A case that is laboratory confirmed by one of the following:

1. positive culture for *M. tuberculosis* or *M. bovis*
2. positive microscopic examination for acid-fast bacilli when a culture has not been or cannot be obtained
3. demonstration of *M. tuberculosis* nucleic acid in specimens
4. histology strongly suggestive of tuberculosis.

If you are ticking “Confirmed” then one of the categories under “Laboratory Criteria” should be ticked “yes.”

**Not a case** - A case that has been notified, investigated, and subsequently has been shown not to meet the case definition.

### Previous history of tuberculosis (relapses/reactivations only)

| Date of first tuberculosis diagnosis | Give the date (day, month and year if available) that tuberculosis was first diagnosed and the name of the doctor who made the diagnosis if known. If the date is unknown, tick the "Unknown" box. |
| Place where diagnosis made | Specify the city and country where the initial diagnosis was made. |
| Laboratory confirmation | Indicate whether the initial diagnosis was confirmed by laboratory testing. If not known or unavailable then tick the “Unknown” box. |
| Was the case treated? | Indicate whether the case was treated for tuberculosis at the time of initial diagnosis. If not known or unavailable then tick the “Unknown” box. If “Yes”, specify the duration of treatment in months. |
### Additional clinical details

<table>
<thead>
<tr>
<th>Site of disease</th>
<th>Indicate whether the case is pulmonary or extrapulmonary. Pleural disease or mediastinal/hilar adenopathy without parenchymal lung involvement should be classified as extrapulmonary. If the disease is extrapulmonary, specify the site(s).</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-ray appearance</td>
<td>Indicate whether the radiological appearance suggests active disease, uncertain activity or normal. If an X-ray has not been done, indicate so. Otherwise tick the “Unknown” box.</td>
</tr>
<tr>
<td>How was case/infection discovered?</td>
<td>Indicate whether the person was identified by contact tracing, attending a practitioner (e.g., GP) with symptoms, screening of immigrants/refugees, or “Other” method. If “Other” please give details. Otherwise tick the “Unknown” box.</td>
</tr>
</tbody>
</table>

### Additional laboratory details

<table>
<thead>
<tr>
<th>If organism isolated, specify species (disease only)</th>
<th>For cases of tuberculosis disease (new or relapse/reactivation) where an organism was isolated, indicate whether the organism was <em>M. tuberculosis</em>, <em>M. bovis</em> or another species. If “Other”, specify the species.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Susceptibility testing results (disease only)</td>
<td>For cases of tuberculosis disease (new or relapse/reactivation) where an organism was isolated, specify the susceptibility results. If the organism was susceptible to the antibiotic listed, tick the “Yes” option, if resistant tick the “No” option. If the results of the susceptibility tests are not yet available, tick “Awaiting results”. If susceptibility tests were not carried out for a particular antibiotic, tick “Not Done”. If testing was carried out for other antibiotics which are not listed, specify the antibiotic(s) and indicate whether they were susceptible or not.</td>
</tr>
</tbody>
</table>

### Clinical course and outcome (apart from what has already been discussed in section 2.6 – page 8)

| Asymptomatic | Tick this box if the case/infection is asymptomatic (i.e., there is no date for onset of symptoms). |

### Outbreak details

| Is this case part of an outbreak? | Indicate if the case is part of an outbreak, and if “Yes” enter the outbreak number if known. An outbreak is defined as two or more cases that are linked (by epidemiological investigation or DNA fingerprinting). A cluster of cases all living in a single household is not considered to be an outbreak. |

### Risk factors

<table>
<thead>
<tr>
<th>Has HIV test been performed</th>
<th>Indicate whether the person has been tested for HIV or not. Otherwise, tick “Unknown”.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other immunosuppressive illness</td>
<td>Indicate whether the person has an immunosuppressive illness such as chronic renal failure, alcoholism, diabetes or gastrectomy. If not known or unavailable then tick the “Unknown” box.</td>
</tr>
<tr>
<td>Immunosuppressive medication</td>
<td>Indicate whether the person is taking immunosuppressive medication. If not known or unavailable then tick the “Unknown” box.</td>
</tr>
<tr>
<td>Contact with a confirmed case of tuberculosis</td>
<td>Indicate whether the person had contact with a confirmed case of tuberculosis. If “Yes”, specify the nature of the contact and whether the contact occurred in New Zealand. If contact occurred in New Zealand give the name of the confirmed case. If not known or unavailable then tick the “Unknown” box.</td>
</tr>
<tr>
<td>Born outside New Zealand</td>
<td>Indicate whether the person was born in a country other than New Zealand. If not known or unavailable then tick the “Unknown” box. If “Yes”, specify the country of birth and date (or approximate date) of arrival in New Zealand. If unknown tick the “date unknown” option.</td>
</tr>
</tbody>
</table>
Current/recent residence in a household with person(s) born outside New Zealand | Indicate whether the person has resided recently in a household with person(s) not born in New Zealand. If “Yes”, specify the main country or countries of birth of such person(s) in the household. If not known or unavailable then tick the “Unknown” box.

Exposure in a health care setting | Indicate whether the person has been exposed to tuberculosis in a health care setting. If “Yes”, specify the type of exposure. If not known or unavailable then tick the “Unknown” box.

Current/recent residence in an institution | Indicate whether person is currently residing or has recently resided in an institution such as a prison, psychiatric hospital, rest home, or reform centre. If “Yes”, specify the details. If not known or unavailable then tick the “Unknown” box.

Exposure to animals or animal products in work or recreation (M. bovis only) | For cases of tuberculosis disease due to M. bovis, indicate whether the case has had any contact with cattle, deer, possums, or other wild animals or animal products (eg, leather, hide, fur), in the course of their work or recreation. If “Yes”, specify the exposure. If not known or unavailable then tick the “Unknown” box.

Other risk factor for tuberculosis | Specify any other risk factors under surveillance for tuberculosis.

<table>
<thead>
<tr>
<th><strong>Protective factors</strong></th>
</tr>
</thead>
</table>

Immunisation with BCG vaccine | Indicate whether the case had been immunised with BCG vaccine at any time before becoming ill. If not known or unavailable then tick the “Unknown” box. If “Yes”, specify the date of vaccination and indicate the source of the information – BCG scar, patient/caregiver recall or documented evidence.

<table>
<thead>
<tr>
<th><strong>Management</strong></th>
</tr>
</thead>
</table>

Case under specialist care | Indicate whether the case is under specialist care. If “Yes”, give the name of the specialist. If not known or unavailable then tick the “Unknown” box.

Date treatment started | Indicate the date treatment started. If not known or unavailable then tick the “Unknown” box.

Date treatment ended in New Zealand | Indicate the date treatment started. If not known or unavailable then tick the “Unknown” box. Complete this even if you believe the case is still on treatment outside New Zealand (see below).

Reasons for ending the treatment | Indicate the reason or reasons for ending the treatment in New Zealand. Tick as many as apply to the case. If not known or unavailable then tick the last box “reason unknown”: NB. This information may not be available when the case is first notified to the Public Health Unit. However, it is the responsibility of the public health officer to complete this field whenever the information becomes available.

DOT received throughout the course of treatment | Indicate whether the case received Directly Observed Therapy throughout treatment. If not known or unavailable then tick the “Unknown” box. DOT definition: person trained in DOT observes every dose taken.
### Contact management

**Contacts at risk of infection (disease only)**

For cases of tuberculosis disease (new or reactivation), indicate whether there were any contacts at risk of infection. If not known or unavailable then tick the “Unknown” box. If “Yes”, specify the number of close and casual contacts identified.

A **contact** is defined as follows: A person who has had contact with a confirmed case of active tuberculosis disease.

**Close contact**: members of the same household as the index case (sharing a kitchen and/or bathroom facilities), or who are very close contacts of the case.

**Casual contact**: all other contacts.

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Ministry of Health 1996 #246.
Appendix 1.2: Tuberculosis Case Report Form
### Chapter 1: The Epidemiology and Surveillance of Tuberculosis in New Zealand

**PREVIOUS HISTORY OF TUBERCULOSIS** (relapses or reactivations only)

<table>
<thead>
<tr>
<th>Date of first tuberculosis diagnosis</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of doctor who made diagnosis</td>
<td></td>
</tr>
<tr>
<td>Place where diagnosis made (town/city country)</td>
<td></td>
</tr>
<tr>
<td>Was diagnosis confirmed by laboratory testing?</td>
<td></td>
</tr>
<tr>
<td>Was the case treated?</td>
<td></td>
</tr>
<tr>
<td>If yes, duration of treatment</td>
<td></td>
</tr>
</tbody>
</table>

**ADDITIONAL CLINICAL DETAILS**

<table>
<thead>
<tr>
<th>Site of disease (disease only)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td></td>
</tr>
<tr>
<td>Radiology</td>
<td></td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td></td>
</tr>
<tr>
<td>How was case infection discovered?</td>
<td></td>
</tr>
<tr>
<td>If yes, specify site</td>
<td></td>
</tr>
</tbody>
</table>

**ADDITIONAL LABORATORY DETAILS (DISEASE ONLY)**

<table>
<thead>
<tr>
<th>If organism was isolated, specify species</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycobacterium tuberculosis</td>
<td></td>
</tr>
<tr>
<td>H. bovis</td>
<td></td>
</tr>
<tr>
<td>Other (specify)</td>
<td></td>
</tr>
</tbody>
</table>

**Specify results of susceptibility testing**

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Susceptible?</th>
<th>Other Antibiotic</th>
<th>Susceptible?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isozone susceptible</td>
<td>Yes</td>
<td>No</td>
<td>Not Done</td>
</tr>
<tr>
<td>Rifampin susceptible</td>
<td>Yes</td>
<td>No</td>
<td>Not Done</td>
</tr>
<tr>
<td>Ethambutol susceptible</td>
<td>Yes</td>
<td>No</td>
<td>Not Done</td>
</tr>
<tr>
<td>Pnemotux susceptible</td>
<td>Yes</td>
<td>No</td>
<td>Not Done</td>
</tr>
</tbody>
</table>

**Clinical Course and Outcome (disease only)**

<table>
<thead>
<tr>
<th>Date of onset</th>
<th>Unknown</th>
<th>Asymptomatic</th>
<th>Died</th>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
<th>Hospitalised</th>
<th>Unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date hospitalised</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Date died</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital name</td>
<td>Unknown</td>
<td>If died from disease other than tuberculosis, specify</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Outbreak Details**

Is this case part of an outbreak? If yes, are there 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 to be an outbreak.)

If yes, specify Outbreak No. | DNA Code No.

**Risk Factors**

Has HIV test been performed

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
</table>

Other immunosuppressive illness (chronic renal failure, alcoholism, diabetes, gastrectomy)

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
</table>

Immunosuppressive medication

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
</table>

Contact with a confirmed case of tuberculosis

If yes, specify nature of contact

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
</table>

If yes, did contact occur within New Zealand

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
</table>

If yes, specify name of case

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
</table>

Born outside New Zealand

If yes, specify country of birth

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
<th>Unknown</th>
</tr>
</thead>
</table>

If yes, date of arrival in NZ |  |
### Risk Factors Continued

<table>
<thead>
<tr>
<th>Current or recent residence in a household with a person(s) born outside New Zealand</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Exposure in health care setting</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Current or recent residence in an institution (eg prison)</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Exposure to cattle, deer, possums, other wild animals or animal products in work or recreation (M. bovis infection only)</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Other risk factor for tuberculosis (specify)</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

### Protective Factors

<table>
<thead>
<tr>
<th>At any time prior to onset, has this case been immunised with BCG vaccine?</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If yes, specify date given</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If yes, how was this confirmed</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

### Management

#### CASE MANAGEMENT

<table>
<thead>
<tr>
<th>Under specialist care</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name of specialist</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date treatment started</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Date treatment ended in NZ</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason treatment ended</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>All that apply</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment completed to the satisfaction of the prescribing doctor</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Work overseas</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Died</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Relucted to complete treatment</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stopped treatment because of adverse effects</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Lost to follow-up</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Discontinuation of anti-TB treatment for LTBI (child &lt; 5 years)</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reason unknown</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Did case receive DOT throughout the course of treatment?</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

### CONTACT MANAGEMENT (disease only)

<table>
<thead>
<tr>
<th>Did the case have any contacts at risk of infection</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>If yes, type of contact</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Name identified</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Close contacts</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Casual contacts</th>
<th>Episery No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>[ ] Yes [ ] No [ ] Unknown</td>
<td></td>
</tr>
</tbody>
</table>

### Comments:

**PLEASE POST THE COMPLETED FORM TO THE LOCAL MEDICAL OFFICER OF HEALTH**

--

Guidelines for Tuberculosis Control in New Zealand 2003

Chapter 1: The Epidemiology and Surveillance of Tuberculosis in New Zealand
Appendix 1.3: Proposed TB Surveillance Information Flows

CLINICAL/DIAGNOSTIC LEVEL

Specimens

Diagnosis and management by clinician

Lab results and reminder to notify

Laboratory investigation

LOCAL PUBLIC HEALTH LEVEL

Consultation regarding case management

Suspected cases referred

Suspected cases detected in the community

Case management (disease and infection)

Screening programmes

Contact investigation

TB disease and infection database

Identified contacts

TB contact 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

Reporting

Ministry of Health

KEY: 

TB control activity

TB database

information flows
References

Chapter 2: Mantoux Testing

Dr Peter Martin
Respiratory Medicine Physician, Capital and Coast District Health Board

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  2.1.2 Dose of tuberculin 6
  2.1.3 Multiple-puncture techniques 6
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  2.3.1 Positive Mantoux result: predictive value for latent TB infection 13
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Summary

Uses of the Mantoux test

- The tuberculin skin test is used:
  - to detect latent TB infection (the size of the Mantoux reaction is correlated with future risk of development of disease, so the extent of the increase beyond the cutting point should be taken into account as one of the risk factors for progression to disease)
  - to detect recent infection, as shown by conversion of the Mantoux from negative to positive
  - as part of the diagnosis of TB disease. (However, the test has a poor positive predictive value for current active disease. There is no correlation between size of reaction and likelihood of active disease, and diagnosis of disease will usually depend on isolation of the organism.)

Administration

- Those administering the tuberculin test should refer to the Ministry of Health's Technical Guidelines for Tuberculin Testing and BCG Vaccination.
- Only the 5 tuberculin unit (TU) Mantoux test should be used in New Zealand.
- Multiple-puncture techniques, such as the Heaf and Tine tests, have poorer sensitivity and specificity than the Mantoux, and should not be used.

Reading the Mantoux reaction

- The area of induration, measured transversely to the long axis of the forearm, is recorded in millimetres.
- The reaction should be read as close as possible to 72 hours after placement (injection), but if this is not possible, readings from 48 hours to 7 days are acceptable. The exception to this is when the two-step Mantoux test is done to identify the booster effect (see below). Here the reading should be done at 48 hours, where possible.

Conversion

- Mantoux conversion is defined as an increase in the diameter of the tuberculin reaction of \(10\) mm on a second Mantoux test (compared with a previous reaction). It indicates that infection has occurred and that there is a significant risk of development of TB disease.
- When testing contacts for conversion:
  - the first test is done as soon as the contact is identified
  - the second tuberculin test should be done eight weeks after the date of last contact with the source case (in the past, the traditional 'window period' or interval of 12 weeks was used)
  - in a contact whose exposure to the index case ceased more than eight weeks after treatment of the case began, looking for conversion is inappropriate. Only a single test is needed: if infection has occurred, conversion will already have taken place within the eight-week period.
Those who convert should be investigated for TB disease (see Chapter 14: ‘Clinical Investigation and Assessment of Tuberculosis’). If the need for full treatment is excluded, they should be considered for treatment of latent TB infection (LTBI, see Chapter 3).

**Boosting**

When sensitisation to mycobacteria has occurred many years earlier, an initial intradermal injection of tuberculin may produce a negative or weakly positive 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 result that should be used for decision-making or future comparison.

The boosting phenomenon is most likely to occur in the elderly, or if tuberculin sensitivity has been produced by BCG or infection with non-tuberculous mycobacteria.

**The two-step test**

The two-step test is performed when there is a need to establish a true baseline Mantoux reaction in someone who has not been tested in the preceding two years. The second test is only needed if the initial reading is negative (see Table 2.1). Re-testing should be undertaken one week after the first test.

Two-step testing is indicated in the following situations, when the first Mantoux test in the two-step series is negative:
- where serial tuberculin tests are to be used, as in health care workers
- when tuberculin testing those with previous BCG vaccination – this does not apply to contacts, because if they have had significant exposure to TB they will have already been boosted by the time the first test is placed (see Chapter 6: ‘Contact Investigation’ for more information on Mantoux testing contacts)
- before travel to high-incidence countries (for high-risk travellers only).

**Definitions of a positive Mantoux test**

(Definitions are given in Table 2.1, but the following points should be noted.)

Children are at greater risk of severe and life-threatening TB disease, and the cutting points given are conservative.

In those who are immune suppressed, the degree and duration of impairment should be documented and the appropriate cutting point selected, as shown in the next two bullet points.

The 5 mm cutting point: This is appropriate with:
- immunosuppressive treatment for organ transplantation
- aggressive immunosuppressive cancer treatment
- end-stage renal failure
- cytotoxic immune suppressive agents such as cyclophosphamide or methotrexate
- systemic corticosteroid treatment that is prolonged (eg, for more than six weeks) and in a dose of prednisone \( \leq 15 \text{ mg/day} \) (or equivalent with another steroid; the higher the dose, the greater the risk of reactivation of dormant TB)
- combinations of immunosuppressive conditions (eg, prednisone \( < 15 \text{ mg/day} \) plus diabetes mellitus (on treatment), moderate/severely advanced malignancy or malnutrition (this advice is empirical, not evidence-based).

The 10 mm cutting point should be used with:
- doses of prednisone less than 15 mg/day long term
- diabetes mellitus (including insulin-dependent)
- alcoholism, malnutrition or disseminated malignancy.

The predictive value of the Mantoux test for latent tuberculosis infection is discussed in Chapter 3.

False reactions

There are many causes of false negative Mantoux reactions. For this reason, a negative Mantoux does not absolutely exclude LTBI or TB disease.

Anergy testing is not recommended as a method to discover whether a negative Mantoux result is a true or a false negative, either in HIV-positive subjects or non-HIV subjects.

The effect of BCG vaccination on tuberculin reactivity

The level of reactivity in a vaccinated person is variable, ranging between 0 and 15 mm. Reversion can occur (eg, the reaction wanes with time).

A Mantoux reaction of > 15 mm induration should not be attributed to BCG vaccination.

There is no relationship between the post-vaccination Mantoux result and protection against TB disease. Routine post-BCG vaccination tuberculin testing serves no purpose.

Situations where Mantoux testing is not recommended

Past Mantoux reactions ≥ 15 mm: repeating the test will provide no new diagnostic information and will create discomfort.

Previous TB disease: no useful diagnostic information will be gained and significant discomfort is likely.

Infants under 12 weeks old: this is a relative contra-indication, and the following should be noted.
- A positive reaction is very important, but a negative reaction may indicate that the child is too young to mount a response, and the test will need to be repeated if exposure has occurred.
- Pre-vaccination Mantoux testing before 12 weeks of age is not necessary unless the baby has been exposed to TB (see Chapter 8: ‘BCG Vaccination’).
**Introduction**

The tuberculin skin test is one of the few investigations dating from the 19th century that is still widely used. It was developed by Koch in 1890, but the intradermal technique currently in use was described by Mantoux in 1912. After such a long history it is surprising that the interpretation of the test remains controversial.

The tuberculin most widely used is purified protein derivative (PPD), which is derived from cultures of *Mycobacterium tuberculosis*. When tuberculin is injected intradermally in a subject previously infected with *M. tuberculosis*, a hypersensitivity reaction occurs at the site of injection. This comprises an inflammatory response characterised by the accumulation of CD4 and CD8 T-lymphocytes, and the consequent release of inflammatory mediators. This hypersensitivity is not the same phenomenon as immunity, although it is usually associated with immunity.
2.1 Using and reading the Mantoux test

2.1.1 When to use the Mantoux test

The tuberculin skin test is used:

- to detect latent TB infection (the size of the Mantoux reaction is correlated with future risk of development of disease, so the extent of the increase beyond the cutting point should be taken into account as one of the risk factors for progression to disease)
- to detect recent infection, as shown by conversion of the Mantoux from negative to positive
- as part of the diagnosis of TB disease. (However, the test has a poor positive predictive value for current active disease, in that there is no correlation between size of reaction and likelihood of active disease. Diagnosis of disease will usually depend on isolation of the organism. For further information on diagnosis of TB disease, see Chapter 14: ‘Clinical Investigation and Assessment of Tuberculosis’.)

Those administering the tuberculin test should refer to the Ministry of Health’s *Technical Guidelines for Tuberculin Testing and BCG Vaccination*. Medical officers of health should work with organisations offering tuberculin tests to assist in the initial and ongoing training of those undertaking the tests.

2.1.2 Dose of tuberculin

In order to minimise variability in Mantoux results, only the 5 tuberculin unit (TU) Mantoux test should be used in New Zealand. Tuberculins ranging between 1 and 250 TU per dose are available, but the weaker and stronger tests offer no useful advantages.

The 5 TU dose is used in New Zealand, the US and Canada, while the 10-unit dose is used in the UK and Australia. However, ‘the difference in response to these two doses in humans should be small, as the potency of tuberculins in animal tests is related to the logarithm of the dose used’. As a result, the 10-unit dose causes reactions averaging only 1.5 mm larger than the 5-unit dose in the same subjects.

2.1.3 Multiple-puncture techniques

Multiple-puncture techniques, such as the Heaf and Tine tests, have poorer sensitivity and specificity than the Mantoux and should not be used, except:

- (possibly) in population tuberculin surveillance
- in rare instances, where a child is intolerant of the intradermal injection.
2.1.4  Reading the Mantoux reaction

The area of induration, measured transversely to the long axis of the forearm, is recorded in millimetres.

In positive reactors induration appears from 24 hours, with a maximum around 72 hours. The reaction should be read as close as possible to 72 hours after placement (injection) but, if this is not possible, readings from 48 hours to seven days are acceptable. (The exception to this is when the two-step Mantoux test is done to identify the booster effect, as discussed below. Here the reading should be done at 48 hours, where possible.) Readings after 72 hours are of less certain significance because their interpretation is not informed by epidemiological data. However, positive reactions that develop after 72 hours should be considered true positives.

Some positive tests will blister, but this does not add any additional significance. The reading is still determined by the area of induration.

2.1.5  Repeat tuberculin tests

The booster effect

When sensitisation to mycobacteria has occurred many years earlier, an initial intradermal injection of tuberculin may produce a negative or weakly positive response due to there being 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 result that should be used for decision-making or future comparison. Boosting is maximal if the second test is placed between one and five weeks after the initial test, and it may continue to be observed for up to two years.

Boosting varied with the time of reading of the second test in a small study of previously BCG-vaccinated UK health service employees. It was maximal if the second test was read 48 hours after placement (injection) compared with 72 and 96 hours, hence the recommendation (in 2.1.4) for the second Mantoux in a two-step test to be measured at 48 hours, wherever possible, in subjects with previous BCG vaccination.

The boosting phenomenon is most likely to occur in the elderly, or if tuberculin sensitivity has been produced by BCG or infection with non-tuberculous mycobacteria. See section 2.3.3 for further discussion of the effects of BCG vaccination on the Mantoux result.

The two-step test

The two-step test is performed when there is a need to establish a true baseline Mantoux reaction. Two-step testing is done to distinguish boosting from conversion in people who are having serial Mantoux tests. The second test is only needed if the initial reading is negative (see Table 2.1). Re-testing should be undertaken one week after the first test.
Because boosting lasts up to two years, two-step testing is unnecessary in someone who has been tested in the preceding two years. Avoid giving the two tests at exactly the same site because this can result in increased reaction size.  

Two-step testing is indicated in the following situations, where serial tuberculin tests are to be used:

- in health care workers, who are likely to be subjected to serial testing as part of tuberculin surveillance programmes, or following exposure to a TB case.  
- before travel to high-incidence countries (see Chapter 10: ‘Tuberculosis in Non-Clinical Settings’), although this only applies to people about to live or work in such countries for many months (eg, more than six months), or if they are likely to have contact there with people with TB (eg, health care workers going to work in a high-incidence country).

Two-step testing is not necessary for the initial Mantoux test in contacts exposed to TB: if they have had significant exposure to TB they will have already been boosted by the time the first test is placed (see Chapter 6: ‘Contact Investigations’).

**An example of the value of two-step testing**

A 25 year nurse, who is new to a hospital, reports having had BCG as a student at age 18; there is a doubtful BCG scar and the Mantoux result is 3 mm. When repeated a week later it is 10 mm (ie, the correct, 'boosted' reading is 10 mm). Six months later there is unprotected exposure to a highly infectious case of pulmonary TB, where diagnosis was delayed and the nurse provided care for several days. Eight weeks after exposure the nurse is Mantoux tested, and the reaction is 14 mm. Hence there is no evidence of new TB infection as the change from 10 mm to 14 mm is less than the 10 mm 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 managed as a Mantoux conversion.

**Mantoux conversion**

**Mechanism**

Whereas boosting is a recall of the hypersensitivity response in the absence of new infection, conversion is the development of new or enhanced hypersensitivity due to infection with tuberculous or non-tuberculous mycobacteria, including BCG vaccination.

**Definition**

Mantoux conversion is defined [American Thoracic Society, 2000 #232] as a change (within a two-year period) of Mantoux reactivity which meets either of the following criteria:

- a change from a negative to a positive reaction
- an increase of 2 10 mm.
The interval between Mantoux tests in contacts of TBD

There is debate about the time required for the immunological changes that produce Mantoux conversion following infection. After inadvertent vaccination with *M. tuberculosis* (the Lubeck disaster), children developed positive reactions in three to seven weeks. Other studies have shown clinical illness, with a positive tuberculin test, from 19 to 57 days after exposure, with a mean of 37 days.2

Therefore, when testing TB contacts for conversion, the second tuberculin test is done *eight weeks* after the date of last contact with the source case. (In the past, the traditional window period, or interval, of 12 weeks was used.)

Testing for conversion in people with a documented Mantoux result

If there is a documented Mantoux result within the past 12 months, two tests for conversion are unnecessary. The documented pre-exposure result may be used as the baseline in testing for conversion. Positive reactions older than 12 months may wane and cannot therefore be relied on for a valid baseline.

Thus, if a person who has a documented Mantoux test result within the past 12 months is exposed to infectious TB, only one test is necessary to detect conversion. This should be done eight weeks after the date of last exposure. This advice applies particularly to people whose previous Mantoux result may have been positive as a result of prior BCG vaccination (as is often the case with health care workers). It is unlikely that Mantoux reactivity of former cases of TB disease would wane to the same extent. Former cases of TB disease never need Mantoux testing after a new TB exposure.

Significance

Conversion has been associated with an annual incidence of TB disease of 4% in adolescents7 or 6% in contacts of smear-positive cases.8

Action

Those who convert should be investigated for TB disease (see Chapter 14: ‘Clinical Investigation and Assessment of Tuberculosis’). If the need for full treatment is excluded, they should be considered for treatment of latent TB infection (see Chapter 3).

Where the Mantoux test increases between testing by less than 10 mm, the second test is the correct reading but should not be regarded as a conversion. Sometimes the second test may be positive but the change in diameter of induration does not meet the criterion for conversion. The question then arises as to what to do with these individuals.

There is no evidence to guide a decision about how to proceed in this situation. The Ministry of Health’s Tuberculosis Working Group recommends that:

- a CXR be done
- treatment for LTBI *not* be given unless:
there are risk factors for TB infection progressing to disease (ie, a child aged less than five years, immunosuppressive treatment, or medical conditions associated with immunosuppression, as shown in Table 3.3 in Chapter 3); or

– there has been close contact with a smear-positive pulmonary case.

This should not be regarded as an inviolable guideline, however.

**Mantoux reversion**

Mantoux reversion is defined as the change to a negative Mantoux result following a previous positive result. Generally this phenomenon is uncommon in healthy individuals, occurring in less than 10% of such people with a previously positive Mantoux.

Reversion is more common:\(^6\)

¶ in older adults (estimated at 8% per year)

¶ when the initial Mantoux is < 14 mm

¶ in those where the initial positive reaction was a boosted result (identified by two-step testing).
2.2 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 data from New Zealand, so those collected in similar communities, such as Canada,2 must be used to establish appropriate points for New Zealand. Readings at these points or higher should be regarded as positive. They are summarised in Table 2.1.

Table 2.1: Definition of a positive Mantoux in New Zealand (cutting points)

<table>
<thead>
<tr>
<th>Categories</th>
<th>Adults (≥15 years)</th>
<th>Older children (5–14 years)</th>
<th>Young children (&lt;5 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Zealand born</td>
<td>2 10 mm</td>
<td>2 10 mm</td>
<td>2 5 mm</td>
</tr>
<tr>
<td>No BCG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous BCG</td>
<td>2 15 mm</td>
<td>2 10 mm</td>
<td>2 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</td>
<td>2 10 mm</td>
<td>2 10 mm</td>
<td>2 5 mm</td>
</tr>
<tr>
<td>Previous BCG</td>
<td>2 10 mm</td>
<td>2 10 mm</td>
<td>2 10 mm</td>
</tr>
<tr>
<td>With immunosuppressive illness or taking immunosuppressive drugs (BCG or not)</td>
<td>5–10 mm**</td>
<td>2 5 mm</td>
<td>2 5 mm</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(BCG or not)</td>
<td>2 5 mm</td>
<td>2 5 mm</td>
<td>2 5 mm</td>
</tr>
<tr>
<td>Close contacts of smear-positive cases (any origin)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(BCG or not)</td>
<td>&gt;10 mm</td>
<td>&gt;5 mm</td>
<td>≥5 mm</td>
</tr>
</tbody>
</table>

* Defined in Chapter 8: ‘BCG Vaccination’.

** See 2.2.1: Comments on the cutting points in Table 2.1.

2.2.1 Comments on the cutting points in Table 2.1

Children are at greater risk of severe and life-threatening TB disease, and therefore cutting points are conservative.4,7,8 In those who are immune-suppressed, the degree and duration of impairment should be documented, and the appropriate cutting point selected, as shown below.

The 5 mm cutting point is appropriate with:

1. immunosuppressive treatment for organ transplantation
2. aggressive immunosuppressive cancer treatment
3. cytotoxic immune-suppressive agents such as cyclophosphamide or methotrexate
4. systemic corticosteroid treatment that is prolonged (eg, for more than six weeks) and in a dose of prednisone ≥ 15 mg/day (or equivalent with another steroid); the higher the dose, the greater the risk of reactivation of TB
combinations of immunosuppressive conditions (e.g., prednisone < 15 mg/day plus diabetes mellitus (on treatment), moderate/severely advanced malignancy or malnutrition (this advice is empirical, not evidence-based))

end-stage renal failure.

The 10 mm cutting point should be used with:

- doses of prednisone <15 mg/day long term
- diabetes mellitus (including insulin-dependent)
- alcoholism, malnutrition or disseminated malignancy.

Table 2.1 shows that prior BCG vaccination does affect the cutting point in New Zealanders who have not resided in high-incidence countries. It does not, however, affect the cutting point of a person who has resided in a high-incidence country.
2.3 Interpretation of the Mantoux Test

2.3.1 Positive Mantoux result: predictive value for latent TB infection

The positive predictive value represents the percentage of those with any given Mantoux reading who truly have TB infection. It varies with different clinical situations. Where the expected prevalence of true infection is low, as in screening situations, 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 is less likely to be due to TB and more likely to be caused by another factor such as BCG. 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.

2.3.2 Does size matter: what is the significance of a strongly positive Mantoux?

There is no correlation between size of reaction and likelihood of active disease. The test has a poor positive predictive value for current active disease. However, size of the Mantoux reaction is correlated with future risk of development of disease. Therefore, as the size of the Mantoux 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.

2.3.3 The effect of BCG vaccination on tuberculin reactivity

The effect of prior BCG on the timing of reading the Mantoux result was discussed above (see 2.1.5 ‘Repeat tuberculin tests’). Post-BCG vaccination tuberculin sensitivity has been extensively studied, but a full review of this topic is beyond the scope of this chapter.

The level of reactivity varies between 0 and 15 mm. A Mantoux reaction > 15 mm induration should not be attributed to BCG vaccination. There is no relationship between the post-vaccination Mantoux result and protection against TB disease. Routine post-BCG vaccination tuberculin testing serves no purpose.

The age at which BCG vaccination was performed affects tuberculin reactivity when the latter is measured several years later (see Table 2.2: Previous BCG and the tuberculin result).

<table>
<thead>
<tr>
<th>Age when BCG vaccinated</th>
<th>% tuberculin positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infancy</td>
<td>7.9</td>
</tr>
<tr>
<td>1–5 years old</td>
<td>18</td>
</tr>
<tr>
<td>&gt; 5 years old</td>
<td>25.4</td>
</tr>
</tbody>
</table>

(% similar to non-vaccinated subjects) (unaffected by interval between BCG and tuberculin testing, or repeated BCG)
2.3.4 False positive reactions

When utilising the Mantoux test as a test of LTBI, the following causes of false positive reactions should be borne in mind:

- Prior BCG vaccination
- Exposure to non-tuberculous mycobacteria
- Factitious false positives, which may occur due to rubbing or scratching of the injection site.

2.3.5 Negative Mantoux result

A negative Mantoux result usually signifies that the individual has never been exposed to *M. tuberculosis*. However, there are factors that may cause a false negative result or diminished ability to respond to tuberculin.\(^{15,16}\)

**False negative results**

Causes of false negative include the following.

a. 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 (typhoid, brucellosis, typhus, leprosy, pertussis)
- Metabolic disorders, especially renal failure and diabetes
- Disorders of lymphoid organs (sarcoidosis, lymphoma, leukaemia)
- Corticosteroids or other immunosuppressive drugs (these include commonly used agents such as prednisone \(^{2}\) 15 mg/day,\(^ {16}\) cyclophosphamide, methotrexate and azathioprine, together with many drugs used to treat cancer)
- Age (the elderly, where sensitivity wanes, or the newborn)
- Stress (surgery, burns, severe illness of any type).

b. Factors related to the tuberculin used, including:

- Improper storage (exposure to light or heat)
- Dilution
- Denaturation, contamination or adsorption to glass surface (partly controlled by the addition of Tween 80).

c. Factors related to the method of administration, including:

- Injecting too little antigen
- Antigen escapes from the intradermal location, leaking out onto the skin.

However, these factors are not thought to be an important source of error.\(^ {17}\)

d. Factors related to the reading of results, including:
incorrect reading of the reaction, such as terminal digit bias or rounding, can be reduced by the use of simple calipers, which are highly recommended;\(^2\) self-reading by patients resulted in 11% misclassification in one series,\(^{18}\) and is discouraged

inter-reader variation in measuring the size of Mantoux reactions, even in properly trained operators.\(^{19,20}\)

Please refer to the Ministry of Health’s technical guidelines\(^1\) for a fuller discussion of points b, c and d.

As stated above, one of many limitations of the Mantoux test is the fact that it is impossible to discover with certainty whether a negative result is a true or a false one. For this reason, a negative Mantoux does not absolutely exclude LTBI or TB disease. (For further discussion about TB disease and a negative Mantoux, see Chapter 14: ‘Clinical Investigation and Assessment of Tuberculosis’.)

**Is anergy testing helpful when the Mantoux test is negative?**

Anergy testing is not recommended as a method to discover whether the negative Mantoux result is a true or a false negative, either in HIV-positive subjects\(^{21}\) or non-HIV subjects.\(^{22}\)
2.4 Situations where Mantoux testing is not recommended

Mantoux testing is not recommended in the following situations:

- past Mantoux reactions ≥ 15 mm: repeating the test will provide no new diagnostic information and will create discomfort
- previous TB disease: no useful diagnostic information will be gained and significant discomfort is likely
- infants under 12 weeks old: a positive reaction is very important, but a negative reaction may indicate that the child is too young to mount a response, and the test will need to be repeated if exposure has occurred. Pre-vaccination Mantoux testing before 12 weeks of age is not necessary unless the baby has been exposed to TB (see Chapter 8: ‘BCG Vaccination’).
2.5 Future developments

The Mantoux test is technically difficult to administer and read, so false readings may occur if the tester has insufficient skill. It may require four visits by the patient if a two-step test is performed, and compliance with this is sometimes difficult. A test that can be done on a single patient visit, such as a blood test, would be easier.

The QuantiFERON-TB test, which has been developed in Australia,\textsuperscript{23,24} measures interferon gamma released from whole blood after this is incubated with PPD. At present the position of QuantiFERON-TB in the diagnosis of LTBI is not clear (see Chapter 12: ‘Mycobacteriology: Laboratory Methods and Standards’). It may be possible in future to replace the skin test with this, or an alternative \textit{in-vitro} assay.
References

Chapter 3: Latent Tuberculosis Infection

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References
Summary

Latent tuberculosis infection (LTBI)

- TB is currently conceptualised as three distinct clinical states: latent tuberculosis infection (LTBI), inactive tuberculosis disease and active tuberculosis disease.
- LTBI is defined in these guidelines as the presence in an individual of live, dormant (not reproducing) *Mycobacterium tuberculosis* organisms. The term ‘latent’ indicates that the infection is not clinically apparent.
- In LTBI the CXR will be normal, or have only trivial and stable evidence of past TB (eg, a small scar or patch of calcium). The number of TB organisms will be low.
- The traditional diagnostic test for LTBI is the Mantoux test (see Chapter 2). The test has limited specificity, sensitivity, positive predictive value and negative predictive value. A positive test may be caused by prior BCG vaccination or exposure to non-tuberculous mycobacteria, in addition to LTBI. Different cutting points for a positive test are adopted for different population groups to enhance the positive predictive value of the test in each group.

Risk factors

- Risk factors for infection are summarised in Table 3.2. Important risk factors include the extent of exposure and the infectivity of the source case.
- People with LTBI have widely varying risks of progression to TB disease, depending on factors listed in Table 3.3. Important factors include time since infection, age, the dose of infectious agent, and the immune status and general health of the infected person.

Treatment of LTBI

- Treatment of LTBI aims to prevent the development of TB disease. In the past this has been referred to as ‘chemoprophylaxis’ or ‘preventive therapy’.
- In non HIV-infected people isoniazid for 6–12 months remains the treatment of choice for LTBI. Shorter-course regimens have been found to be effective, including 3R and 3RH.*
- In HIV-infected people 9H or 2RZ are the recommended regimens. Several regimens (6–9H, 3RH, 3RHZ† and 2RZ) reduce the risk of TB in people with HIV infection. The effect is restricted to skin test-positive people. Treatment prolongs survival in HIV-infected, tuberculin-positive patients.
- The cost-effectiveness of treatment for LTBI is enhanced if treatment is restricted to people with a higher probability of LTBI. Six months seems to be the most cost-effective duration of treatment for H. 4RH is cost-saving compared with H alone.

---

* H = isoniazid; R = rifampicin.
† Z = pyrazinamide.
Who should and should not have treatment for LTBI?

**Indications**

- Criteria for initiating treatment for LTBI in New Zealand are listed in Table 3.4.
- Mantoux testing and treatment of LTBI in immigrants is not necessary unless they have:
- a known history of exposure to an infectious case within the preceding two years
- immunosuppression or a predisposing medical condition (see Table 3.3 and Table 3.4)
- a fibrotic lesion on CXR, and disease requiring full multi-drug treatment has been excluded.
- Children under five years of age who are close contacts of pulmonary cases should be referred to a specialist regardless of their tuberculin reaction.
  - If Mantoux-positive they should receive treatment for presumed LTBI.
  - If Mantoux-negative (< 5 mm) they should be assessed by a paediatrician with experience in TB. If treatment (for possible LTBI) is decided on, it should be given for eight weeks and then a second Mantoux test should be done. If the Mantoux converts (> 10 mm increase), continue treatment until complete. If the Mantoux does not convert, stop treatment and consider BCG vaccination.
  - Children under five years with other contact profiles should be referred to a specialist only if the tuberculin test is positive, or becomes positive on a second test.
- All patients with chronic renal failure should have their Mantoux status determined with a two-step test. This is essential for those on dialysis. If Mantoux-positive they should be considered for treatment of LTBI. Treatment for Mantoux-negative renal patients is not recommended.

**Contraindications**

- Treatment for LTBI is contraindicated if there is:
  - any clinical, radiological, or bacteriological evidence of TB disease: investigation is needed to assess whether the disease is active or inactive, and treatment for TB disease should be administered.
  - acute or chronic liver disease.

**Precautions**

- The two-month RZ treatment regimen for LTBI should be used with caution, especially in patients concurrently taking other medications associated with liver injury and those with alcoholism, even if alcohol use is discontinued during treatment.
- Other precautions are:
  - age over 35 years (this is no longer a contraindication to treatment for LTBI, if the clinical indications are strong)
  - other interacting drugs (see Chapter 15: ‘M. tuberculosis, Tuberculosis Medicines and Monitoring’)
  - regular alcohol use, especially if excessive
  - major concerns about adherence to treatment
  - major concerns about adherence to arrangements for biochemical or clinical monitoring
  - peripheral neuropathy or risk factors for its development
  - pregnancy.
- Breastfeeding is not a contraindication.
Deciding whether to treat

A decision about whether or not to treat depends on an assessment of the following questions:

- How likely is it that a person has been infected?
- How likely is it that disease will develop?
- What are the risks of an adverse reaction to treatment?
- What is the likely adherence to treatment?

Recommended regimens and dosages

- Suggested regimens are shown in Table 3.5.
- Dosages for drugs commonly used for treatment of LTBI are shown in Table 3.6.

Adverse effects and drug interactions

Isoniazid (H)

- Problems include:
  - hepatitis: the risk of death can be reduced by careful monitoring and prompt cessation of treatment if symptoms develop.
  - central nervous system toxicity
  - peripheral neurotoxicity (prophylactic pyridoxine is prescribed for those at risk).

Rifampicin and pyrazinamide (RZ)

- Problems include hepatitis, so this regimen should be prescribed only for those:
  - at high risk of TB disease
  - for whom 6H or 9H are not suitable
  - for whom thorough pre-treatment education about side-effects and monitoring during treatment can be carried out reliably.

Rifampicin alone, and rifampicin/isoniazid in combination (R, and RH)

- Trials for the treatment of LTBI suggest that rifampicin, alone or in combination with H, seems to carry a slightly lower risk of adverse events than H or RZ.

Monitoring during treatment

Before treatment

- Carry out:
  - liver function tests; full blood count, ESR.
  - creatinine, urea and electrolytes only if renal failure suspected.

During treatment

- Carry out liver function tests:
Clinical monitoring

The interval between commencing H treatment and the appearance of hepatitis varies widely. Biochemical monitoring throughout treatment is impracticable, so regular clinical monitoring is essential, particularly in adults over 35 years. This should be at least monthly for H or R, and fortnightly for RZ. At each visit, health care providers conversant in the patients’ language should instruct patients that if abdominal pain, vomiting, jaundice or other hepatitis symptoms develop they should stop taking treatment immediately and seek medical consultation and immediate liver function tests.

Pyridoxine

In those on H, pyridoxine 10 mg or 25 mg daily should be prescribed for:

- all adults, including pregnant women
- some early teenagers, depending on nutritional status and body size
- children who develop paraesthesiae
- children who have poor nutrition and therefore are at risk of pyridoxine deficiency
- breastfed infants on H
- a fully breastfed infant if the mother is on H, regardless of whether the infant is on anti-TB treatment
- those with seizure disorders, diabetes, uraemia, alcoholism, malnutrition or HIV.

Practical considerations in the treatment of LTBI

Assess HIV risk factors before starting treatment

Assess HIV risk factors and have a low threshold for HIV testing people whom you are considering for treatment for LTBI. HIV-infected people require a longer course of treatment and more treatment supervision than HIV-negative people.

Adherence

- Efficacy is affected by both duration of treatment and adherence. Adherence monitoring is important. If adherence is not excellent, directly observed therapy (DOT) must be carried out and a shorter-course regimen should be considered.
- Check that the regimen prescribed is appropriate to the antibiotic susceptibility of the source case (if known).
- If the client has been started on treatment before the susceptibility of the source case is determined, a change in regimen may be needed.

Ending treatment

- Extend treatment to compensate for missed weeks on treatment.
For adults, an end-of-treatment CXR is needed only if the pre-treatment chest X-ray was abnormal. Most children will need an end-of-treatment CXR.

If treatment is not given, the person and their GP should be alerted to the risk of future TB disease. There should be a lifelong low threshold for clinical assessment of any symptoms of active TB disease, particularly cough lasting more than three weeks.

**Monitoring**

Monitoring with CXRs over two years is recommended only for untreated, Mantoux-positive:

- children (under five years) who are close contacts of smear- or culture-positive cases
- HIV-infected contacts
- contacts of multi-drug-resistant source cases
- people with inactive fibrotic scars on CXR.

CXR monitoring of other people who are untreated for LTBI is not recommended because of limited evidence for its usefulness in immigrants and contacts.

**Search for a source case**

When a person is put on treatment for LTBI, public health staff must search for the source case if it is not known.

**Missed opportunities for treatment**

Opportunities for treatment of LTBI are often missed because those at risk are not screened, or treatment is not prescribed when indicated.

**Management of previously treated people who are re-exposed**

It is possible to develop disease a second time following reinfection with TB. People who are reinfected are difficult to distinguish by Mantoux testing from those who are positive from their prior episode of infection.

Repeat Mantoux testing is not advised. Consider re-treatment only for those who have been close contacts of a smear-positive case and have risk factors for progression to TB disease (Table 3.3).

**Surveillance**

**Notification – liaison with public health**

Persons treated for LTBI should be notified to the medical officer of health using the Tuberculosis Case Report Form (see Chapter 1: 'The Epidemiology and Surveillance of Tuberculosis in New Zealand'). Although not required by law, this step is important, as it helps to ensure that public health has a complete picture of TB infection, disease and treatment in the community.
Current extent of treatment for LTBI in New Zealand

Although treatment recommendations for LTBI seem to be widely implemented, it is possible that treatment is being under-utilised and/or under-reported outside of Auckland, Waikato and Wellington.

Screening for LTBI

The Mantoux test has low specificity and its positive predictive value is low in New Zealand sub-populations which have a low prevalence of infection. The benefit:cost ratio of treating LTBI depends heavily on the risk that the person is truly infected and is at substantial risk of developing TB disease.

Accordingly, Mantoux screening for LTBI should be reserved for those groups with a high risk of recent infection or who are at high risk of progression from LTBI to TB disease. Such groups include:
- close contacts of newly diagnosed cases of active disease
- people with comorbidities that increase the risk of progression to active disease, particularly HIV and renal failure (see Table 3.3)
- health care workers with exposure to patients or infectious materials. (This is justifiable to establish baseline Mantoux status against which to compare subsequent testing in the event of exposure to a pulmonary case – see Chapter 9: ‘Infection Control’. Screening of the health care worker population to detect LTBI is probably much less justifiable.)

Mantoux screening in refugees from high-incidence countries is not cost-effective and is no longer recommended unless they have:
- a known history of exposure to an infectious case within the preceding two years
- immunosuppression or a predisposing medical condition (see Table 3.3 and Table 3.4)
- a fibrotic lesion on CXR, and disease requiring full multi-drug treatment has been excluded.

Mantoux screening is best conducted by public health, hospital occupational health services and hospital clinicians caring for people with risk factors for progressing to TB disease (see Table 3.3). GPs should refer to the local public health office any patients who consult them about TB exposure.

Routine screening of asymptomatic general practice patients merely because they are immigrants or from high-risk ethnic groups is not advised.

Prevention of LTBI

BCG vaccination prevents progression to TB disease but does not prevent TB infection. The only way to prevent LTBI is early identification and treatment of cases of infectious TB disease.
3.1 Definition, diagnosis and epidemiology of LTBI

3.1.1 Definition

TB is currently conceptualised as three distinct clinical states: latent tuberculosis infection (LTBI), inactive tuberculosis disease and active tuberculosis disease. LTBI is defined in these guidelines as the presence in an individual of live, dormant (not reproducing) *Mycobacterium tuberculosis* organisms. The term 'latent' indicates that the infection is not clinically apparent. (Active and inactive TB are defined in section 14.3, ‘Assessment of TB activity, extent and severity’.)

In both LTBI and inactive TB disease, TB organisms are considered to be dormant, although much is still unknown about the dormant metabolic states of the bacilli in LTBI. In LTBI the CXR will be normal, or have only trivial and stable evidence of past TB (eg, a small scar or patch of calcium). The number of TB organisms will be low.

Inactive TB refers to the situation where CXR evidence of past TB is not trivial. In this situation a person is likely to have far more dormant TB organisms than the person with, for example, a Mantoux conversion (see Chapter 2) and a normal CXR. Indeed, sometimes the previous disease is so extensive that the treatment given is the same as if they had active TB. Because of the potentially greater number of organisms, treatment of inactive TB requires more substantial treatment than that for LTBI. (CXR features, investigation and treatment regimens for inactive TB are discussed in Chapter 13: ‘Awareness, Clinical Features and Early Identification of Tuberculosis’, and Chapter 16: ‘Treatment of Tuberculosis’.)

The present chapter is confined to people with LTBI and no (or only minimal) radiological abnormalities. It will be assumed that active and inactive TB disease have been excluded.

The most comprehensive current review of LTBI has been produced by the American Thoracic Society / Centers for Disease Control. This document is recommended for further reading.

3.1.2 Diagnosis

The traditional diagnostic test for LTBI is the Mantoux test. The interpretation of a positive Mantoux test is discussed in Chapter 2; immunological tests for LTBI are discussed in Chapter 12: ‘Mycobacteriology: Laboratory Methods and Standards’.

The Mantoux test has limited specificity, sensitivity, positive predictive value and negative predictive value. A positive test may be caused by prior BCG vaccination or exposure to non-tuberculous mycobacteria, in addition to LTBI. Different cutting points for a positive test are adopted for different population groups in order to enhance the positive predictive value of the test in each group (see Chapter 2). A positive test is used as evidence of infection, but must always be interpreted according to the clinical context.
There are no published likelihood ratios for the Mantoux test. Calculating the likelihood ratio for a given Mantoux result requires a knowledge of the frequency distributions of Mantoux reactions in infected and uninfected populations. These have not been worked out for New Zealand populations.

Notwithstanding the limitations, a positive Mantoux reaction in a contact of an infectious TB index case should raise concern about the possibility of new LTBI. TB disease is the other important possibility, and if this is excluded by testing (see Chapter 14: ‘Clinical Investigation and Assessment of Tuberculosis’), new LTBI must be assumed.

### 3.1.3 Epidemiology

Little is known about the current prevalence of LTBI in New Zealand. An estimated annual risk of infection cannot be calculated because population-based tuberculin surveys are no longer carried out. Rates of tuberculin (Heaf) positivity at age 13 declined below 1% in the 1980s, at which time routine screening in schools was discontinued. Few data are currently available on groups that receive Mantoux tests in New Zealand (see Table 3.1). The results of screening done in public health offices, general practice or hospital occupational health settings are not routinely published.
### Table 3.1: Tuberculin positivity rates for various groups in New Zealand

<table>
<thead>
<tr>
<th>Setting</th>
<th>No. participants</th>
<th>% positive</th>
<th>Definition of positive</th>
<th>Source of data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mangere Refugee Resettlement Centre refugees - routine screening</td>
<td>Children 1421 Adults 2418</td>
<td>23.5 47</td>
<td>2 5 mm 2 10 mm</td>
<td>Auckland Public Health Office data 1995–2000</td>
</tr>
<tr>
<td>Asylum seekers in Auckland – routine screening</td>
<td>869</td>
<td>36.3</td>
<td>2 10 mm</td>
<td>Auckland Public Health Office data 1999–2000</td>
</tr>
<tr>
<td>Christchurch immigrants 1982–92</td>
<td>69</td>
<td>17</td>
<td>2 10 mm</td>
<td>Patchett et al 1993³</td>
</tr>
<tr>
<td>Christchurch prisoners - survey following case notifications among prison inmates, 1991</td>
<td>597</td>
<td>4.6 (no past BCG) 3.3 (past BCG)</td>
<td>2 15 mm (no past BCG) 2 20 mm (past BCG) (10 TU Mantoux test)</td>
<td>Horton 1991⁷</td>
</tr>
<tr>
<td>Christchurch prisoners - survey following case notifications among prison inmates, 1991</td>
<td>597</td>
<td>4.6 (no past BCG) 3.3 (past BCG)</td>
<td>2 15 mm (no past BCG) 2 20 mm (past BCG) (10 TU Mantoux test)</td>
<td>Horton 1991⁷</td>
</tr>
<tr>
<td>Mt Eden prison inmates, 1994</td>
<td>322</td>
<td>32 (no past BCG) 43 (past BCG)</td>
<td>2 5 mm (no past BCG) 2 10 mm (past BCG)</td>
<td>Lawson and Caygill 1995¹⁵</td>
</tr>
<tr>
<td>Middlemore Hospital - medical students and doctors</td>
<td>Students 77 House officers 46 Registrars 43</td>
<td>4 13 35</td>
<td>2 15 mm</td>
<td>McNaughton et al 1994⁸</td>
</tr>
<tr>
<td>Wakan hospital staff - survey following case notifications</td>
<td>372</td>
<td>23</td>
<td>2 10 mm (no past BCG) 2 15 mm (past BCG)</td>
<td>Walls 1996¹¹</td>
</tr>
<tr>
<td>Green Lane/National Women's Hospital staff 1992–95, pre-vaccination screening</td>
<td>Nursing 361 Doctors 48 Technical 185 Other 83</td>
<td>23 27 21 20</td>
<td>2 10 mm (no past BCG) 2 15 mm (past BCG)</td>
<td>Walls 1996¹¹</td>
</tr>
<tr>
<td>Auckland contacts of active cases</td>
<td>1417</td>
<td>29.4</td>
<td>As in Ministry of Health 1996</td>
<td>Auckland Public Health Office data, 2000</td>
</tr>
<tr>
<td>Northland children 12–14 years, 1993; school Heaf survey following case notifications</td>
<td>372</td>
<td>0</td>
<td>Heaf grades 2–4</td>
<td>1994¹³</td>
</tr>
</tbody>
</table>
3.2 Risk factors

3.2.1 Risk factors for LTBI

Risk factors for infection are summarised in Table 3.2. TB is almost always transmitted by active pulmonary or laryngeal cases ('open' TB). Transmission does not occur from 'closed' TB, such as renal or bone disease.

**Table 3.2: 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. See Chapter 6 for more information on assessing the risk of transmission.</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/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 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 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 infection.</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>
<tr>
<td>Race: black at higher risk than white in US.</td>
<td></td>
</tr>
</tbody>
</table>
### 3.2.2 Risk factors for LTBI progressing to TB disease

By definition, people with LTBI do not have active or inactive TB disease. They are non-infectious and asymptomatic. They have widely varying risks of progression to TB disease depending on the factors listed in Table 3.3.

#### Table 3.3: 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. 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 (e.g., 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/early adulthood. The lifetime risk of progressing from infection to active TB is:</td>
</tr>
<tr>
<td></td>
<td>1. 5–15% in adults(^{14})</td>
</tr>
<tr>
<td></td>
<td>2. Inversely proportional to age:</td>
</tr>
<tr>
<td></td>
<td>- up to 38% in Canadian native American contacts aged 0–14 years(^{18})</td>
</tr>
<tr>
<td></td>
<td>- 16% in 11–15-year-olds</td>
</tr>
<tr>
<td></td>
<td>- 8–25% in 6–10-year-olds</td>
</tr>
<tr>
<td></td>
<td>- 11–24% in 1–5-year-olds</td>
</tr>
<tr>
<td></td>
<td>- 23–43% in &lt;1-year-olds(^{22})</td>
</tr>
<tr>
<td>Dose of infection</td>
<td>The risk is highest if the source case is smear-positive; less if smear-negative/culture-positive; minimal if culture-negative.(^{18})</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.(^{20 24 25})</td>
</tr>
<tr>
<td>Predisposing medical conditions</td>
<td>HIV is the strongest risk factor (particularly high risk, especially if CD4 cell count is &lt; 200/mm(^3); see Chapter 18: Tuberculosis and HIV). Other risk factors include: diabetes, alcoholism and drug addiction, silicosis, gastrectomy, intestinal bypass and chronic malabsorption syndromes and immuno-suppressive diseases (leukaemia, lymphoma, end-stage renal disease). Underlying illnesses such as diabetes mellitus, renal failure, chronic obstructive pulmonary disease and HIV infection are also strong predictors of death from TB.(^{26})</td>
</tr>
<tr>
<td>Immunosuppressive treatment</td>
<td>Current or recent oral steroid therapy (&gt; 15 mg prednisone or equivalent per day for 2–3 weeks); some cancer chemotherapy; immuno-suppressive drugs used in transplantation.</td>
</tr>
<tr>
<td>Immigrants who have recently arrived from a high-incidence country</td>
<td>Risk is highest in the first 1–2 years.(^{27 28})</td>
</tr>
<tr>
<td>Body weight</td>
<td>There is increased risk associated with being underweight or malnourished.</td>
</tr>
</tbody>
</table>
Other factors considered as possible risk factors for LTBI progressing to disease, but for which evidence is lacking, include the following.

- Socioeconomic status: the relationship between socioeconomic status and TB is complex. The clear relationship between TB and poverty\textsuperscript{29,30} may be mediated through many factors, such as crowding, infectivity of source case, access to medical services, and attitudes to and priority given to health.

- 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{32,33}

- No ethnic differences in susceptibility (with appropriate control for confounders) have been documented. Twin and blood group studies suggest some genetic predisposition.\textsuperscript{14}

- Emotional and/or physical stress may increase risk.\textsuperscript{14}

- No study with adequate control for confounders (such as alcohol consumption and HIV infection) has demonstrated that smoking is a risk factor for the development of LTBI or TB disease.\textsuperscript{33}
3.3 Treatment aims, efficacy and cost-effectiveness

3.3.1 Aim of treatment

Treatment of LTBI is intended to prevent the development of TB disease. In the past this has been referred to as ‘chemoprophylaxis’ or ‘preventive therapy’. The term ‘treatment of LTBI’ has been adopted to highlight the fact that the patient is considered to be infected with live bacilli, which could cause active TB disease in the future, and that there is effective treatment available for this infection.2

3.3.2 Efficacy of treatment for LTBI

Several excellent reviews of efficacy have been published recently.34 2 These should be referred to for further information. Recommended regimens are discussed in a later section. (Note: abbreviations for drug names used in this chapter are explained in Chapter 16: ‘Treatment of Tuberculosis’.)

Efficacy in non-HIV-infected people

Isoniazid (H)

Isoniazid for six to 12 months for LTBI has been shown in a Cochrane review35 to prevent the development of TB disease (relative risk of 0.40 (95% CI 0.31–0.52), and to reduce deaths from TB disease, but not all-cause mortality. The number needed to treat (NNT) to prevent one case of TB disease was 100.35 This is an overall figure, and clearly, efficacy will be affected by the level of risk for infection progressing to disease.

Efficacy increases with duration of treatment, but efficacy of six- and 12-month courses does not vary significantly. The small advantage of 12- over six-month courses may not be worthwhile, except for those at high risk of developing TB. The optimal duration of treatment may be nine months,2 though six months may be the most cost-effective regimen (see 3.3.3 ‘Cost-effectiveness’). Guidelines for treatment duration are provided below in 3.5, ‘Recommended regimens and dosages’.

The impact on efficacy of rising rates of H resistance in some populations is debated in the literature. Some analyses suggest that resistance can partially nullify benefit, weakening the rationale for H treatment of LTBI. Others argue that since resistance is a matter of degree, the partial susceptibility of organisms means that H may still be effective in reducing disease risk.36 There is published evidence for the efficacy of rifampicin (R) or RH for treatment of LTBI in people exposed to H-resistant TB.34 Only 10% of New Zealand isolates between 1995 and 2000 were H-resistant,37 and resistance is rare in New Zealand-born patients.
Shorter-course regimens

Shorter-course regimens have been investigated, with the following results.

- In tuberculin-positive persons with silicosis in Hong Kong, 6H, 3R, and 3RH did not differ significantly in efficacy and all were better than placebo.\(^{38}\)
- 3RH is used in the UK because epidemiological data suggest it is effective in children with LTBI.\(^{39}\)
- There are no data on the use of R or RZ (rifampicin and pyrazinamide) in treatment of LTBI in children.
- RZ has not been studied in non HIV-infected people.
- In a study of patients with radiographic evidence of prior TB who had not been previously treated, 12H and 4RH had similar rates of treatment completion and adverse effects, but the study was not adequately powered to assess efficacy.\(^{40}\)

Efficacy in HIV-infected people

9H or 2RZ are the recommended regimens. (See also Chapter 18: ‘Tuberculosis and HIV’, which discusses anti-retroviral treatment in relation to the following regimens.)

- Most studies of efficacy in HIV-infected people precede the availability of highly active anti-retroviral therapy (HART).
- Several regimens (6H, 12H, 3RH, 3RHZ and 2RZ) reduce the risk of TB in people with HIV infection. The effect is restricted to skin-test-positive people.\(^{41, 42}\)
- Treatment prolongs survival in HIV-infected, Mantoux-positive patients,\(^{43}\) and survival is longer with 3HR and 3HRZ than for 6H.\(^{44}\)
- In one meta-analysis the NNT to prevent one case of TB disease was 36 for all those treated, including skin-test-positive and -negative people.\(^{42}\) The incidence of TB was lowest among HIV-positive people with a positive tuberculin skin test who received preventive therapy. In this subgroup mortality may also be reduced, but not significantly. NNT was 19 for TB disease and 28 for death.
- Direct comparison between H given for six months and RZ given for two to three months suggests little difference in efficacy between regimens. Adverse drug reactions were more frequent among patients receiving any drug compared with placebo.\(^{42}\)
- Although anergic HIV-infected people are sometimes assumed to be at high risk for active TB and are administered treatment for LTBI, the effectiveness of this intervention has not been established for this population.\(^{45}\)

3.3.3 Cost-effectiveness

The cost-effectiveness of treatment for LTBI compares favourably with that of other medical interventions, though it is enhanced if:

- treatment is restricted to people with a higher probability of LTBI
- marginal costs are minimised by incorporating treatment into existing TB control programmes.\(^{46, 47, 48, 49}\)
directly observed therapy (DOT) is used.$^{50}$

Six months seems to be the most cost-effective duration of treatment for H.$^{51}$ 4RH is cost saving compared with H,$^{50}$ and 2RZ more cost-effective than 12H.$^{34}$
3.4 Who should and should not have treatment for LTBI?

3.4.1 Indications

Decision analyses have yielded conflicting suggestions about who should receive treatment for LTBI.\(^2\) Criteria for initiating treatment in New Zealand are listed in Table 3.4. However, a range of factors go into a decision to treat (see section 3.4.4 ‘Deciding whether to treat’).

**Immigrants from high-incidence countries**

At a population level, treatment of recently infected people contributes more value for TB control than treatment of people infected in the remote past.\(^{52}\) It has been argued that treatment of LTBI in tuberculin-positive immigrants from high-incidence countries may not always be a cost-effective control strategy, since most immigrants who develop active disease do so in their first year after arrival and their infection may be H-resistant.\(^{27}\) Adult immigrants with a normal chest X-ray and no known recent contact have probably been infected in the remote past and are at low risk of developing TB disease.\(^{48}\)

Consequently, tuberculin-positive recent immigrants from high-incidence countries should only have treatment for LTBI if they have:

- a known history of exposure to an infectious case within the preceding two years
- immunosuppression of a predisposing medical condition (see Tables 3.3 and 3.4)
- a fibrotic lesion on CXR, and disease requiring full multi-drug treatment has been excluded.

**Children aged under five**

In young children the risk of developing TB disease after infection is as high as 40%, especially in infancy,\(^{53}\) and disease can develop within weeks of infection.\(^{54}\) The Mantoux reaction takes up to eight weeks to convert after exposure.\(^{3}\) (See also Chapter 2: ‘Mantoux Testing’.)

Children under five who are close contacts of pulmonary cases should be referred to a specialist, regardless of their tuberculin reaction, and managed as follows:

- If Mantoux-positive they should receive treatment for presumed LTBI.
- If Mantoux-negative (< 5 mm) they should be assessed by a paediatrician with experience in TB. If treatment (for possible LTBI) is decided on, it should be given for eight weeks and then a second Mantoux test done. If the Mantoux converts (\(^2\) 10 mm increase), continue treatment until complete. If the Mantoux does not convert, stop treatment and consider BCG vaccination.
If, during the eight weeks between the first and second Mantoux test, pulmonary specimens from the presumed source case are found to be culture-negative, treatment may be discontinued immediately. The second Mantoux should still be performed, but it is extremely unlikely that the Mantoux will convert if the case is culture-negative. (Analysis of Auckland data from 1997 to 2000 shows that no child contacts of culture-negative cases converted.)

Children under five years who are not close contacts of pulmonary cases should be referred to a specialist only if the tuberculin test is positive, or becomes positive on a second test.

Table 3.4: Criteria for initiating treatment of LTBI

<table>
<thead>
<tr>
<th>Mantoux status*</th>
<th>Treatment by age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mantoux (+)</td>
<td>&lt; 5 years of age</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Mantoux (-)</td>
<td>&lt; 5 years of age</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Mantoux conversion within the last two years</td>
<td>&lt; 5 years of age</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* See Chapter 2: ‘Mantoux Testing’.

** This does not include small calcified granulomas. (See also Chapter 14: ‘Clinical Investigation and Assessment of Tuberculosis’.)

**Mantoux test increases from negative to positive, but the increase is less than 10 mm**

Where the Mantoux reaction increases between testing by <10 mm, the change in diameter of induration does not meet the criterion for conversion. The question then is, what should be done with these individuals?

There is no evidence to guide a decision about how to proceed in this situation. The Tuberculosis Working Group of the Ministry of Health recommends that:

¶ a CXR be done

¶ treatment of LTBI not be given unless:

(a) there are risk factors for TB infection progressing to disease (ie, child aged under five years, immunosuppressive treatment or medical conditions associated with immunosuppression), as shown in Table 3.3; or

(b) there has been close contact with a smear-positive pulmonary case.
Renal failure

Patients who are on renal dialysis or are recipients of renal transplantation are at increased risk of developing TB disease. Treatment for TB disease in these patients is usually curative, but a higher risk of mortality has been noted for patients on dialysis compared to other TB patients. The use of TB drugs in renal failure is discussed in section 17.3: ‘Renal impairment and treatment of TB’.

In New Zealand many renal patients come from ethnic communities that have relatively high rates of TB disease, such as Pacific peoples, Māori and Asians. They are therefore at risk of LTBI and subsequent TB disease.

Treatment of LTBI is well tolerated by renal transplant recipients, but encephalopathy resulting in temporary confusion and convulsions have been documented in uraemic patients.

It is recommended that all patients with chronic renal failure have their Mantoux status determined with a two-step test. This is essential for those on dialysis. If Mantoux-positive, they should be considered for treatment of LTBI. A New Jersey survey found that this intervention was under-utilised: most haemodialysis centres surveyed reported performing tuberculin skin tests on health workers but not on patients. This may be the case in New Zealand as well: anecdotal experience suggests that renal patients notified with TB disease in Auckland had not received prior screening for LTBI.

Treatment for Mantoux-negative renal patients is not recommended. While they may be anergic and have false-negative Mantoux reactions (and be at greater risk for TB disease than those who are Mantoux-positive), there are no data supporting the protective efficacy of treatment in Mantoux-negative renal failure patients. Efficacy trials in other immunosuppressed groups (eg, HIV) also do not support treatment of those who are Mantoux-negative. However, if the CXR shows evidence of past – presumably inactive – disease in a Mantoux-negative patient, then:

1. compare old X-rays, if possible
2. consider investigating for possible active TB disease
3. consider discussing the need for treatment of either LTBI or inactive TB disease with a clinical expert in TB.

3.4.2 Contraindications

Clinical, radiological, or bacteriological evidence of TB disease

Treatment for LTBI is contraindicated in these cases. Investigation is needed to assess whether the disease is active or inactive, and treatment for TB disease should be administered. Investigation is discussed in Chapter 14: ‘Clinical Investigation and Assessment of Tuberculosis’, and treatment of active and inactive TB disease is discussed in Chapter 16: ‘Treatment of Tuberculosis’.
Acute and chronic liver disease

Treatment of LTBI is not contraindicated in hepatitis B (surface antigen-positive) carriers who have no evidence of liver disease. However, Hepatitis B e antigen positivity (HBeAg) represents an important risk factor for severe isoniazid hepatitis. Note that in chronic active hepatitis, the liver function tests may be only mildly disturbed. Patients who develop liver failure from H are sometimes HBsAg-positive people who, in retrospect, had advanced chronic liver disease prior to the anti-TB treatment, and this was not appreciated by their physicians at the time of commencing anti-TB treatment (Dr Ed Gane, personal communication, Auckland Hospital Liver Transplant Unit, 2001).

Treatment of LTBI may occasionally need to be strongly considered in a person who has acute liver disease and a high risk of TB infection progressing to disease. For example, if a person with severe liver disease is discovered to have had close and prolonged contact with a highly infectious TB case – particularly if the contact is receiving some sort of immunosuppressive treatment – then treatment for LTBI must be strongly considered. The risks and benefits of the treatment need to be explained to the contact. A clinician experienced in TB should be consulted during evaluation of such people.

3.4.3 Precautions

RZ treatment regimen

The two-month RZ treatment regimen for LTBI should be used with caution, especially in patients concurrently taking other medications associated with liver injury, and those with alcoholism, even if alcohol use is discontinued during treatment. RZ is not recommended for people with underlying liver disease, or for those who have had H-associated liver injury. People being considered for treatment with RZ should be informed of potential hepatotoxicity and asked whether they have had liver disease or adverse effects from H. (See also sub-section ‘Rifampicin and pyrazinamide’ in 3.6.1.)

Age

H hepatotoxicity rises with age and underlying disease (maximum risk of hepatotoxicity of 2.3% for those > 35 years); see Chapter 15: ‘M. tuberculosis, Tuberculosis Medicines and Monitoring’, Table 15.6). UK guidelines recommend treatment only up to age 16. American statements recommend no age limit because they consider that the risk of severe or fatal hepatotoxicity is low, even in those over 35 years, and that if testing and treatment are targeted at the high risk then the risk:benefit ratio should be acceptable. On the other hand, the elderly have fewer years left in which to benefit from treatment. Rifampicin also carries a small risk of hepatotoxicity, but the risk does not appear to increase with age. Our recommendation for New Zealand is that age over 35 years should no longer be a contraindication to treatment for LTBI, if the clinical indications are strong.
Other interacting drugs

One example of an interacting drug is phenytoin (the serum level of phenytoin tends to decrease). Provided adequate education and regular serum phenytoin levels are carried out, and the patient consents, interacting drugs should not stand in the way of treatment of LTBI. For other interacting drugs, see Chapter 15: ‘M. tuberculosis, Tuberculosis Medicines and Monitoring’, Table 15.8.

Other precautions

Other precautions include:

- regular alcohol use, especially if excessive
- major concerns about adherence to treatment
- major concerns about adherence to arrangements for biochemical or clinical monitoring
- peripheral neuropathy or risk factors for its development (eg, insulin-dependent diabetes mellitus or type II diabetes mellitus with reno-vascular complications, alcohol abuse, chronic renal failure, malnutrition)
- pregnancy: although treatment of active TB disease is justified in pregnancy, treatment of LTBI is more controversial. Data suggest that isoniazid in particular is safe (see section 17.4, ‘Pregnancy, lactation and oral contraceptive use’). Nonetheless, we recommend postponing treatment for LTBI until after pregnancy unless the risk of progression is high: eg, the woman is HIV-positive or recently infected (documented conversion or Mantoux 20 mm after exposure to a smear- or culture-positive case). H or R should be used, not Z.

Note: breastfeeding is not a contraindication. H and R are not secreted in sufficient quantities in breast milk to harm the baby, or to treat an infected baby (see section 17.4, ‘Pregnancy, lactation and oral contraceptive use’).

3.4.4 Deciding whether to treat

The patient needs to be closely involved with the decision-making process. The decision to treat needs to be a joint one by patient, public health nurse and doctor.

Table 3.4 presents a simplified summary of the indications for treatment. However, a decision about whether or not to treat depends on an assessment of the following questions:

- How likely is it that a person has been infected? (see Chapter 2: ‘Mantoux Testing’ and section 3.2.1 ‘Risk factors for LTBI’).
- How likely is it that disease will develop? (see section 3.2.2 ‘Risk factors for LTBI progressing to TB disease’).
- What are the risks of an adverse reaction to treatment (see section 3.6).
- What is the likely adherence to treatment? (see Chapter 4: ‘Adherence to Treatment’).
If the risks of infection and/or disease outweigh the risk of adverse reactions, then the patient should be offered treatment. For more information on this balance of considerations, see Smieja et al and Enarson. For example, in an immunosuppressed person who has recently been exposed to an infectious case and converted their Mantoux reaction, the risks of infection and progression to disease will be high and a directly observed nine- or even 12-month course of H will be appropriate. At the opposite extreme, 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 health care worker whose supposed LTBI is discovered during routine occupational Mantoux screening.

Prior BCG vaccination should be a factor in decision-making about treatment of LTBI. This is in contrast to policy in the US, where BCG vaccination is rarely carried out, so prior vaccination is disregarded as a factor when assessing the need to treat a Mantoux-positive person.
3.5 Recommended regimens and dosages

3.5.1 Regimens

Suggested regimens are shown in Table 3.5. The choice of regimen will depend on:
- presence or absence of risk factors for progression to TB disease
- assessment of the likely adherence level of the client
- the amount of time available for completion of the client’s treatment
- antibiotic susceptibility of the presumed source case
- drug tolerance of the client.

Levels of evidence for the various regimens are not discussed here, as the table seeks to provide guidance for a wide range of clinical scenarios. However, levels of evidence for the basic regimens are available.\(^2\)
### Table 3.5: 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>Appropriate for adherent clients with multiple risk factors (see Table 3.3)</td>
<td>H</td>
<td>Self, daily</td>
<td>9–12</td>
</tr>
<tr>
<td>Standard regimen for non-adherent clients</td>
<td>H</td>
<td>DOT, twice weekly</td>
<td>6</td>
</tr>
<tr>
<td>Appropriate for non-adherent clients with multiple risk factors (see Table 3.3)</td>
<td>H</td>
<td>DOT, twice weekly</td>
<td>9–12</td>
</tr>
<tr>
<td>If short course regimen is needed</td>
<td>RH</td>
<td>Self, daily</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>RZ</td>
<td>Self, daily</td>
<td>2</td>
</tr>
<tr>
<td>If short-course regimen is needed</td>
<td>RH</td>
<td>DOT, twice weekly</td>
<td>4</td>
</tr>
<tr>
<td>Source case H-resistant or client cannot tolerate H</td>
<td>R, or RZ</td>
<td>Self, daily</td>
<td>4</td>
</tr>
<tr>
<td>Source case H-resistant; short-course regimen is needed; client is compliant with</td>
<td>RZ</td>
<td>Self, daily</td>
<td>2</td>
</tr>
<tr>
<td>regular clinical monitoring for hepatitis and understands risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Source case H-resistant; short-course regimen is needed; doubtful adherence*</td>
<td>RZ</td>
<td>DOT, twice weekly</td>
<td>2</td>
</tr>
<tr>
<td>Source case multidrug-resistant**</td>
<td>ZE, or Z+quinolone</td>
<td>Self, daily</td>
<td>6 (if immuno-competent) or alternatively no treatment 12 (if immunosuppressed)</td>
</tr>
<tr>
<td>Client cannot tolerate Z and source case-resistant only to H</td>
<td>R, or RH</td>
<td>Self, daily</td>
<td>4</td>
</tr>
<tr>
<td>Client HIV positive</td>
<td>H</td>
<td>Self, daily</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>RZ82</td>
<td>Self, daily</td>
<td>2</td>
</tr>
<tr>
<td>Client HIV (+); on protease inhibitors or nucleoside reverse transcriptase inhibitors</td>
<td></td>
<td>See Chapter 18: ‘Tuberculosis and HIV’</td>
<td></td>
</tr>
</tbody>
</table>

* No evidence of efficacy in HIV-negative people; evidence of efficacy in HIV-positive people.

** Co-case management with a hospital TB consultant is essential. Efficacy of these regimens is unproven. A South African study suggests efficacy of appropriate regimens in children.

Note: pyrazinamide (Z) is not prescribed for children for treatment of LTBI because of lack of evidence of efficacy and lack of assessment of side-effects.
3.5.2 Dosage

Dosages for drugs commonly used for treatment of LTBI are shown in Table 3.6. For treatment with other drugs, referral to a clinician experienced in TB is advised – particularly for contacts of multi-drug-resistant TB. With twice-weekly multi-drug treatment of TB disease, a period on daily treatment prior to the initiation of intermittent treatment is essential for efficacy. There is no information in the literature on whether this is essential to efficacy in treating LTBI, so intermittent treatment may be started from the outset.

Table 3.6: Dosages of medications to treat LTBI

<table>
<thead>
<tr>
<th>Drug</th>
<th>Oral dose (mg/kg) (maximum dose)</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Adults</strong></td>
<td><strong>Children</strong></td>
<td><strong>Adults</strong></td>
<td><strong>Children</strong></td>
<td></td>
</tr>
<tr>
<td>Isoniazid</td>
<td>5 (300 mg)</td>
<td>5–10 (300 mg)</td>
<td>15 (900 mg)</td>
<td>15 (900 mg)</td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td>10 (600 mg)</td>
<td>10–20 (600 mg)</td>
<td>10 (600 mg)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>20–35 (2.0 g)</td>
<td>-</td>
<td>50 (4.0 g)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
3.6 Adverse effects and drug interactions

3.6.1 Adverse effects and drug interactions

Detailed information on adverse effects and drug interactions of anti-TB drugs is given in Chapter 15: ‘M. Tuberculosis, Tuberculosis Medicines and Monitoring’. Doctors who prescribe treatment for LTBI should ensure they understand and have access to those sections. This section will only discuss hepatitis and neurotoxicity, which are particular problems when treating LTBI and have been studied in this context.

**Isoniazid (H)**

**Hepatitis**

In studies with diverse populations and methodologies, reported rates of H-induced hepatotoxicity have varied from 0.8% to 2.3% and mortality from 0 to 89/100 000 person years. The largest trial found an average rate of 1%, and risk was age-related (0 in those under 20 years and 2.3% in those over 50 years). In HIV-infected people hepatitis is not significantly more common in those treated with H than in those treated with placebo. The risk of hepatitis and drug discontinuation for hepatitis C virus-infected (HCV) people receiving H is within the range reported for populations with lower HCV prevalence.

The risk of death can be reduced by careful monitoring and prompt cessation of treatment if symptoms develop. The risk is not clearly related to acetylator status.

**Other adverse effects**

Central nervous system toxicity has been documented following overdose due to dispensing error, accidental ingestion or attempted suicide in the absence of overdose, and in uraemic patients. Mild-central nervous system effects may necessitate adjustments in the timing of administration.

Peripheral neurotoxicity (dysaesthesiae) occurs in those who are poorly nourished and those at risk of developing peripheral neuropathy, such as alcoholics. Prophylactic pyridoxine is prescribed for all adults and some children. (See section 3.6.3 ‘Pyridoxine’.)

**Rifampicin and pyrazinamide (RZ)**

There have been recent reports of fatal hepatitis during RZ treatment for LTBI. One concerned an elderly woman; another described 21 cases of hepatitis, five of whom died. All fatal cases in the latter report had onset of hepatitis during their second month of treatment. Case reports such as this have no denominator, so the risk of injury and death and the number needed to harm cannot be calculated. Studies where denominator data are collected suggest the risk of hepatitis with RZ is no greater than that with H.
It must be remembered that there is a long history of clinical experience with the safe use of these drugs in full treatment regimens for active TB disease. Nonetheless, the above reports have highlighted the importance of prescribing this regimen only for those:

- who are at high risk of TB disease (see Table 3.3)
- for whom 6H or 9H are not suitable
- for whom thorough pre-treatment education about side-effects and monitoring during treatment can be carried out reliably.

Until there is further clarification of the potential risks with this regimen, the health care provider supervising adherence (usually the public health nurse) must be aware of the concerns in the literature (explained above), and be in telephone contact with the patient at least fortnightly.

**Rifampicin alone and rifampicin/isoniazid in combination (R and RH)**

Trials for the treatment of LTBI suggest that R, alone or in combination with H, seems to carry a slightly lower risk of adverse events than H or RZ.2

### 3.6.2 Monitoring during treatment

Laboratory and clinical monitoring for hepatitis is expensive but may help to prevent expensive liver disease (see Table 3.7). There is no evidence that monitoring does in fact detect hepatitis early enough to prevent serious disease. We recommend monitoring, because treatment of LTBI is a potentially harmful intervention in a person who is clinically well.

**Table 3.7:** Estimated costs of monitoring H treatment for LTBI in Auckland over 15 years

<table>
<thead>
<tr>
<th>Cost of hepatitis</th>
<th>Cost of biochemical monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assume 2% of those treated develop hepatitis</td>
<td>2% of 450 cases per year over 15 years = 135</td>
</tr>
<tr>
<td>All hepatitis cases need:</td>
<td>Each person treated receives 3 x LFTs @ $28.79 each</td>
</tr>
<tr>
<td>- three extra LFTs @ $28.79 each</td>
<td>135 x $86.37 = $11,660</td>
</tr>
<tr>
<td>- three GP visits with blood tests etc @ differential diagnosis @ $150 each</td>
<td>135 x $450 = $60,750</td>
</tr>
<tr>
<td>10% of hepatitis cases need hospitalisation for five days @ $500 per day</td>
<td>675 x 2500 = $1,687,500</td>
</tr>
<tr>
<td>1/7000 courses of H lead to liver transplant = one liver transplant in 15 years</td>
<td>$130,000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$1,889,910</strong></td>
</tr>
<tr>
<td></td>
<td><strong>$582,997</strong></td>
</tr>
</tbody>
</table>

Note: excludes unnecessary public health follow-up for wrongly suspected infectious hepatitis, and indirect and social costs.
Laboratory tests before and during treatment

Before treatment do:
- liver function tests
- FBC, ESR
- urea and electrolytes only if renal failure is suspected.

During treatment do liver function tests:
- for anyone who develops symptoms of hepatitis.
- for adults four weeks after starting treatment (not necessary for children).

Clinical monitoring

The interval between commencing H treatment and the appearance of hepatitis varies widely.\textsuperscript{36} Biochemical monitoring throughout treatment is impracticable, so regular clinical monitoring is essential, particularly in adults over 35 years. This should be at least monthly for H or R, and fortnightly for RZ.

At each visit health care providers conversant in the patient’s language should instruct patients that if abdominal pain, vomiting, jaundice or other hepatitis symptoms develop, they should stop taking treatment immediately and seek medical advice and immediate liver function tests (see section 3.7.2 ‘Education’). The prescribing doctor must make arrangements to ensure that the monthly check is carried out by a registered nurse in between visits to the doctor. The nurse must be trained in the recognition of side-effects of anti-TB drugs, particularly hepatitis.

It has been recommended that RZ be prescribed only in fortnightly amounts to ensure clinical and laboratory monitoring.\textsuperscript{75} This is very labour-intensive in terms of prescribing and dispensing medication, and we recommend that it be considered only if there are concerns about a patient’s ability to report side-effects. Normally prescriptions at monthly intervals will be satisfactory.

Threshold for stopping treatment in the event of hepatitis

If AST or ALT reach three times the upper limit of normal, continue treatment if the person has no nausea or malaise. Arrange repeat tests three to four days later and recheck symptoms then. Treatment should not be interrupted if the person is well.

Provided the person remains well, transaminases may be allowed to rise to at least five times the upper limit of normal. If this occurs, weekly tests should be done till the situation is stable, and less frequently thereafter if they remain at that level.
If the person becomes nauseated or otherwise obviously ill, discontinue treatment and consider:

- whether to treat nausea symptomatically, to allow completion of the treatment course – this may well be possible at this low level of hepatic dysfunction; or
- whether to discontinue treatment and, when liver function tests (LFTs) normalise, change to a different antibiotic regimen.

If ALP or GGT exceed twice the upper limit of normal, discontinue treatment, and when LFTs normalise consider treatment with a different antibiotic. This may entail starting again from the beginning if the interruption has been longer than one month. Discuss this with a clinical TB expert. If treatment has been discontinued for hepatitis, it should not be attempted again unless the person has a risk factor for progression to TB disease (see Table 3.3). An alternative drug should be selected that has a different mechanism for hepatitis from R and H. See Chapter 15: ‘M. Tuberculosis, Tuberculosis Medicines and Monitoring’. More information on the management of drug-induced hepatotoxicity can also be found in that chapter.

### 3.6.3 Pyridoxine

In those on H, pyridoxine 10 mg or 25 mg daily should be prescribed for:

- all adults, including pregnant women
- some early teenagers, depending on nutritional status and body size
- children who develop paraesthesiae
- children who have poor nutrition and are at risk of pyridoxine deficiency
- breastfeeding infants on H
- a fully breastfed infant if the mother is on H, regardless of whether the infant is on anti-TB treatment
- those with seizure disorders, diabetes, uraemia, alcoholism, malnutrition or HIV.
3.7 Practical considerations in the treatment of LTBI

3.7.1 Assess HIV risk factors before starting treatment

Assess HIV risk factors and have a low threshold for HIV-testing people you are considering for treatment for LTBI. HIV-infected people require a longer course of treatment and more treatment supervision than HIV-negative people.

3.7.2 Education

Patients should be informed (using interpreters and written translations if needed) about:

- TB disease, LTBI and the difference between the two
- the fact that LTBI is not infectious
- the adverse effects of treatment (provide written information about the symptoms of hepatitis)
- timing for monitoring visits and blood tests
- who to contact for further advice.

Health education materials available for TB can be found at www.healthed.govt.nz. See also Chapter 11: ‘Health Promotion and Health Education’.

3.7.3 Communication with the GP

The prescriber of treatment for LTBI should advise the patient’s GP in writing of the indications, medication, dosage and duration of treatment, and discuss with the GP the management of adverse reactions and potential drug interactions. The letter should stress the potential for hepatitis from H, R and Z.

3.7.4 Adherence

Efficacy is affected by both duration of treatment and adherence. It seems to depend on the total number of doses taken rather than the regularity of dosing. Adherence is thus crucial to the success of treatment of LTBI, and adherence monitoring is important. If adherence is not excellent, DOT must be carried out (see Chapter 4: ‘Adherence to Treatment’, and Chapter 5: ‘Directly Observed Therapy’), and a shorter-course regimen should be considered.

Because of the need for adherence monitoring, a public health nurse should be involved in the care of all who receive treatment for LTBI. The medical officer of health will arrange this on receipt of a Tuberculosis Case Report Form, unless there is another standing arrangement specific to a health district or location.
3.7.5 **Check antibiotic susceptibility of source case**

Check the antibiotic susceptibility of the presumed source case. If the client has been started on treatment before the susceptibility of the source case is determined, a change in regimen may be needed. (The commonest scenario necessitating a change in the LTBI regimen is that the source case is H-resistant, in which case stop H and start 4R.) The period during which the contact took the agent to which there is probable resistance must be ignored, because it has no influence on the duration of the next regimen selected.

3.7.6 **Changing regimens because of drug side-effects**

In this situation (unlike that above), the whole period of treatment on the first agent counts toward the eradication of LTBI. Depending on the duration of the first regimen (ie, days or weeks), it may be possible to give a lesser period on the second regimen.

3.7.7 **Ending treatment**

Extend treatment to compensate for 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 (at the discretion of the paediatrician) because subtle radiological changes are more often seen in children, and children are at higher risk of undetected progression to disease than adults.

Provide the patient with a record of their Mantoux result, their treatment and a reminder of the symptoms of TB to be alert for in the future.

3.7.8 **If treatment is not given**

If treatment is contraindicated, declined or considered inappropriate (eg, because of likely non-adherence), the person and their GP should be alerted to the risk of future TB disease. There should be a lifelong low threshold for clinical assessment of any symptoms of active TB disease, particularly cough lasting more than three weeks.

Monitoring with CXRs over two years is recommended only for untreated Mantoux-positive:

- children (under five years) who are close contacts of smear- or culture-positive cases
- HIV-infected contacts
- contacts of multi-drug-resistant source cases
- people with inactive fibrotic scars on CXR.

CXR monitoring of other people who are untreated for LTBI is not recommended because of limited evidence for its usefulness in immigrants and contacts. Evidence in these two groups is as follows.
**Immigrants**

Radiological surveillance of inactive TB in immigrants has low cost-effectiveness. An Australian historical cohort study of radiological follow-up of 24,610 predominantly South East Asian refugees between 1984 and 1994 concluded that enhanced passive case finding is likely to be more effective than active case finding for the control of TB among refugees.

**Contacts**

It has been suggested that routine CXR follow-up of contacts for two years in low prevalence areas is not cost-effective. All nine new cases identified by screening 806 contacts of TB cases examined over four years in Edinburgh were found within three months, and only 36% of contacts completed two years of CXR follow-up.

*¶* In Leeds, of 42 cases diagnosed in contacts 19% were found six months after the first visit and a further 10% after an interval of one year or more.

*¶* In Blackburn, 51% of 47 cases were found at the initial stage of contact investigation, 13% at six months, 28% at one year, and 8% at two years.

*¶* Anecdotally the yield from CXR follow-up of contacts beyond six months is low in New Zealand. In Auckland, 784 serial CXRs were done for contacts (from cases in 1997–98) who all started with normal CXRs. Eighteen (2.2%) had evidence of TB on the first CXR; seven (0.9%) on the second and three (0.4%) on the third. Some of these people presented with TB symptoms in between X-rays or after the X-rays were completed. CXRs and the clerical and nursing time required to achieve compliance are expensive.

3.7.9 **Search for a source case**

When a person is put on treatment for LTBI, public health staff must search for the source case if it is not known. The immediate family or household should be assessed if this has not already been done.

3.7.10 **Missed opportunities for treatment**

Programmes vary considerably in the completeness with which they implement treatment of LTBI. Opportunities for treatment of LTBI are often missed because those at risk are not screened, or treatment is not prescribed when indicated.

Since the the risk of TB disease is highest soon after infection, speed in diagnosis and treatment of LTBI are important. Missed opportunities for treatment can be expensive. For example, a 15-year-old Mantoux-positive girl of African origin who immigrated to Switzerland was not treated for LTBI. She subsequently developed active disease and infected 24 of her household, school and social contacts.
3.7.11 Management of previously treated people who are re-exposed

People who have adhered to a previous course of treatment for LTBI or TB disease have very low risk of developing TB disease. Their protection comes from their treatment and from innate and acquired resistance. However, it is possible to develop disease a second time following reinfection with TB. People who are reinfected are difficult to distinguish by Mantoux testing from those who are positive from their prior episode of infection. Repeat Mantoux testing is not advised.

Consider retreatment only for those who have been close contacts of a smear-positive case and have risk factors for progression to TB disease (Table 3.3).

3.7.12 Impact of treatment of LTBI on antibiotic susceptibility of TB

Concern that one-drug treatment for LTBI might generate drug-resistant strains has not been completely addressed. Ferebee reviewed the information on drug susceptibility of cases in trials of isoniazid chemoprophylaxis and concluded that the number of resistant strains among cases who had received the chemoprophylaxis was not greater than the number among cases who received placebo, with the possible exception of cases previously treated with isoniazid. However, only a small proportion of isolates were available for testing. Similar conclusions have been reached in other trials.

In New Zealand, H treatment of LTBI has been in use for some 30 years but there has not been an increase in the rate of H resistance among New Zealand-born TB cases. Between 1995 and 2001 the average resistance rate for isolates among New Zealand-born TB cases has been 3%, compared with 8% for foreign-born cases (Helen Heffernan, personal communication, ESR, 2002).

3.7.13 Acetylator status

Limited evidence suggests that acetylator status does not have a clinically important effect on H efficacy. (See section 15.5.6, ‘Pharmacological considerations with antituberculous agents’.)
3.8  Surveillance

3.8.1  Notification – liaison with public health

Persons treated for LTBI should be notified to the medical officer of health using the Tuberculosis Case Report Form (see Chapter 1, Appendix 1.2). Although not required by law, this step is important, because it helps to ensure that public health has a complete picture of TB infection, disease and treatment in the community. The information may be both relevant and important in future TB control.

3.8.2  Current extent of treatment for LTBI in New Zealand

Treatment for LTBI has been recommended by New Zealand guidelines since a 1990 workshop, but there is only limited information on the extent of implementation. In 2000 and 2001, respectively, 561 and 513 people were reported as starting treatment for LTBI (ESR surveillance data); 97% of them lived in Auckland, Waikato and Wellington. Since these three areas accounted for only 72% of notifications of TB disease in 2000–2001, it is possible that treatment for LTBI is being under-utilised and/or under-reported in other parts of New Zealand.

The regimens prescribed included H (80%), RZ (7%), R (5%), RH (4%) and other or unknown regimens (9%). Ninety-five percent of the courses were prescribed for people under 40 years (see Figure 3.1). The predominance of treatment in the 15–39 years age group probably reflects the large number of refugees treated in Auckland, Waikato and Wellington: 88% of those treated came to attention as the result of immigrant or contact screening.

In 2000, 1115 contacts of smear-positive cases plus about 1500 refugees were screened for LTBI. Assuming that 10% of the contacts and 20% of the refugees were infected, we would expect 411 to be infected. This suggests that 561 cases of LTBI treatment in one year represents a reasonably high level of implementation, if we allow for the fact that in some of those people treatment would have been contraindicated or declined, and that sundry other people would require treatment (eg, infected contacts of smear-negative cases and infections identified by GPs and occupational health screening).
Figure 3.1: Age distribution of those treated for LTBI in New Zealand, 2000–2001

- 15–39 years: 60%
- 5–14 years: 16%
- <5 years: 19%
- 40+ years: 5%
3.9 Screening for LTBI

Some of the basic criteria for a worthwhile population-based screening programme are not fulfilled for LTBI at present. The Mantoux test has low specificity and its positive predictive value is low in New Zealand sub-populations which have a low prevalence of infection. The benefit:cost ratio of treating LTBI depends heavily on the risk that the person is truly infected and is at substantial risk of developing TB disease.

Accordingly, Mantoux screening for LTBI should be reserved for those groups with a high risk of recent infection or who are at high risk of progression from LTBI to TB disease. These groups include:

- close contacts of newly diagnosed cases of active disease
- people with comorbidities that increase the risk of progression to active disease, particularly HIV and renal failure (see Table 3.3)
- health care workers with exposure to patients or infectious materials – this is justifiable to establish baseline Mantoux status against which to compare subsequent testing in the event of exposure to a pulmonary case (see Chapter 9: ‘Infection Control’). Screening of the health care worker population to detect LTBI is probably much less justifiable.

Tuberculin screening in refugees from high-incidence countries is not cost-effective and is no longer recommended unless they have:

- a known history of exposure to an infectious case within the preceding two years
- immunosuppression or a predisposing medical condition (see Tables 3.3 and 3.4)
- a fibrotic lesion on CXR, and disease requiring full multi-drug treatment has been excluded (see Chapter 14: ‘Clinical Investigation and Assessment of Tuberculosis’).

Radiological screening for TB disease is effective among immigrants as a means of reducing disease severity and duration of infectiousness by early detection.

Mantoux screening is best conducted by public health, hospital occupational health services and hospital clinicians caring for people with risk factors for progressing to TB disease (see Table 3.3). GPs should refer to the local public health office any patients who consult them about TB exposure. Routine screening of asymptomatic general practice patients merely because they are immigrants or from high-risk ethnic groups is not advised.
3.10 Prevention of LTBI

BCG vaccination (see Chapter 8) prevents progression to TB disease, but does not prevent TB infection. The only way to prevent LTBI is early identification and treatment of cases of infectious TB disease. Eradication of TB is not possible with current medical technology. (See Chapter 8 for more information on future vaccine developments.)
3.11 Future directions

LTBI should be made notifiable in New Zealand so that data on infection and treatment can be gathered. National surveillance should regularly report the percentage of infected high-risk people who are offered and who complete treatment. This would require the collection of data on the treatment eligibility status for all screened contacts and high-risk immigrants such as refugees and asylum seekers. Computerisation of prescription data would help identify unnotified cases.

It is likely that research into new agents and shorter-course regimens will continue worldwide, leading to further changes in recommended regimens. Similarly, research on the cost-effectiveness and cost:benefit of treatment will help to clarify the groups that should be prioritised for treatment and preferred regimens.

Development of diagnostics that can distinguish individuals with TB infection from those infected with non-tuberculous mycobacteria or BCG vaccine organism will enable clearer identification of those who would benefit from treatment of LTBI.

Research into immunotherapy, such as cytokines and post-infection vaccination, may also lead to new control measures.
References


Chapter 4: Adherence to Treatment

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Summary

TB control requires a high level of adherence to medication. Poor adherence may lead to inadequate outcomes, such as prolonged infectiousness, subsequent reactivation, or development of drug resistance.

Adherence is particularly difficult to achieve with TB treatment. Health care staff need to make every effort to support patients and enable them to adhere to the full course of treatment.

Factors influencing adherence

These include:
- the acceptability and responsiveness of the health service (health care factors)
- the nature of the treatment itself (treatment factors)
- TB stigma and cross-cultural misunderstandings (cultural factors)
- the existence of more pressing personal problems (patient factors).

Risk factors for non-adherence

Recognised risk factors include:
- homelessness
- previous history of TB
- substance abuse
- denial of diagnosis
- living alone.

Some people may identify themselves as likely to have poor adherence. It is difficult for health care workers to predict a patient’s adherence with accuracy. Demographic variables such as age, gender and ethnicity do not predict adherence.

Recommended levels of supervision

Directly observed therapy (DOT) is provided by highly trained outreach health care staff who observe the patient taking every dose of medication. DOT is required if there is:
- resistance to rifampicin
- multi-drug resistance
- relapse/reactivation
- clear inability to self-medicate (eg, homelessness, alcoholism, marked memory impairment)
- clinic non-attendance
- poor adherence despite close monitoring.

Close supervision involves frequent but not daily visits by an outreach worker and intensive attempts to explore and alleviate barriers to adherence. Close supervision is required if there is:
- extensive disease / high infectiousness
- weak or absent social support
- psychiatric illness
- troublesome drug side-effects
- previous non-adherence to treatment for other diseases
- concern about adherence.

Self-administered treatment means the patient is able to self-medicate if there are no risk factors and regular monitoring confirms good adherence.
Levels of supervision may change during treatment, depending on monitoring results.

**Monitoring adherence**

- Adherence must be systematically monitored in *all patients* on TB medication.
- *Clinical staff* should assess the rate of response to medication and any clinic non-attendance, and assess likely adherence.
- *Public health staff* should allocate a case worker (usually a public health nurse) who is responsible for closely assessing adherence. This includes regular discussion with the patient about progress and problems, monthly pill counts, monitoring that medication is dispensed as prescribed, and monitoring changing risk factors for non-adherence.
- *Clinical and public health staff* must communicate well with each other and the patient, rapidly communicate concerns on adherence, and hold regular joint case reviews.

**Detention order**

- A detention order may be sought by the local medical officer of health under the Tuberculosis Act 1948 if a patient with TB who is infectious or potentially infectious refuses to take medication. Prior to this every effort should be made to explore the barriers to treatment and enable the patient to adhere.

**Improving adherence**

**Optimising the TB health service**

- Clinical and public health services providing treatment and follow-up of TB must ensure:
  - 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 regarding side-effects
  - excellent communication, and written and verbal health education
  - interpreters and culturally appropriate workers, if required.

**Additional incentives and enablers**

- A number of strategies have been developed to overcome poor adherence. These include:
  - additional reminder letters
  - additional health education
  - assistance with transport, food or other goods
  - monetary incentives.

**Conclusion**

- TB programmes need to use multiple strategies to ensure patient adherence. 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.
Introduction

‘Adherence’ refers to the extent to which patients follow the instructions they are given for prescribed treatment, and it is a critical factor in successful TB control. Non-adherent clients remain infectious longer, take longer to complete treatment and are more likely to relapse or develop drug resistance. Non-adherence places at risk the health of the individual, their family and the wider community, as well as wasting health resources.

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

TB treatment presents particular challenges for adherence: the treatment is long and involves taking a large number of medications, side-effects are common, and the patient usually feels better long before the treatment has been completed. Additionally, the disease itself is stigmatised in many communities, which may lead patients to deny their illness or conceal the fact that they are taking medication.

These factors are also relevant in the treatment of latent tuberculosis infection (LTBI), where the patient does not even feel unwell prior to starting treatment (see Chapter 3 ‘Latent TB Infection’). Although treatment of LTBI does not have the same clinical or public health urgency as treatment of TB disease, incomplete adherence will result in waste of time and effort for the patient, waste of health care resources, and a risk of drug resistance if the patient develops TB disease at a later stage. If the patient with LTBI or the clinician considers that non-adherence is likely, strategies to improve adherence should be implemented or treatment should not proceed.

An overview of monitoring and improving adherence is shown in Figure 4.1.
Figure 4.1: Monitoring and improving adherence to TB treatment

Person with TB or LTBI

Prerequisites:
- Optimal TB health service (section 4.4.1)
- Monitoring system (Table 4.3)

Determine level of supervision required (Table 4.2)

Systematic monitoring of adherence (Table 4.3)

Adherence satisfactory
- Continue

Adherence inadequate
- Close supervision and strategies for improved adherence (Table 4.4)

Commence DOT

Adherence inadequate despite strategies to improve adherence
- Risk to public health?
  - Yes
    - Detention order
  - No
    - Close supervision

Self-medication

DOT

Detention order
4.1 Factors influencing adherence

Factors that influence adherence include:

- the accessibility and responsiveness of the health service
- the nature of the treatment itself
- cultural concepts of TB
- the existence of other more pressing problems, such as unemployment, poor housing and poverty.

One study found that the relative influence of these factors differed between men and women. Women were found to be more sensitive to interactions with health staff and stigma in society, whereas men cited insufficient knowledge and cost as barriers.

Health care providers need to recognise factors relating to non-adherence and do everything possible to support the patient to take medications as prescribed, and to complete treatment. This includes close appraisal of the health care service offered to the patient and a commitment to removing health service barriers, where possible. It also includes developing a relationship with patients and their families so that ‘patient factors’ can be understood and addressed, where appropriate.

Table 4.1: Reasons for non-adherence

<table>
<thead>
<tr>
<th>Health care factors</th>
<th>Treatment factors</th>
<th>Patient factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inaccessible service – long travelling distance and lack of transport</td>
<td>Long duration of treatment</td>
<td>Life stressors (lack of resources, unemployment, life events)</td>
</tr>
<tr>
<td>Expenses incurred attending hospital</td>
<td>Large pills, or large number of pills</td>
<td>Low educational level or illiteracy</td>
</tr>
<tr>
<td>Long waiting times</td>
<td>Side-effects</td>
<td>Health beliefs, including cultural beliefs and attitudes, stigma and community attitudes</td>
</tr>
<tr>
<td>Unfriendly staff</td>
<td>Disruption of daily life</td>
<td>Poor understanding about TB and treatment rationale</td>
</tr>
<tr>
<td>Inadequate confidentiality</td>
<td>Prescribing or dispensing errors</td>
<td>Substance abuse, including alcoholism</td>
</tr>
<tr>
<td>See different health workers each time</td>
<td>Cost</td>
<td>Patient may not believe need for treatment as does not feel sick</td>
</tr>
<tr>
<td>Poor communication style (use of jargon, patronising language, lack of information, no opportunity for questions, lack of participation in interview)</td>
<td></td>
<td></td>
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<tr>
<td>Lack of interpreters or culturally appropriate staff</td>
<td></td>
<td></td>
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<tr>
<td>Other personal and social characteristics of providers</td>
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</tbody>
</table>
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

The following factors have been found to be associated with non-adherence:

- homelessness
- psychiatric illness
- substance abuse
- previous history of TB
- denial of diagnosis
- living alone

Patients identify themselves as likely to have poor adherence. This list is not comprehensive, but reflects the factors that have been formally studied and reported in the literature.

Some studies have found adherence to be associated with ethnicity, while others have not. Demographic variables such as age, gender and ethnicity cannot be used to predict adherence. The predictability of adherence in individual patients is quite limited. For this reason, ongoing adherence should be systematically monitored for all patients.

4.2.2 Determining the initial level of supervision

Adherence to a long course of medication is difficult for most people. When considering the optimal level of supervision, consider all possible risk factors for non-adherence. Note that the optimal level of supervision is influenced by factors other than patient factors. For example, clinical factors, such as multi-drug resistance and the presence of side-effects, also influence the level of supervision required (Table 4.2).
### Table 4.2: Recommended level of supervision

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Level of supervision</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cases on intermittent regimens (twice or thrice weekly doses)</td>
<td>DOT*</td>
</tr>
<tr>
<td>All cases resistant to rifampicin</td>
<td></td>
</tr>
<tr>
<td>All multidrug-resistant cases (resistance to INH and rifampicin)</td>
<td></td>
</tr>
<tr>
<td>All relapses/re-activations</td>
<td></td>
</tr>
<tr>
<td>Cases who clearly demonstrate an inability/unwillingness to self-medicate (eg, substance abuse, denial of diagnosis, homelessness, intellectual limitations)</td>
<td></td>
</tr>
<tr>
<td>Failure to comply with ward or outpatient clinic requests</td>
<td></td>
</tr>
<tr>
<td>All cases whose adherence is poor during close supervision</td>
<td></td>
</tr>
<tr>
<td>Extensive disease and high infectiousness</td>
<td>Close supervision: consider DOT</td>
</tr>
<tr>
<td>Weak or absent social support</td>
<td></td>
</tr>
<tr>
<td>Psychiatric illness</td>
<td></td>
</tr>
<tr>
<td>Troublesome drug side-effects</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</td>
<td>Self-administered treatment</td>
</tr>
</tbody>
</table>

* DOT = directly observed therapy
4.3 Monitoring adherence

4.3.1 Methods

Adherence must be systematically monitored in all patients on TB medication. This involves all health staff involved in the care of TB patients. It is essential that clinical and public health staff communicate frequently so that concerns about adherence can be quickly detected and acted on.

Self-reporting of adherence is not highly reliable. The best approach in research investigations on adherence is to use multiple measures, including a combination of urine assays, pill counts and detailed patient interviews. Urine assays are rarely used in routine practice.

Electronic lid monitors are highly reliable for evaluating adherence for research purposes. These devices record the date and time that medication container lids are removed. While this does not prove that medication has been ingested, research shows a close correlation between lid removal and taking medication. As well as monitoring adherence, these devices may help improve adherence for some patients. Electronic lid monitors currently cost about $NZ200 and last for three years. The machine that ‘reads’ the lids and the software cost about $NZ800 as a one-off purchase. Only larger units with many clients on treatment are likely to find this useful at the current time. For further information, contact Dr L Calder, Public Health Protection Service, Auckland.

Record keeping sheets help public health nurses to record pill counts and enable early recognition of adherence problems. (See Appendix 4.2 for recommended forms, and Appendix 4.1 for examples.)

4.3.2 Level of supervision

The required level of supervision may change during the treatment course. Some patients may be initially assessed as requiring close supervision or DOT and subsequently be able to self-administer treatment, while others may need to progress in the direction of increasing supervision.

Self-administered treatment

Some patients will have no risk factors for non-adherence and are able to self-medicate. Table 4.3 shows the routine requirements for monitoring where there are no concerns about adherence.
Table 4.3: Routine activities for monitoring adherence

<table>
<thead>
<tr>
<th>Clinical Monitoring including:</th>
<th>Public health Regular assessment of patient by public health nurse, including:</th>
<th>Clinical and public health</th>
</tr>
</thead>
<tbody>
<tr>
<td>¶ clinic non-attendance</td>
<td>¶ discussion on progress and problems, including side-effects and adherence</td>
<td>¶ Good communication between case workers, clinicians and patient</td>
</tr>
<tr>
<td>¶ physician assessment of adherence</td>
<td>¶ monthly pill counts or syrup volume checks</td>
<td>¶ Rapid communication if concerns about adherence</td>
</tr>
<tr>
<td>¶ rate of clinical response to medication</td>
<td>¶ check medications dispensed as prescribed</td>
<td>¶ Regular case review meetings between clinical and public health services</td>
</tr>
<tr>
<td></td>
<td>¶ monitor changing risk factors for non-adherence</td>
<td></td>
</tr>
</tbody>
</table>

**Close supervision**

Close supervision is an intermediate step between self-medication and DOT. This will involve more frequent visits by the case worker – usually weekly – and intensive attempts to explore and alleviate barriers to non-adherence.

Trigger points that might lead to closer supervision or DOT should be agreed between the clinical and public health services, and might include any of the following:

- ¶ 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
- ¶ more than 15% of daily medication has been missed at any pill count.

**Directly observed therapy (DOT)**

Concerns about adherence are not the only criterion for commencing a patient on DOT (see Table 4.2). In New Zealand DOT is provided by specialised outreach staff, usually nurses based in public health units. In Auckland, non-nursing community health workers provide DOT to some patients. The use of non-health care workers to deliver DOT requires careful thought and training, and is discussed in Chapter 5: ‘Directly Observed Therapy’.

Poor adherence can occur while a patient is on DOT. This will be evident if the patient is not at the agreed place to meet the health worker and take the medication. Non-adherence while on DOT is a serious sign of a breakdown in the relationship between the health care provider and the patient. Every effort should be made to overcome the barriers to full adherence with DOT. Ultimately, if all other avenues have failed and the non-adherence cannot be solved promptly, consideration may be given to a detention order.
**Treatment contracts**

These can be used at all levels of supervision but are most applicable where adherence is doubtful. Patients can be asked to sign an agreement including:

- the time and place for delivery of medication
- an agreement to contact their case worker if there is a change of plan
- an intention to attend all appointments.

This should be dated and countersigned by the medical officer of health.

**Detention order**

A three-month detention order may be sought by the local medical officer of health under the Tuberculosis Act 1948 if all other attempts to make the patient adhere to treatment have failed. It is important to involve the medical officer of health from an early stage, once it is apparent that a detention order may be necessary.

A protocol for detention of patients has been produced by the Ministry of Health as a guide to medical officers of health. It outlines the legal implications and steps to follow if this situation arises. The booklet is called *A Guide to Section 16 of the Tuberculosis Act 1948.*

**Alternatives to detention orders**

A detention order is a last resort, and there is no guarantee that it will be successful. In fact, while a detention order may bring some people to a realisation of the gravity of TB and the need for co-operation, with others it may reinforce their determination to be unco-operative.

Building relationships and allies is far more likely to provide a mutually satisfactory outcome than imposing a detention order. This may involve:

- locating culturally appropriate individuals who can communicate effectively with the patient and his/her family
- switching case management to another public health nurse
- visits to the patient and their family by the medical officer of health at a time and place that suit the family
- discovering the real obstacles – which often lie outside the TB problem – and how they might be solved creatively.
4.4 Improving adherence

4.4.1 Optimising TB health services

During treatment for TB the patient interacts with primary care providers, hospital and outpatient staff and public health staff. Under the Code of Health and Disability Services Consumers’ Rights, the patient has a number of legal rights. These rights are also best clinical practice, and include:

- respect – this includes respect for cultures, values, beliefs and the right to personal privacy
- communication
- confidentiality
- information – including treatment, options and side-effects
- a support person
- the right to complain.

The following are health service requirements for people with TB in New Zealand.

Free service

Inpatient, outpatient and core public health services are free to all New Zealand residents. In the case of non-residents who do not have health insurance, the local medical officer of health can require a patient to have compulsory investigation and treatment by writing the patient a letter under section 9 of the Tuberculosis Act 1948. This means that the District Health Board is obliged to provide diagnosis and treatment of TB free of charge because the patient is eligible for free health services according to the Ministry of Health’s gazetted notice, Eligibility Criteria for Health and Disability Services in New Zealand.

Medications

Anti-TB medication is free to patients. However, ancillary drugs such as pyridoxine, prednisone and antihistamines are not. The public health service should consider covering the cost of the ancillary medications, if required, to assist adherence. Medication regimens need to be kept as simple as possible, with the number of pills to be taken minimised. At each visit the case worker should check that medications are dispensed as prescribed. Blister packs may be required to aid adherence.

Case management

Ideally, there should be a designated physician and a single case worker (usually a public health nurse) who will communicate regularly with the patient. These two key health professionals need to establish good communication – both with the patient and with each other.
Outpatient services need good systems to ensure adherence to clinic visits. Patient reminders should be issued for follow-up of non-attendance. A copy of the appointment should be sent to the public health service as the public health staff may know about recent changes of address, and transport or other problems affecting ability to attend.

**Clinic environment**

As far as possible, minimise waiting times and ensure a comfortable environment. Streamlining investigations while the patient is at the outpatient clinic (eg, getting blood tests while waiting to be seen by the clinician) will reduce the time spent at the appointment for the patient. Communication with the patient and their family when delays are anticipated is important.

**Advice on side-effects**

Clients need clear, written and verbal instructions about the potential side-effects of medication, and what action needs to be taken should these occur, including detailed information on who to contact (see Chapter 11: ‘Health Promotion and Health Education’, for written resources). A poor understanding of side-effects has been reported in regard to treatment of LTBI.\(^7\)\(^{13}\) Warning people about side-effects does not appear to affect adherence to treatment,\(^2\) and it is thought that if patients are warned about self-limiting side-effects (eg, dizziness and tiredness when isoniazid is started), this may improve adherence.\(^{13}\)

**Communication**

Good communication is critical to improving adherence. Health care providers should feel confident that patients understand all aspects of their treatment. The Patient Code of Rights specifies that:

- information should be given in a form, language and manner that the client can understand
- a competent interpreter should be available if required and if this is reasonably practical
- communication should take place in a way that supports open and honest discussion.

The case worker needs to spend time at the initial interview learning as much as possible about the patient’s health history, beliefs and attitudes about TB, sources of social support, and barriers to treatment. Initial information should be presented clearly. Too much information at the first visit may be difficult to absorb, so information should be presented in a progressive manner with the most important points first.

Treatment success depends on a partnership between the patient and provider, so it is important to establish rapport and trust. In a South African study, TB advice was given by nurses with extra training in communication techniques. In the interview at the beginning of treatment the patient was encouraged to talk about the diagnosis and to identify potential perceived barriers to maintaining daily supervised treatment. This intervention improved adherence.\(^{14}\)
Written health education materials should be provided. A review of consumer health information in Victoria, Australia, found that clinicians under-estimated consumer need for written information. Consumers wanted printed information to complement verbal information, and needed this to participate in decision-making about their care.

At the first visit the case worker should explore with the patient whether a culturally appropriate health care worker should be involved for support. If the patient is not fluent in English, translated materials should be provided, if possible. Health education resources should be culturally appropriate, and can include posters, flipcharts and videos as well as written materials. (See Chapter 11: ‘Health Promotion and Health Education’ for a list of health education resources.)

Family members may need to be involved in education sessions so that they understand the patient’s diagnosis and what the patient needs to do, to allow coping strategies for the family to be considered. This should always be discussed with the patient first, as they may not want this.

**Use of interpreters**

All patients whose first language is not English should be asked whether they would like an interpreter at their first contact with the health service. The use of a sticker on the outside of the medical notes, which draws attention to the need for an interpreter and the language required, is recommended. Remember that a longer consultation time will be needed to allow for the interpreting process.

Professional interpreters are bound by professional codes of ethics, which place great emphasis on impartiality, accuracy and confidentiality. Health professionals should not assume that family or other untrained personnel can interpret adequately. This risks miscommunication and compromises confidentiality. Health staff should try to ascertain whether the interpreter met the needs of the patient; this has inherent difficulties if the client speaks no English and there is no other person available to assist cross-checking.

Access to interpreters varies from region to region. *Refugee Health: A handbook for health professionals* is available on the Ministry of Health web site (www.moh.govt.nz) under publications: November 2001. This useful resource provides guidelines for communicating effectively with refugee clients (pp. 31–35), and a current list of interpreting services in main centres (pp. 97–99). Comprehensive information on communicating effectively using interpreters is found in a guide produced by the Office of Ethnic Affairs, *Let’s Talk: Guidelines for government agencies hiring interpreters*. This is available online at http://www.ethnicaffairs.govt.nz/oeawebsite.nsf/Files/ethnicLett`sTalk.
Tips for communication through an interpreter

- Speak slowly and clearly, using one or two sentences at a time.
- Make sure your client is the focus of the attention, 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: Refugee Health: A handbook for health professionals

4.4.2 ‘Incentives and enablers’: additional strategies to improve adherence

Many strategies have been developed to overcome poor adherence to TB treatment, some aimed at the health staff and some at the patient. A systematic review of strategies to promote adherence found that the following measures were successful in various groups:

- two reminder letters to patients following clinic non-attendance
- a monetary incentive or paid peer health advisor (for homeless people)
- health education to mothers of children receiving treatment for LTBI (the study found that attendance at clinic visits was better when the nurse visited or phoned the patient at home than when health education was provided by a doctor at the clinic)
- a monetary incentive combined with health education
- intense supervision by staff.

Other strategies found useful include:

- tokens for transport or food
- provision of other goods
- provision of a liquid nutritional supplement in HIV-positive individuals.

A meta-analysis of DOT and treatment adherence concluded that DOT programmes consist of more than the five elements of the WHO strategy and include incentives, tracing of defaulters, legal sanctions, patient-centred approaches, staff motivation, supervision and additional external funds.
<table>
<thead>
<tr>
<th>Health care system: prerequisites</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Free, accessible and acceptable service</td>
<td>Discussion of barriers and attempts to overcome them</td>
</tr>
<tr>
<td>Free medication</td>
<td>More intensive supervision</td>
</tr>
<tr>
<td>Simple packaging of medication</td>
<td>Additional reminders</td>
</tr>
<tr>
<td>Clear advice on side-effects</td>
<td>Additional health education sessions</td>
</tr>
<tr>
<td>Good case management: case workers, clinical/public health communication, good record keeping</td>
<td>Assistance with transport, food, or other goods</td>
</tr>
<tr>
<td>Supportive clinic environment: friendly, minimal waiting, appointment reminders, convenient appointments</td>
<td>Monetary incentives</td>
</tr>
<tr>
<td>Excellent communication with clients</td>
<td></td>
</tr>
<tr>
<td>Written information</td>
<td></td>
</tr>
<tr>
<td>Interpreters</td>
<td></td>
</tr>
<tr>
<td>Culturally appropriate workers</td>
<td></td>
</tr>
</tbody>
</table>
4.5 Future directions

In future we are likely to see:

- the increased use of electronic lids for monitoring and improving adherence
- simplification of medications (e.g., 300 mg isoniazid tablets, fixed-dose combination tablets and slow-release formulations)
- evaluations of programme acceptability to clients
- increasing use of culturally appropriate outreach workers to provide support to clients and administer DOT where required.
Appendix 4.1: Example of medication records for pill counts for patients on self-administered treatment

Example of medication record for patient on self-medication: *pyrazinamide*.

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
<th>K</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Date</td>
<td>No. of days since last visit</td>
<td>Prescribed dose</td>
<td>No. tabs in a dose</td>
<td>No. tabs left last visit</td>
<td>No. doses left (E/D)</td>
<td>No. tabs today</td>
<td>No. doses today (G/D)</td>
<td>Expected doses today (F–B)</td>
<td>Doses missed (H–I)</td>
</tr>
<tr>
<td>1/5/01</td>
<td>0</td>
<td>3250</td>
<td>6.5</td>
<td>390</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8/5/01</td>
<td>7</td>
<td>3250</td>
<td>6.5</td>
<td>390</td>
<td>60</td>
<td>360</td>
<td>55</td>
<td>53</td>
<td>2</td>
<td>29</td>
</tr>
<tr>
<td>18/5/01</td>
<td>10</td>
<td>3250</td>
<td>6.5</td>
<td>360</td>
<td>55</td>
<td>300</td>
<td>46</td>
<td>45</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>23/5/01</td>
<td>5</td>
<td>3250</td>
<td>6.5</td>
<td>300</td>
<td>46</td>
<td>270</td>
<td>42</td>
<td>41</td>
<td>1</td>
<td>20</td>
</tr>
</tbody>
</table>

Example of medication record for patient on self-medication: *rifampicin*.

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
<th>K</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Date</td>
<td>No. of days since last visit</td>
<td>Prescribed dose</td>
<td>No. tabs in a dose</td>
<td>No. tabs left last visit</td>
<td>No. doses left (E/D)</td>
<td>No. tabs today</td>
<td>No. doses today (G/D)</td>
<td>Expected doses today (F–B)</td>
<td>Doses missed (H–I)</td>
</tr>
<tr>
<td>30/4</td>
<td>0</td>
<td>600</td>
<td>1</td>
<td>44</td>
<td>44</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25/5</td>
<td>25</td>
<td>600</td>
<td>1</td>
<td>44</td>
<td>44</td>
<td>21</td>
<td>21</td>
<td>19</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>10/6</td>
<td>16</td>
<td>600</td>
<td>1</td>
<td>21</td>
<td>21</td>
<td>10</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td>31</td>
</tr>
<tr>
<td>10/7</td>
<td>30</td>
<td>600</td>
<td>1</td>
<td>40</td>
<td>40</td>
<td>21</td>
<td>21</td>
<td>10</td>
<td>11</td>
<td>37</td>
</tr>
<tr>
<td>20/7</td>
<td>10</td>
<td>600</td>
<td>1</td>
<td>21</td>
<td>21</td>
<td>11</td>
<td>11</td>
<td>11</td>
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</tr>
<tr>
<td>20/7</td>
<td>0</td>
<td>450</td>
<td>3</td>
<td>90</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>27/7</td>
<td>7</td>
<td>450</td>
<td>3</td>
<td>90</td>
<td>30</td>
<td>45</td>
<td>15</td>
<td>23</td>
<td>+8</td>
<td>too many</td>
</tr>
<tr>
<td>3/8</td>
<td>7</td>
<td>450</td>
<td>3</td>
<td>45</td>
<td>15</td>
<td>24</td>
<td>8</td>
<td>8</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Appendix 4.2: Medication records for pill counts for patients on self-administered treatment

Medication record for patient on self-medication: *isoniazid*.

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
<th>G</th>
<th>H</th>
<th>I</th>
<th>J</th>
<th>K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>No. of days since last visit</td>
<td>Prescribed dose</td>
<td>No. tabs in a dose</td>
<td>No. tabs left last visit</td>
<td>No. doses left last visit (E/D)</td>
<td>No. tabs today plus No. dispensed today</td>
<td>No. doses today (G/D) plus No. dispensed</td>
<td>Expected doses today (F–B)</td>
<td>Doses missed (H–I)</td>
<td>Percentage of doses missed (J/B%)</td>
</tr>
</tbody>
</table>

Medication record for patient on self-medication: *rifampicin*.

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
<th>F</th>
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<th>H</th>
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<th>J</th>
<th>K</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td>No. of days since last visit</td>
<td>Prescribed dose</td>
<td>No. tabs in a dose</td>
<td>No. tabs left last visit</td>
<td>No. doses left last visit (E/D)</td>
<td>No. tabs today plus No. dispensed today</td>
<td>No. doses today (G/D) plus No. dispensed</td>
<td>Expected doses today (F–B)</td>
<td>Doses missed (H–I)</td>
<td>Percentage of doses missed (J/B%)</td>
</tr>
</tbody>
</table>
Medication record for patient on self-medication: *rifinah*.

| A | Date | B | No. of days since last visit | C | Prescribed dose | D | No. tabs in a dose | E | No. tabs left last visit | F | No. doses left last visit (E/D) | G | No. tabs today plus No. dispensed today | H | No. doses today (G/D) plus No. dispensed | I | Expected doses today (F–B) | J | Doses missed (H–I) | K | Percentage of doses missed (J/B%) |
|---|-----|---|-----------------------------|---|-----------------|---|-------------------|---|------------------------|---|-------------------------|---|-----------------------------|---|--------------------------|---|-----------------------|---|----------------------|
|   |     |    |                             |   |                 |    |                   |   |                        |    |                         |    |                           |    |                         |    |                       |    |                      |

Medication record for patient on self-medication: *pyrazinamide*.

| A | Date | B | No. of days since last visit | C | Prescribed dose | D | No. tabs in a dose | E | No. tabs left last visit | F | No. doses left last visit (E/D) | G | No. tabs today plus No. dispensed today | H | No. doses today (G/D) plus No. dispensed | I | Expected doses today (F–B) | J | Doses missed (H–I) | K | Percentage of doses missed (J/B%) |
|---|-----|---|-----------------------------|---|-----------------|---|-------------------|---|------------------------|---|-------------------------|---|-----------------------------|---|--------------------------|---|-----------------------|---|----------------------|
|   |     |    |                             |   |                 |    |                   |   |                        |    |                         |    |                           |    |                         |    |                       |    |                      |

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Chapter 4: Adherence to Treatment
Medication record for patient on self-medication: *ethambutol*.

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E</th>
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<th>G</th>
<th>H</th>
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<th>K</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Date</td>
<td>No. of days since last visit</td>
<td>Prescribed dose</td>
<td>No. tabs in a dose</td>
<td>No. tabs left last visit</td>
<td>No. doses left last visit (E/D)</td>
<td>No. tabs today plus No. dispensed today</td>
<td>No. doses today (G/D) plus No. dispensed</td>
<td>Expected doses today (F–B)</td>
<td>Doses missed (H–I)</td>
<td>Percentage of doses missed (J/B%)</td>
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</table>

Medication record for patient on self-medication: *other drug*.

<table>
<thead>
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Guidelines for Tuberculosis Control in New Zealand 2003
Chapter 4: Adherence to Treatment
Recommended reading


References

Chapter 5: Directly Observed Therapy

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Summary

This chapter represents an update of the Ministry of Health publication Directly Observed Therapy (DOT) for Tuberculosis 2001.

Adherence to treatment is difficult for TB patients to maintain. Directly observed therapy (DOT) ensures adherence. The Tuberculosis Working Group of the Ministry of Health strongly supports the use of DOT and urges all medical officers of health to work with prescribing physicians to ensure that DOT is offered to all patients who need it.

Definition of DOT

DOT refers to the procedure whereby a supervisor trained in the administration of DOT watches the patient swallowing the medication for all doses during the course of treatment. The DOT supervisor may be a health worker or a trained and supervised community member.

It is not considered to be DOT if an untrained family or community member administers the treatment to the patient. It is very important that anyone providing DOT is well-trained. If a non-health worker (eg, a guardian) is asked to take responsibility for giving DOT, they must be given training so that they understand TB, the medications, the DOT process, documentation and the limits of their responsibility.

For the purposes of surveillance, DOT is defined as receiving DOT throughout the course of treatment (see Chapter 1: The Epidemiology and Surveillance of Tuberculosis in New Zealand). People who receive DOT for only part of their course of treatment should not be classified on the case report form as having received DOT.

Effectiveness of DOT

The DOT strategy is actively promoted by the World Health Organization for TB patients in an effort to control the global emergency of TB. DOT is being successfully implemented in many other countries.

DOT produces superior treatment completion rates to those achieved by non-supervised interventions and leads to improved relapse and drug-resistance rates.

However, randomised trial evidence for the effectiveness of DOT is limited, and DOT may not always lead to better treatment outcomes than self-administered treatment. Moreover, the published literature does not clearly distinguish the impact of DOT itself from co-interventions such as incentives, enablers, patient-centred programmes and many other programmatic factors that may have contributed to the improved outcomes in published accounts of DOT programmes.

Current use of DOT in New Zealand

Universal DOT is not necessary in New Zealand which has high rates of treatment completion and low rates of drug resistance and relapse.

Completeness of data on DOT in national TB surveillance is unacceptably low, so the proportion of cases who receive DOT is unknown. There is wide inter-district variation in the proportions of cases treated by DOT, but overall the proportion seems low (about 24% of new TB cases in 1999–2001).
Indications for DOT

People with TB who should always be on DOT include all:
- cases on intermittent regimens (twice- or thrice-weekly doses)
- cases resistant to rifampicin
- multidrug-resistant cases (resistant to isoniazid and rifampicin)
- relapses/reactivations
- cases that clearly demonstrate an inability or unwillingness to self-medicate
- cases that have been placed under closer supervision (see Chapter 4: ‘Adherence to Treatment’) and who then fail to improve their commitment to treatment.

People with TB should be considered for DOT when there is:
- extensive disease and/or a high degree of infectiousness
- weak or absent social support
- a complex treatment regimen
- serious multiple drug-resistance, or where side-effects necessitate the use of two or more second-line drugs.

Using DOT for treatment of latent tuberculosis infection (LTBI)

DOT should always be used for intermittent regimens (twice- or thrice-weekly doses) for treatment of LTBI. DOT should also be considered if the client has risk factors for non-adherence and meets one or more of the following criteria:
- can be given DOT at the same time as a case who is on full treatment by DOT in the same household or neighbourhood
- has recently converted their Mantoux test following exposure to an infectious case
- is under five years of age
- has risk factors for progression from infection to disease (see Table 3.3, Chapter 3: ‘Latent Tuberculosis Infection’)
- is a contact of a multi-drug-resistant case.

Practical problems during a DOT regimen

Temporary inability to give DOT: is self-medication acceptable?

Self-administration of twice- or thrice-weekly treatment is not acceptable. If a case is going on holiday overseas and cannot be given DOT, they must change to daily treatment. If they are holidaying in New Zealand every attempt should be made to continue DOT through another public health office, or daily treatment should be prescribed.

Missed DOT doses

The medical officer of health should be advised if the patient misses:
- more than one DOT dose per month (for intermittent DOT)
- more than one dose per week (for daily DOT).

The medical officer of health should meet the patient and discuss any obstacles to adherence (see Chapter 4: ‘Adherence to Treatment’). If the patient has missed any doses of DOT, these must be added on at the end of treatment. This does not apply to doses delayed for a day or two because the patient missed a DOT appointment but the dose was finally given late.
Discontinuing DOT and transferring to self-administered treatment

Occasionally a patient’s understanding and commitment to treatment improves to such an extent that DOT is no longer considered necessary. If a switch is made to self-administered treatment it must be prescribed as daily treatment.

Community DOT workers

Extensive experience overseas has shown that lay DOT workers with appropriate training and supervision can provide DOT reliably. (See Appendix 5.1 for information on establishing a community DOT worker programme.)

Health professionals outside the public health workforce as DOT workers

It may be appropriate to recruit and train health professionals from outside the public health workforce to administer DOT to some clients.

Incentives and enablers

Measures other than DOT that have been shown to promote adherence include reminder cards, help by health workers, financial incentives, health education, and intensive supervision of staff in TB clinics. These interventions may be more appropriate in the first instance for a patient with questionable adherence.

Future developments

Complete DOT information should be recorded in EpiSurv by public health offices.

ESR should establish longitudinal reporting on the proportion of cases that relapse over time.
Introduction

This chapter represents an update of the Ministry of Health publication *Directly Observed Therapy (DOT) for Tuberculosis*.

Detection and cure of cases are the cornerstones of TB control. Cure and the prevention of drug resistance are contingent on patients’ adhering to an appropriate anti-TB treatment regimen. Proponents of DOT argue that in the case of TB, a global pandemic of a drug-resistant disease with public health implications, it is the medical practitioner’s responsibility as much as the patient’s to ensure cure.

Adherence is difficult for TB patients to maintain. People always need assistance and support to stay on anti-TB medication because:

- everybody finds it difficult to remember to take long courses of treatment without support
- the pills prescribed are sometimes hard to swallow
- large numbers of pills have to be taken, especially during the initiation phase of treatment
- there are sometimes unpleasant side-effects from the medication
- abstention or reduced intake of alcohol is necessary while on medication
- there may be difficulties filling prescriptions because not all pharmacies are aware of the fact that anti-TB medications are fully government-subsidised
- the stigma associated with TB often affects the patient’s treatment and illness from co-morbid conditions may result in the total number of tablets becoming intolerable
- drug interactions compound the difficulties already faced by the patient and their family.

Adherence is also difficult for health care providers to predict and measure. (For a detailed discussion of adherence see Chapter 4: ‘Adherence to Treatment’.) DOT ensures adherence. The Tuberculosis Working Group of the Ministry of Health strongly supports the use of DOT and urges all medical officers of health to work with local medical practitioners to ensure that DOT is offered to all patients who need it.
5.1 Using DOT

5.1.1 Definition

DOT refers to a procedure whereby a supervisor trained in the administration of DOT watches the patient swallowing the medication for all doses over the course of treatment. This ensures that a TB patient takes the correct drugs, the correct dose, at the correct times. DOT may happen on an inpatient or outpatient basis. The DOT supervisor may be a health worker or a trained and supervised community member. There is some evidence that DOT by guardians can be just as effective as health-centre-based DOT. However, there must be a clearly defined line of accountability between the TB control staff and the person administering DOT.

It is not considered to be DOT if an untrained family or community member administers the treatment to the patient. It is very important that anyone providing DOT is well trained. If a non-health worker (eg, a guardian) is asked to take responsibility for giving DOT, they must be given training so that they understand TB, the medications, the DOT process, the documentation and the limits of their responsibilities. It is crucial that the prescribing clinician and the supervising public health nurse have absolute confidence in the ability of the DOT giver to carry out the role dependably.

DOT may be prescribed and taken daily or intermittently. Regimens of proven efficacy are available for twice- or thrice-weekly administration. These are detailed in Chapter 16: ‘Treatment of Tuberculosis’.

For the purposes of the Case Report Form, DOT is defined as ‘Receiving DOT throughout the course of treatment’ (see Chapter 1: ‘The Epidemiology and Surveillance of Tuberculosis in New Zealand’). Therefore people who receive DOT for only part of their course of treatment should not be classified on the case report form as having received DOT.

DOT has been successfully administered by videophone.

5.1.2 Current use of DOT in New Zealand

The proportion of patients managed by DOT in New Zealand is described in Chapter 1: ‘Epidemiology and Surveillance’. Completeness of data on DOT in national TB surveillance is, however, unacceptably low, so the proportion of cases who receive DOT is unknown. There is wide inter-district variation in the proportions of cases treated by DOT, but overall the proportion seems low (about 24% of new TB cases in 1999–2001).
5.2 Effectiveness of DOT

The DOT strategy is actively promoted by the World Health Organization (WHO) for TB patients in an effort to control the global emergency of TB. The World Bank considers DOT to be one of the ‘most cost-effective of all health interventions’. DOT is more cost-effective than self-administered treatment.6

Favourable reports of the use of DOT in the US have been published in Texas,8 Baltimore,9 San Francisco,10 New York City,11,12 and Haiti.13 DOT is also being successfully implemented in many other countries.14

DOT produces superior treatment completion rates to those achieved by non-supervised interventions. Median treatment completion rates with DOT range from 78.6% to 91.0% (depending on the degree to which incentives and enablers are used), compared to 61.4% for non-supervised therapy.15 DOT also leads to improved relapse and drug-resistance rates.8,16,17

However, randomised trial evidence for the effectiveness of DOT is limited.18,19,20 and DOT may not always lead to better treatment outcomes than self-administered treatment.21,22,23 There is not enough evidence to compare fully intermittent, rifampicin-containing short-course chemotherapy and similar daily therapy in patients with pulmonary TB, and larger randomised studies are required.24 Moreover, the published literature does not clearly distinguish the impact of DOT itself from co-interventions such as incentives, enablers, patient-centred programmes and many other programmatic factors that may have contributed to the improved outcomes in published accounts of DOT programmes.25

Programme acceptability and confidentiality are important.26 An unpopular programme might deter patients from seeking care, resulting in reduced programme effectiveness.27 High levels of patient satisfaction with DOT programmes can be achieved.28
5.3 Selective versus universal DOT

The merits of selective versus universal DOT (DOT for all TB patients) are debated. WHO espouses DOT for all smear-positive cases. Universal DOT may be unnecessary for communities with low relapse rates and proven high treatment completion rates.\textsuperscript{29,30,31}

Universal DOT is not necessary in New Zealand as long as we have high rates of treatment completion and low rates of drug resistance and relapse. Of these three measures, we have quality data only on drug resistance. Drug-resistance rates are low in New Zealand (see Chapter 1: ‘Epidemiology and Surveillance’). Treatment completion rates have not been published but are thought to be high.

The percentage of New Zealand-treated cases that relapse has not been determined by a published longitudinal follow-up study. However, since TB incidence in New Zealand has changed little in the past 20 years, a reasonably accurate estimate of the relapse rate may be obtained by determining the percentage of each year’s cases that are relapses. Such data are available for the last few years in New Zealand.

The proportion of Auckland notifications that are relapses and were originally New Zealand-treated seems to be small. Of 36 relapses/reactivations notified in Auckland from September 1995 to July 1997, only eight had been treated in New Zealand. This constitutes 2.2\% (8/358) of all cases notified. Four of these had clear indicators of non-adherence in their documentation and would now be put on DOT at their first diagnosis.

Thus, of the relapses currently occurring in Auckland, at most 1.1\% (4/358), or two cases per year, would not have been prevented by our current (selective) DOT policy. This suggests that universal DOT would not be cost-beneficial, since to increase our DOT numbers from (currently) 32\% to 100\% would cost $486,880 (122 more DOT cases x $4000 per DOT). This means that each of the two cases per year prevented by universal DOT would have to cost $243,440 for universal DOT to be cost-beneficial in Auckland.

Of 97 relapses/reactivations notified in New Zealand between January 1995 and May 1998, only 29 were documented to have been previously treated in New Zealand. This constitutes 2.5\% (29/1164) of all cases notified during that period. (However, 33 other cases had no information collected about where they had received their previous treatment and some of these may also have been treated in New Zealand).

We cannot be too complacent over our apparently low relapse rates, however. We have only been collecting analysable data on relapses in recent years, and relapses due to poor adherence may not occur for years after the primary treatment. In addition, the Auckland relapse rate may be low because in the past most cases in New Zealand were treated as inpatients for much longer than is the fashion nowadays. This meant they received DOT for a substantial part of their treatment, and had prolonged exposure to education about TB and its treatment. Therefore, ironically and despite the recent interest in DOT, we may in effect be managing fewer patients with DOT than we did in past decades.
5.4  **Indications for DOT**

As emphasised in Chapter 4: ‘Adherence to Treatment’, a decision to administer DOT should follow a careful assessment of the patient by hospital and public health staff.

People with TB who should always be on DOT include all:

- cases on intermittent regimens (twice- or thrice-weekly doses)
- cases resistant to rifampicin
- multi-drug-resistant cases (resistant to isoniazid and rifampicin)
- relapses/reactivations
- cases that clearly demonstrate an inability or unwillingness to self-medicate
- cases that have been placed under closer supervision (see Chapter 4) and who then fail to improve their commitment to treatment.

People with TB should be considered for DOT when there is:

- extensive disease and/or a high degree of infectiousness
- weak or absent social support
- a complex treatment regimen
- serious multiple drug-resistance, or where side-effects necessitate the use of two or more second-line drugs.
5.5 Using DOT for treatment of latent tuberculosis infection (LTBI)

Treatment for LTBI requires a long course of treatment for a well person. Adherence may therefore be even more difficult to attain than in cases on full treatment for active TB disease. DOT has been shown to be cost effective for treatment for LTBI in drug users at high risk of TB.32

It may be inappropriate to use DOT for everyone on treatment for LTBI. However, DOT should always be used for intermittent regimens (twice- or thrice-weekly doses). DOT should also be considered if the client has risk factors for non-adherence and meets one or more of the following criteria:

- can be given DOT at the same time as a case who is on full treatment by DOT in the same household or neighbourhood
- has recently converted their Mantoux test following exposure to an infectious case
- is under five years of age
- has risk factors for progression from infection to disease (see Table 3.3, Chapter 3)
- is a contact of a multi-drug-resistant case.

Non-adherent cases on full treatment should have priority for DOT resources ahead of people requiring DOT treatment for LTBI.
5.6  Practical issues during a DOT regimen

5.6.1  Temporary inability to give DOT: is self-medication acceptable?

Self-administration of twice- or thrice-weekly treatment is not acceptable. Only a medical officer of health or a clinical TB specialist may override this instruction. If a case is going on holiday overseas and cannot be given DOT, he or she must change to daily treatment. If he/she is holidaying in New Zealand, every attempt should be made to continue DOT through another public health office, or daily treatment should be prescribed.

The reason for this rigid instruction is that any missed doses from a DOT regimen constitute a much larger proportion of the regimen than if the same number had been missed from a daily treatment regimen. There is thus a greater potential for missed DOT doses to compromise cure.

5.6.2  Missed DOT doses

The medical officer of health should be advised if the patient misses:

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

The above standards are not based on evidence from the literature. There are no published data (for daily or intermittent regimens) on how much treatment a person can miss and still be cured.

The medical officer of health should meet the patient and discuss any obstacles to adherence. Ultimately, detention under section 16 of the Tuberculosis Act 1948 may be needed. Alternative measures before this stage is reached are discussed in Chapter 4: ‘Adherence to Treatment’.

If the patient has missed any doses of DOT, these must be added on at the end of treatment. This does not apply to doses that were delayed for a day or two because the patient missed a DOT appointment but the dose was finally given late.

5.6.3  Discontinuing DOT and transferring to self-administered treatment

Occasionally a patient’s understanding and commitment to treatment improves to such an extent that DOT is no longer considered necessary. This should be a decision involving the patient, the public health nurse and the clinical staff. If a switch is made to self-administered treatment it must be prescribed as daily treatment.

5.6.4  Community DOT workers

Lay DOT workers (personnel without formal health care training) are referred to as ‘community DOT workers’. Extensive experience overseas has shown that community DOT workers with appropriate training and supervision can provide DOT reliably.
Using community DOT workers may:

- help contain the costs of providing DOT
- facilitate communication and rapport with patients in some instances
- facilitate provision of DOT by workers who may be more culturally or linguistically suitable for TB clients
- increase personal skills in affected communities
- help to develop a suitable workforce for similar projects
- provide a greater choice for clients over the settings in which DOT is provided.

See Appendix 5.1 for information on establishing a community DOT worker programme.

5.6.5 Health professionals outside the public health workforce as DOT workers

It may be appropriate to recruit and train health professionals from outside the public health workforce to administer DOT to some clients. Examples include:

- practice nurse
- pharmacist
- district nurse
- occupational health nurse
- school nurse
- dental nurse
- Plunket nurse
- hospital staff.

5.6.6 Incentives and enablers

Measures other than DOT that have been shown to promote adherence include reminder cards, help by health workers, financial incentives, health education, and intensive supervision of staff in TB clinics. These interventions may be more appropriate in the first instance for a patient with questionable adherence.

Overseas experience has shown that using incentives and enablers (things that help the client to overcome barriers) will increase adherence with DOT. In a US randomised study of drug users with LTBI, incentives achieved higher adherence rates than outreach workers.

Examples of incentives include:

- money
- books
- birthday party
- vouchers
- English lessons
star chart
celebration at the midpoint and end of treatment.

Examples of enablers include:
transport to the clinic or DOT appointments
taxi chits
thinking creatively about convenient sites for DOT
reducing the stigma of the disease
addressing psychological and cultural barriers
helping the client address other problems (eg, alcohol abuse).
5.7 Future developments

It is recommended that:

1. complete DOT information be recorded in EpiSurv by public health offices
2. ESR should establish longitudinal reporting on the proportion of cases that relapse over time.
Appendix 5.1: Establishing a community DOT worker programme

Material in this appendix is provided courtesy of Otara Health Inc and Auckland Public Health.

Attributes needed by a DOT worker

Suitable people may include ethnic community health workers, or a church minister, teacher or employer. DOT workers should:

- have patience, tact, maturity, good judgement and honesty
- be flexible regarding times and settings to suit the client
- have the ability to communicate information, and the skill to listen and answer relevant questions
- understand the client’s and family’s right to confidentiality and privacy
- recognise the limitation of their role and knowledge, and know when to ask for help
- be tidily presented
- be able to manage a workload and accurately record the work done
- not have a criminal record
- be safe with children and young people
- give authority to obtain police clearance
- be fluent in speaking languages commonly spoken by TB clients (this is desirable but not essential)
- be able to accept the client’s beliefs and values and not try to change or influence them (eg, religion)
- be able to attend training programmes and review meetings
- be physically fit, reliable and punctual
- have their own car and current driving licence
- know the community and be able to access clients or other key people
- have time to be present for the entire time needed for the client to swallow the medication
- feel comfortable working with people who have an infectious disease.

Job description for a DOT worker

The community DOT worker should:

- carry the correct medication for the client
- administer the correct dose
- observe the medication being taken
- sign the drug sheet (held with the drugs)
安排下一次DOT的日期

- 联系公共卫生护士（PHN）进行每周进度报告以及必要时的其他时间（例如讨论副作用、倡导、问题和查询）
- 让PHN知道他们在不能提供DOT剂量时（提前足够时间安排替代安排）
- 妥善和准时地完成日志和时间表
- 在提供任何激励或奖励给客户之前，与PHN协商
- 准时到达DOT与客户的预约
- 跟踪未按时出现的客户
- 及时识别和记录所有不良事件，并向监督PHN报告

管理

管理将根据每个组织有所不同，但考虑以下事项：
- 职位描述
- 人员规格
- 合同
- 薪酬
- 清晰的责任线
- 绩效评估
- 行政支持
- 时表
- DOT访问日志和里程报销记录
- 保密协议。

培训

在为社区DOT工作者开发培训课程时，应考虑以下事项。

1. 背景培训，包括结核病感染、疾病和治疗。
2. 视频，如《结核病：被遗忘的瘟疫》和《你可以战胜结核病》。
3. DOT的实施。这包括：
   - 案例的分配
   - 为DOT工作者选择合适的客户
   - 确保每位案件的监督PHN
   - 案例负载
   - 协商书面合同
   - 文件
   - 当报告不遵守时，何时向PHN报告不遵守情况
when to arrange a three-way interview with the PHN
when and how to transfer a client back to the PHN
side-effects to watch out for
occupational health risks such as TB, violent clients.

4 Building relationships with the DOT client. This includes:
- accepting their norms and environment
- getting to know people and their habits
- being patient
- meeting the client with the PHN before starting DOT
- meeting the client’s family/whānau (or other people involved with the client)
- remembering you are a visitor to the family/whānau
- recognising that the client may have different time constraints
- use of motivation and incentives
- privacy.

5 Role play.

6 Getting practical field experience with PHNs before working alone.

7 The legality of the administration of medicines. DOT workers do not prescribe or dispense medicines. They administer them in the same way as any family member might do for a child. There is no legal obstacle to this. Blister packs may facilitate the work.

8 Having the community worker undergo a two-step baseline Mantoux test before starting work.

A manual for training community DOT workers has been developed by the Auckland District Health Board’s public health service. Copies are available at a cost (contact Public Health, Community Services, Auckland District Health Board, Private Bag 92-605, Symonds Street, Auckland, ph 09 262 1855).

Criteria for clients suitable for management by a community DOT worker

These are as follows:
- the DOT worker can communicate well with the client
- the client is stabilised on treatment, has had a period on DOT and has displayed no side-effects (for at least a month)
- the client accepts the need for TB treatment.
The role of the public health nurse

The PHN is fully accountable for client care, and remains the case manager who:

- has the primary key worker role and is accountable for resource utilisation and outcome
- assesses needs and plans interventions
- co-ordinates (eg, medical officer) as necessary and requests assistance from PHN colleagues to provide input
- monitors progress and achievement of goals
- modifies plans
- evaluates outcomes.

The PHN introduces the DOT worker to the client personally and discusses with the DOT worker the client’s history, characteristics, contract, access to the client, drugs and record-keeping. The hand-over phase needs to continue until the client, PHN and DOT worker are comfortable.

The PHN must receive and acknowledge weekly reports from the DOT worker (even if there is nothing unusual to report). The PHN continues to communicate relevant issues to the clinician responsible for the patient.

The PHN:

- can make a decision to resume responsibility for a DOT client if concerned about continuity, broken contracts, dynamics, etc
- must let the community DOT worker know of the alternative PHN who will act as case supervisor if he/she is away for any reason
- must advise his/her supervisor if the DOT worker fails to carry out any contracted duties
- conducts a monthly check for each DOT client to ensure that visits take place as claimed by the DOT worker (frequent checks may be necessary if the patient is on a complex or difficult regimen, or when the DOT worker is inexperienced).

PHNs may need training if they have no experience in the supervision and monitoring of work delegated to non-health professionals. They must be aware that a non-health professional may not detect or report details of clinical significance, including drug side-effects. This adds another dimension to case management. "The Health Service Assistant and the Registered Nurse" is a useful paper that addresses these issues.
References


Chapter 6: Contact Investigation

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Summary

The aim of medical assessment of contacts is to minimise morbidity and transmission of TB. The objectives are to:
- identify infected contacts who require treatment of TB disease or latent TB infection
- identify the source case if possible
- identify uninfected contacts who may benefit from vaccination
- identify environmental factors that may be contributing to the transmission of TB
- educate contacts about TB.

The period of infectiousness

Calculate the period of infectiousness for the index case.
- This begins with the onset of symptoms (if known) or, if not known, the three months prior to diagnosis.
- The period of infectiousness ends:
  - when three consecutive negative sputum smears have been obtained (for sputum smear-positive cases)
  - when the source case has received two weeks of appropriate chemotherapy (for sputum smear-negative, culture-positive cases).

Prioritising contacts

Classify contacts into higher- and lower-risk groups. This needs to take into account the risk of infection and the risk of progression to disease if infected. (These risks are listed in Tables 3.2 and 3.3 in Chapter 3: ‘Latent Tuberculosis Infection’). Close or high-risk contacts may not all be in the case’s household. Contacts in work and leisure settings outside the household may be intensely exposed.
- Closeness of contact is not the only factor affecting risk. Assessment of susceptibility to disease is also essential. Casual contacts who are immuno-compromised, for example, may be a higher priority for assessment than well adults with closer contact.
- Screen the highest-risk contacts first and assess the infection rate before screening lower-risk contacts.

Evaluating contacts

Contacts are investigated by:
- inquiring into symptoms of TB
- assessing their risk profile and BCG vaccination status
- Mantoux testing
- CXR examination (if appropriate).

The results of the investigation will 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 focus of TB education necessary.
An overview is shown in Figure 6.2.

If the contact is identified more than eight weeks after their last exposure to the case, then only one Mantoux test is necessary. If the contact is identified less than eight weeks after their last exposure to the case, then it may be possible to demonstrate Mantoux conversion. Two Mantoux tests are necessary: one as soon as the contact is identified and, if that is negative, a second eight weeks after the last exposure to the case during the period of infectiousness.

Children

- Children under five years of age who are close contacts of pulmonary cases should be referred to a specialist regardless of their tuberculin reaction. If Mantoux-positive, they should receive treatment for presumed latent TB infection.

Chest X-rays

- Contacts do not routinely require a CXR unless treatment is going to be prescribed. Exceptions include contacts who:
  - have symptoms of TB
  - have a positive Mantoux or a Mantoux conversion
  - are children under five years who are contacts of pulmonary cases (such children should have a CXR before starting treatment, irrespective of their Mantoux reaction)
  - may have a false negative Mantoux reaction, especially those on systemic corticosteroids (see Chapter 2: ‘Mantoux Testing’ for causes of false negative Mantoux reactions)
  - are 60 years or older because responsiveness to the tuberculin test declines with age (see Chapter 2).
- Treatment and serial CXR follow-up are discussed in Chapter 3: ‘Latent Tuberculosis Infection’.

BCG vaccination

- BCG should be offered to Mantoux-negative contacts (<5 mm) under the age of five years.
- When two Mantoux tests will be needed to test for conversion, BCG should not be given until after the second test.

HIV infection

- If there is the least chance that a contact may have risk factors for HIV, inquire further and consider HIV testing with pre- and post-test counselling.
- If transmission to an HIV-infected contact may have occurred, rapid medical assessment and treatment of LTBI are essential because rapid progression from infection to disease can occur.

Record keeping

- Data about each contact should be collected as shown in Figure 6.3. A summary such as that in Figure 6.4 (or preferably a computerised equivalent) should be compiled.
Education

Contacts should be provided with education about:
- the contact investigation procedures and the role of public health in supervising community treatment
- the symptoms of TB disease
- transmission of TB
- the difference between TB disease and latent TB infection
- the treatment and treatability of TB infection and disease
- the importance of early medical assessment of TB symptoms.

Re-exposure to TB

Re-exposure to infectious TB necessitates re-evaluation of contacts. If there is treatment failure or relapse of the source case, resulting in infectivity, the contact investigation must be repeated.

If the source case is still smear-positive when discharged on treatment into the community

All contacts newly exposed to a smear-positive case after the case's discharge from hospital should be identified and receive two Mantoux tests eight weeks apart.

Reviewing contact investigation programmes

Medical officers of health should collect, and periodically analyse, contact investigation data to evaluate local screening activities.

Contact investigations involving hospitals and other health care facilities

If a case of pulmonary TB disease has been in a hospital or other health care facility prior to the initiation of anti-TB treatment, early liaison should be established between the public health service and the infection control and occupational health services in the hospital. This will help to prevent confusion of roles and responsibilities.

The medical officer of health must maintain an overview of the investigation.

The public health office should receive documentation on the outcome of contact investigations (eg, the summary of contact tracing, Figure 6.4) carried out in hospitals, and enter it onto EpiSurv.
Communication

1. Every effort should be made by the district to which cases are notified to ensure that:
   - contacts are followed up if they move to another district
   - complete assessment information is obtained on the outcome of screening by that other district.

1. Contact investigation and medical evaluation should not be undertaken by GPs. GPs who are consulted by contacts should refer them to the local public health service.

1. Medical officers of health should ensure that physicians in their districts are aware of local TB control policy and procedures to ensure:
   - full and timely notification of case details
   - full and timely information provided on follow-up visits of cases
   - co-ordinated follow-up of cases and contacts.

1. Medical officers of health should notify overseas health authorities about:
   - TB cases diagnosed in New Zealand who temporarily or permanently travel overseas
   - possible at-risk contacts, living overseas, of cases who have recently arrived in New Zealand
   - possible overseas source cases for TB diagnosed in New Zealand.
Introduction

This chapter provides guidance on structuring a contact investigation, the medical assessment of contacts exposed to TB, and the importance of communication and liaison.

The aim of medical assessment of contacts is to minimise morbidity and transmission of TB. The objectives are to:

- identify infected contacts who require treatment of TB disease or latent TB infection
- identify the source case, if possible
- identify uninfected contacts who may benefit from vaccination
- identify environmental factors that may be contributing to the transmission of TB
- educate contacts about TB.
6.1 The contact investigation

6.1.1 Structuring a contact investigation programme

Establishing priorities
The estimated probability of transmission, based on information obtained by following the steps described below (see 6.2.2), should influence the priority, rapidity and thoroughness with which a contact investigation is conducted. By using this systematic approach, appropriate and productive public health programmes can be implemented.1

Classification of contacts
The most important consideration in a contact investigation is the probability of infection among contacts, so the first step is to allocate contacts into higher- and lower-risk contacts. For each index case, the contact investigation should proceed in an orderly manner, starting with people who are most likely to have been infected.

Members of the immediate household and others who have shared accommodation with the index case are usually the top priority. However, contacts in work, leisure or other settings are not always ‘casual’ contacts. This is depicted in Figure 6.1, which shows that contacts in any of these settings may have been significantly exposed and require evaluation.

Work sites should be visited: some may have such overcrowding and poor ventilation that it would be prudent to designate these contacts as ‘close’.2 Other settings such as church groups may also result in significant exposure.3 Contact tracing is often unnecessarily extensive in schools.4,5 However, one substantial outbreak in a New Zealand school necessitated screening of the whole school.6

Establishing limits for contact investigations
The principle of ‘concentric circles’ or the ‘stone-in-the-pond’ is an important one in limiting contact investigations (see Figure 6.1).7,8
By initially evaluating the higher-risk contacts for evidence of TB infection and/or disease, the actual infectiousness of the index case can be inferred. The following are guidelines for limiting the extent of a contact investigation.

1. Initiate investigation with higher-risk contacts. If there is no evidence of recent transmission of infection in this group, extending the investigation is not appropriate.

2. If data indicate recent infection in the higher-risk group, extend the limits of investigation to progressively lower-risk contacts until the levels of infection detected approximate the levels of infection in the local community.

3. Periodically throughout the investigation the findings should be reviewed by the public health nurse and medical officer responsible for the case. An informed decision can then be made about the need for curtailing or extending the investigation.

### 6.1.2 Determining the period of infectiousness

How far back in the history of the index case should public health staff go in seeking contacts to be considered for screening? In a series of 100 TB cases in Auckland, half of the cases with cough developed it within 10 weeks of diagnosis. It is probable that many of those with cough of longer duration were not highly infectious early in their clinical course. 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 not known or if there is no history of cough. The period of inquiry about contact exposure may also need to be extended if the source case is highly infectious (see 6.2.2 ‘Source case characteristics’).
The period of infectiousness ends:
- when three consecutive negative sputum smears have been obtained (for sputum smear-positive cases)
- when the source case has received two weeks of appropriate chemotherapy (for sputum smear-negative, culture-positive cases).

Note: this is only a general guide – see Chapter 9: ‘Infection Control’ for more detail.

6.1.3 Identifying contacts to be assessed

As soon as the diagnosis is reasonably established on a laboratory and/or clinical basis, the case should be notified and investigation of contacts should begin. Health care personnel should not wait for positive cultures if history, sputum smears or chest radiographs suggest TB.

It is important to minimise delay in diagnosis of LTBI and TB disease (see Chapter 13: ‘Awareness, Clinical Features and Early Diagnosis of Tuberculosis’). Screening of contacts by the public health service should begin as soon as possible after notification. Medical assessment of contacts should begin within the timeframes suggested below:
- contacts of a smear-positive pulmonary case: three working days
- child contacts (under five years of age) of any pulmonary case: three working days
- contacts of a smear-negative pulmonary case: seven working days
- all other cases: seven working days.

As soon as the notification is received, household contacts should be informed by a public health nurse that a contact investigation will be taking place soon and that there is no immediate threat to their health. They should be given an estimated date for the public health nurse’s first visit. This allays anxiety and forestalls the contacts seeking medical advice from sundry providers who are not responsible for public health follow-up.

At the initial interview the importance of identifying infected contacts should be explained. The index case should be asked for a list of all close and casual contacts during the period of infectiousness (see 6.1.2). 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.

Figure 6.1 makes it clear that contacts in any of the three domains of social interaction (leisure, work and household) may be at high risk of infection. This point is highlighted by many published contact investigations. For example, restriction fragment length polymorphism (RFLP) typing has shown that conventional contact tracing, which employed the simple ‘close/casual’ classification of contacts, failed to uncover the true extent of transmission in gay bars during an outbreak in the US.12 A multi-state outbreak in the US, investigated by RFLP, demonstrated that transmission can occur by social activities in nightclubs, social ‘houses’, attending balls or pageants, marijuana use, and prostitution.13 Inquiry into social networks is therefore important in contact tracing.
6.2 Assessing risks

6.2.1 Assessing risks of contacts

The risk factors for each contact should be assessed. Consider risk factors for infection and disease separately.\(^{14}\) (These are listed in Tables 3.2 and 3.3 in Chapter 3: ‘Latent Tuberculosis Infection’). 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.

6.2.2 Assessing the risk of infection

Each of the following factors should be evaluated.

**Source case characteristics.**

Any person who is generating aerosolised particles containing tubercle bacilli is a potential transmitter of infection. The greater the number of bacilli, the higher the risk. Important source case characteristics are:

- sputum status
- extent of pulmonary disease
- cough frequency.

Experiments with guinea pigs exposed to human TB cases have demonstrated that some patients are much more efficient disseminators than others,\(^{15}\) and that a case of TB laryngitis was more infectious than the average child with measles.\(^{16}\)

Although smear-positive cases are far more infectious than smear-negative cases, the infectivity of smear-negative, culture-positive cases is not negligible. If high-risk (eg, immunosuppressed) contacts are exposed to smear-negative, culture-positive cases for prolonged periods they may be at considerable risk of infection.\(^{17-22}\)

Contacts of HIV-positive pulmonary cases are at lower risk of infection than contacts of HIV-negative cases.\(^{23}\) (See also Chapter 18: ‘Tuberculosis and HIV’).

There is further information on the risk of infection in Table 3.2, Chapter 3: ‘Latent Tuberculosis Infection’.

**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 or short exposures may lead to transmission if the case is sufficiently infectious and the environmental air conditions favourable.\(^ {24,25}\)
**Environmental air factors**

Air is the vehicle by which the infectious particle or droplet nucleus is transported from the source case to susceptible people. The greater the concentration of these droplet nuclei in air shared by the index case and his or her associates, the greater the risk to these contacts. The important factor here is the degree of ventilation or filtration in the environment in which contact occurred. Air filtered by high-efficiency particulate attenuation (HEPA) filters, as in modern buildings and large commercial aircraft, greatly reduces the risk of infection (see Chapter 9: ‘Infection Control’). On the other hand, widespread circulation of unfiltered air can mean that contacts who are in an enclosed environment but not seated particularly close to the source case may still be at high risk. This has been demonstrated in an outbreak in a submarine.26

**Strain hardiness and virulence**

The viability, transmissibility and virulence (pathogenicity) of tubercle bacilli is affected by a range of factors. 25 Presently in New Zealand the only information of practical use to contact tracers concerning the virulence of an organism is what they can glean from reviewing the proportion of contacts infected in each investigation. In the future it is hoped that rapid RFLP typing and analysis of molecular epidemiology will alert public health workers to infectious and virulent strains. (See Chapter 12: ‘Mycobacteriology: Laboratory Methods and Standards’.)

6.2.3 **Assessing the risk of progression to TB disease if infected**

Immunosuppression and certain concurrent medical conditions increase the risk of progression to disease. These are listed in Table 3.3, Chapter 3: ‘Latent Tuberculosis Infection’.
6.3 Medical assessment and management of contacts

6.3.1 Overview of medical assessment

Contacts are investigated by:

- inquiring into symptoms of TB (see section 13.3, in Chapter 13: ‘Awareness, Clinical Features and Early Diagnosis of Tuberculosis’)
- assessing the risk profile and BCG vaccination status
- Mantoux testing
- CXR examination if appropriate.

The results of the investigation will determine:

- whether the contact is likely to have been infected (see Chapter 2: ‘Mantoux Testing’)
- if the contact is infected, whether investigation for possible active or inactive TB is needed (see Chapter 13) or treatment for latent TB infection is appropriate (see Chapter 3)
- the focus of TB education necessary.

An overview is shown in Figure 6.2.

**Figure 6.2: Contact investigation flow chart**

<table>
<thead>
<tr>
<th>Mantoux-positive (see Chapter 2)</th>
<th>Mantoux-negative (see Chapter 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-ray</td>
<td>Index case smear- or culture-positive and it is less than eight weeks since exposure</td>
</tr>
<tr>
<td>Abnormal</td>
<td>Yes</td>
</tr>
<tr>
<td>Discuss with experienced TB clinician</td>
<td>Repeat Mantoux eight weeks after last exposure</td>
</tr>
<tr>
<td>Consider treatment for LTBI (Chapter 3)</td>
<td>Conversion or positive Mantoux?</td>
</tr>
<tr>
<td>Investigate for active TB disease</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Chest X-ray</td>
</tr>
<tr>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Discharge* **</td>
<td>No</td>
</tr>
<tr>
<td>BCG**</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Consider CXR as a precaution if contact is over 60 years or if there is a possibility that the Mantoux may be falsely negative (Chapter 2).

** If aged under five years and no previous BCG.
6.3.2 Mantoux testing

For a full description of the Mantoux test, refer to Chapter 2.

If the contact is identified more than eight weeks after their last exposure to the case, then only one Mantoux test is necessary.

If the contact is identified less than eight weeks after their last exposure to the case, then it may be possible to demonstrate Mantoux conversion. Two Mantoux tests are necessary: one as soon as the contact is identified and, if that is negative, a second eight weeks after the last exposure to the case during the period of infectiousness.

If a contact develops symptoms of possible TB disease during this interval, the second test should be administered without further delay and investigations for TB disease should commence.

If the contact has a pre-existing documented Mantoux result, an initial baseline test is not necessary (see Chapter 2).

6.3.3 Children under five years of age

In young children the risk of developing TB disease after infection is as high as 40%, especially in infancy, and disease can develop within weeks of infection. The Mantoux reaction takes up to eight weeks to convert after exposure.

Close contacts

Children under five years of age who are close contacts of pulmonary cases should be referred to a specialist regardless of their tuberculin reaction, and managed as follows.

- If Mantoux-positive they should receive treatment for presumed LTBI.
- If Mantoux-negative (< 5 mm) and treatment is decided on (for possible LTBI), it should be given for eight weeks, when a second Mantoux test should be done. If the Mantoux converts (≥ 10 mm increase), continue treatment until complete. If the Mantoux remains negative, stop treatment and consider BCG vaccination. If the Mantoux becomes positive but does not convert (ie, < 10 mm increase), a decision about treatment is very difficult and will depend on individual circumstances.
- If during the eight weeks between the first and second Mantoux test pulmonary specimens from the presumed source case are found to be culture-negative, treatment may be discontinued immediately. The second Mantoux should still be performed, but it is extremely unlikely that the Mantoux will convert if the case is culture-negative. (Analysis of Auckland data from 1997 to 2000 shows that no child contacts of culture-negative cases converted).

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.
If a Mantoux-positive individual is found in a house containing an infant (up to one year old):

- the Mantoux-positive person should be considered for investigation and treatment; depending on their symptoms and CXR appearance, referral to a TB clinician may be appropriate
- inquiry should be made about TB symptoms in all adults in the household in case there is a source case who many infect the infant.

### 6.3.4 Initial CXRs

Contacts do not routinely require a CXR unless treatment is going to be prescribed. Exceptions include contacts who:

- have symptoms of TB
- have a positive Mantoux or a Mantoux conversion
- are children under five years who are contacts of pulmonary cases; such children should have a CXR before starting treatment irrespective of their Mantoux reaction
- may have a false negative Mantoux reaction, especially those on systemic corticosteroids (see Chapter 2: ‘Mantoux Testing’ for causes of false negative Mantoux reactions)
- are 60 years or older, because responsiveness to the tuberculin test declines with age (see Chapter 2).

### 6.3.5 Serial CXR follow-up

This is discussed in Chapter 3: ‘Latent Tuberculosis Infection’.

### 6.3.6 BCG vaccination and treatment of latent TB infection

BCG should be offered to Mantoux-negative contacts (< 5 mm) under the age of five years. When two Mantoux tests will be needed to test for conversion, BCG should not be given until after the second test (see Chapter 8: ‘BCG Vaccination’). For guidance on treatment for contacts who are considered to be infected or at high risk of developing disease, see Chapter 3: ‘Latent Tuberculosis Infection’.

### 6.3.7 HIV infection

HIV infection is important because it is a potent risk factor for progression from TB infection to disease, and because it may make the Mantoux test falsely negative.

If there is the least chance that a contact may have risk factors for HIV, inquire further and consider HIV testing with pre- and post-test counselling. Risk factors for HIV include a history of unsafe sexual practices (especially in countries with high incidence of HIV), past or present injecting drug use, and having received a blood transfusion outside New Zealand.

In HIV-infected contacts, consider $5$ mm as the cutting point for further action (such as treatment of LTBI) irrespective of BCG history. If transmission to an HIV-infected...
contact may have occurred, rapid medical assessment and treatment of LTBI are essential because rapid progression from infection to disease can occur. (Intervals as short as 20 days have been described). HIV-positive people with positive Mantoux tests are at higher risk of TB disease than those who are Mantoux-negative and anergic.\textsuperscript{30} False negative Mantoux tests are common in HIV-infected people, but anergy testing is not considered helpful.

Further information is available in Chapter 18: ‘Tuberculosis and HIV’.

6.3.8 Pregnant women
The Mantoux test is safe and should be done in pregnant contacts. If the Mantoux test is positive:
- enquire about TB symptoms; if there are no symptoms of TB disease, defer CXRs until after the pregnancy, or at least until after the first trimester
- do a full blood count and midstream urine examination
- discuss the patient with a TB specialist if there are concerns about the risk factor profile, the Mantoux test result (> 15 mm) or symptoms. The public health or clinical TB specialist needs to liaise with the pregnancy health care provider and decide if the TB risk profile warrants further clinical investigation, as outlined in Tables 3.2 and 3.3 of Chapter 3: ‘Latent Tuberculosis Infection’, and Chapter 13: ‘Awareness, Clinical Features and Early Identification of Tuberculosis’.

6.3.9 Midstream urine examination
A midstream urine examination (MSU) may detect sterile pyuria, which indicates possible renal TB. Renal TB occurs only in adults. Mantoux-positive contacts over 15 years of age should have an MSU in addition to a CXR. A finding of more than 20 white or red cells warrants a repeat MSU. If the abnormality persists on a second MSU, then other causes should be excluded (eg, check schistosoma serology in people who have resided in endemic areas), the case discussed with a clinical TB expert, and urine TB cultures performed. TB urine cultures are expensive and should not be performed on the basis of a single abnormal MSU.

6.3.10 Non-tuberculous mycobacteria
Patients with non-tuberculous mycobacteria, such as \textit{Mycobacterium avium-intracellulare}, are of negligible infectivity and do not represent a disease threat to healthy contacts. They do not warrant 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 that contact tracing can be restricted until the diagnosis is clearer.
### 6.4 Practical aspects of contact investigation

#### 6.4.1 Documentation

Data about each contact should be collected as shown in the suggested form in Figure 6.3. A contact investigation may involve 100 contacts or more and cannot always be readily reviewed by perusing individual contacts’ clinical records. A summary such as that suggested in Figure 6.4 (or preferably a computerised equivalent) should be compiled.

**Figure 6.3:** Contact record form

<table>
<thead>
<tr>
<th>Name</th>
<th>NH1 number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>DOB</td>
</tr>
<tr>
<td>General practitioner</td>
<td></td>
</tr>
<tr>
<td>Interpreter details</td>
<td></td>
</tr>
<tr>
<td>Previous BCG: Y/N</td>
<td>Symptoms of TB: Y/N</td>
</tr>
</tbody>
</table>

**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**

<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt;5 years or documented Mantoux conversion:</td>
<td>Y/N</td>
</tr>
<tr>
<td>Immunosuppressed by disease or treatment:</td>
<td>Y/N</td>
</tr>
<tr>
<td>Undernourished:</td>
<td>Y/N</td>
</tr>
</tbody>
</table>

*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? \[ \text{mm (Guidelines Chapter 2)} \]

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

<table>
<thead>
<tr>
<th>1st Mantoux</th>
<th>2nd Mantoux</th>
</tr>
</thead>
<tbody>
<tr>
<td>mm</td>
<td>mm</td>
</tr>
<tr>
<td>R</td>
<td>LTF</td>
</tr>
<tr>
<td>R</td>
<td>LTF</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CXR 1 result</th>
<th>CXR 2 result</th>
<th>CXR 3 result</th>
<th>CXR 4 result</th>
<th>Assessment</th>
<th>Actions</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>TB</td>
<td>R</td>
<td>LTF</td>
<td>NR</td>
<td>N</td>
</tr>
</tbody>
</table>
**Figure 6.4:** Summary of contact information

<table>
<thead>
<tr>
<th>Health district of index case:</th>
<th>Name of contact tracer:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of index case:</td>
<td>EpiSurv number of index case:</td>
</tr>
<tr>
<td>Surname</td>
<td>Given name</td>
</tr>
</tbody>
</table>

<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>LTBI</td>
<td>TB</td>
<td>X-ray</td>
</tr>
<tr>
<td>TBO</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Surname first)</td>
<td>N</td>
<td>Dis</td>
</tr>
<tr>
<td>LTBI</td>
<td>TB</td>
<td>X-ray</td>
</tr>
<tr>
<td>TBO</td>
<td>BCG</td>
<td></td>
</tr>
<tr>
<td>(Surname first)</td>
<td>N</td>
<td>Dis</td>
</tr>
<tr>
<td>LTBI</td>
<td>TB</td>
<td>X-ray</td>
</tr>
<tr>
<td>TBO</td>
<td>BCG</td>
<td></td>
</tr>
<tr>
<td>(Surname first)</td>
<td>N</td>
<td>Dis</td>
</tr>
<tr>
<td>LTBI</td>
<td>TB</td>
<td>X-ray</td>
</tr>
<tr>
<td>TBO</td>
<td>BCG</td>
<td></td>
</tr>
<tr>
<td>(Surname first)</td>
<td>N</td>
<td>Dis</td>
</tr>
<tr>
<td>LTBI</td>
<td>TB</td>
<td>X-ray</td>
</tr>
<tr>
<td>TBO</td>
<td>BCG</td>
<td></td>
</tr>
</tbody>
</table>

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

**Tuberculosis contact tracing: key to Figures 6.3 and 6.4**

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

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

Contacts should be provided with education about:

- the contact investigation procedures and the role of public health in supervising community treatment
- the symptoms of TB disease
- transmission of TB
- the difference between TB disease and LTBI
- the treatment and treatability of TB infection and disease
- the importance of early medical assessment of TB symptoms.

For further information, see Chapter 11: ‘Health Promotion and Health Education’, and Chapter 13: ‘Awareness, Clinical Features and Early Identification of Tuberculosis’.

At the conclusion of screening, contacts with abnormal findings should be given a summary of their results. The summary should 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.

6.4.3 Cross-cultural communication

Public health workers conducting contact investigations need to be trained and ready to address cross-cultural issues in their interactions with clients. These issues are discussed in Chapter 4: ‘Adherence to Treatment’ and Chapter 11: ‘Health Promotion and Education’.

6.4.4 Public health follow-up of non-infectious TB

In public health decision-making about these cases, it is important to consider two questions:

- Is it necessary to do a search for the person who may be the source of this TB case’s infection?
- Is this TB case infectious, and do the contacts of this case need to be screened to determine whether they too have become infected as a result of their exposure to this case?

Accordingly, this is the public health follow-up we advise in the following scenarios.

**Case 1: Adult TB case, normal CXR, non-respiratory TB (such as bone or kidneys)**

A source case is unlikely to be located because the infection leading to the TB disease is probably many years old. Confine the search for a source case to asking whether any of the current close contacts of the case have symptoms of TB, such as fever, sweats, chronic cough, weight loss, and so on. Anybody answering ‘yes’ to these questions should be offered a Mantoux test and CXR. Otherwise, Mantoux testing and CXRs for the case’s social circle are not necessary.
Contact tracing is not necessary because the case is not infectious. Contacts do not require Mantoux testing or CXR.

**Case 2: Paediatric TB case, with or without pulmonary disease (eg, lymph node disease)**

Search for a *source case* is essential since the child is likely to have been infected recently by an adult. All those in the immediate social circle of this paediatric TB case should be given a Mantoux test and CXR. Focusing screening for the adult source case on adults with a history of TB or symptoms of TB increases efficiency.³¹

Contact tracing is seldom necessary since a paediatric case of TB, whether pulmonary or extra-pulmonary, is rarely considered to be infectious. Children under 12 years of age with pulmonary disease seldom infect others because:

- the natural history of primary TB means that children rarely form cavities
- children are usually diagnosed relatively early (after their adult source case is identified)
- younger children do not generate a sufficiently powerful cough to disseminate many acid-fast bacilli.

However, it is wrong to say that a child can never transmit disease.³² The paediatrician should always assess the infectious potential of children with pulmonary parenchymal disease and discuss with the public health service. (See also section 17.5: ‘Tuberculosis in children’, in Chapter 17.)

**Case 3: Person placed on preventive treatment of inactive TB with up to four drugs**

This case may have had active pulmonary disease in the past but does not currently. They are being treated preventively because the prescribing clinician is concerned about a possibility of relapse.

Neither searching for a source case nor doing a contact investigation is necessary because it is likely the case has been non-infectious for a long time. As a precaution, ask whether any of the current close contacts of the case have symptoms of TB, such as fever, sweats, chronic cough, weight loss, and so on. Anybody answering ‘yes’ to these questions should be offered a Mantoux test and CXR. Otherwise Mantoux testing and CXRs for the case’s social circle are not necessary.

Contact tracing is not necessary since it is likely that the case has been non-infectious for a long time.
6.4.5 Repeat contact tracing for re-exposed contacts

Although some people are relatively immune to re-infection, the science in this area is complex and evolving. It is possible to develop disease a second time following re-infection with TB,\textsuperscript{33,35} though it is impossible to predict individual risk.\textsuperscript{36}

Therefore re-exposure to infectious TB necessitates re-evaluation of contacts. This may happen if a case relapses during or after treatment, or because a contact is exposed to a new source case. In this situation all exposed contacts should be screened (even if they have been screened for an earlier exposure). This includes re-exposed contacts who have had TB disease or LTBI in the past. Although the Mantoux test will not be helpful and is contraindicated, they should have a CXR because they may have been reinfected, or they may have reactivated and become an unrecognised source case. (For risk factors for reactivation, see Table 13.8 in Chapter 13: ‘Awareness, Clinical Features and Early Diagnosis of Tuberculosis’).

6.4.6 DNA fingerprinting

This topic is discussed in detail in Chapter 12: ‘Mycobacteriology: Laboratory Methods and Standards’. Only a few points will be made here.

RFLP permits epidemiological links between culture-positive cases to be confirmed or refuted with a high degree of certainty. This is useful in enhancing the capability of conventional epidemiology and in determining the presence of outbreaks.\textsuperscript{37,38–41} It is also valuable for reviewing patterns of transmission in a community,\textsuperscript{45} though there are caveats in its use for this purpose.\textsuperscript{46,47}

6.4.7 If the source case is still smear-positive when discharged into the community

There is still a degree of uncertainty surrounding the duration of infectivity of cases who remain smear-positive for weeks or months after initiation of appropriate treatment (see Chapter 9: ‘Infection Control’):

- all contacts newly exposed to a case who is still smear-positive after discharge from hospital should be identified and receive two Mantoux 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 the need for induced sputum testing.

6.4.8 Contact investigations involving hospitals and other health care facilities

If a case of pulmonary disease has been in a hospital or other health care facility prior to the initiation of anti-TB treatment, staff and inpatients may need assessment. Early liaison should be established between the public health service and the infection control and occupational health services in the hospital. This will help to prevent confusion of roles and responsibilities.
The approach outlined in this chapter should be applied to contacts exposed in hospitals. Those conducting Mantoux testing and other contact assessment procedures should be fully trained in the required skills. It is inappropriate for this role to be carried out by GPs, inexperienced resident medical officers or hospital consultants just because they happen to be approached by patients or staff of the health care facility. Appropriate services are public health, occupational health, and infection control nurses.

Exposed inpatients will often have been discharged by the time the contact investigation begins. Public health should follow these contacts up.

Because compliance with screening recommendations by health care workers is often inferior to that of non-health professionals, the support of management in the health care facility should be sought.

If a health care worker who has a documented Mantoux test result within the past 12 months is exposed to infectious TB, only one test is necessary to detect conversion. This should be done eight weeks after the date of last exposure. (See also ‘Testing for conversion in people with a documented Mantoux result’ in section 2.1.5, Chapter 2, for further discussion.)

The medical officer of health must maintain an overview of the investigation, both of patients and of staff. Data on the outcome of contact investigation in hospitals (eg, the Summary of contact tracing, Figure 6.4) should be routinely supplied to the medical officer of health in the district to which the index case was notified. The medical officer of health should 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.

### 6.4.9 Aircraft contact investigation

Transmission of TB on aircraft has been documented, but the risk is low. Only contacts seated within two rows of infectious cases on flights lasting longer than eight hours need be traced. More extensive contact tracing is probably not warranted (http://www.who.int/tb/publications/aircraft/contents.html).

Passenger information can be divulged to the medical officer of health under the Privacy Act, Rule 11. Passenger lists (often with very limited address information) can be obtained from the New Zealand Immigration Service. The aircraft seating diagram and passengers’ seat numbers can be obtained from the airline. Details of exposed passengers who are no longer in New Zealand can sometimes be referred to an overseas public health service for follow-up.
6.4.10 Reviewing local findings

Guidelines for contact screening – and audits of their structure, process and outcome – are important to ensure screening activities are optimal and to avoid unnecessary screening. The value of such review was shown in a recent survey of US public health programmes, which identified serious deficiencies in contact tracing. Medical officers of health should collect and periodically analyse contact investigation data to evaluate local screening activities.

6.4.11 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 to be an outbreak). Such clusters need to be identified early since the following outbreak control activities must be considered:

- workforce planning
- communications with the affected group
- inter-district communication
- role of ESR in co-ordinating outbreak investigations
- media management
- notification of the outbreak on EpiSurv.

6.4.12 Communication

Communication between districts

Every effort should be made by the district to which cases are notified to ensure that:

- contacts are followed up if they move to another district
- complete assessment information is obtained on the outcome of screening by that other district.

When requesting a public health service in another district to investigate contacts living in their district, provide a fully completed Tuberculosis Case Report Form on the index case (Appendix 1.2 in Chapter 1: ‘Epidemiology and Surveillance’). Forward culture and sensitivity results as soon as they are available.

When asked by another public health service to investigate contacts residing in your district, ensure adequate interim and final outcome information is supplied to the requesting district. Send the ‘Summary of Contact Information’ (Figure 6.4). Do not enter these cases or contacts onto EpiSurv in your district. They should be entered by the requesting district, which initiates, co-ordinates and finalises the contact investigation.
**General practitioners**

Contact investigation and medical evaluation is a specialised task and should be provided by public health. It should not be undertaken by GPs. GPs who are consulted by contacts should refer them to the local public health service.

Medical officers of health should:
- ensure that GPs in their districts are aware of the local TB policy and procedures
- provide information and support to ensure smooth and effective service delivery for patients.

Information provided to GPs should cover:
- the need to liaise with the public health service when contacts (such as relatives) visit GPs before the public health service receives official notification of an index case
- the need for (and the process of) referring contacts to the medical officer of health (and not to the clinician managing the treatment of the index case)
- the process the public health service follows for contact investigation
- the indications for BCG vaccination, and the availability of community BCG clinics.

The public health office should advise a GP if they are investigating any of that GP’s patients as a TB contact, and communicate any abnormal results, hospital referrals and problems to the GP. Alert the GP to the possibility of future TB in all Mantoux-positive contacts, particularly those not receiving treatment for LTBI, and the need for a repeat CXR if the person develops symptoms.

**Specialist physicians**

Management of TB should be confined to chest physicians, infectious disease physicians and paediatricians who are experienced with the disease. Private physicians treating TB have a responsibility to be familiar with local protocols and networks in their area to ensure effective care of patients and contacts and surveillance of TB. Overseas studies suggest that doctors in private practice commonly do not comply with national TB treatment and control guidelines.\(^{54-58}\)

Medical officers of health should ensure that physicians in their districts are aware of local TB control policy and procedures to ensure:
- full and timely notification of case details
- full and timely information provided on follow-up visits of cases
- co-ordinated follow-up of cases and contacts.
Notification to overseas health authorities

Medical officers of health should 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 for TB diagnosed in New Zealand.

The Ministry of Health should provide medical officers of health with regularly updated lists of phone, fax and email details of public health officials in other countries.

6.4.13 Media management

TB contact investigations, particularly outbreaks, are often of interest to the news media. Responsibility for media comment should be agreed between those involved and should usually be carried out by the medical officer of health.
6.5 Future directions

RFLP typing (DNA fingerprinting) of all TB organisms isolated from New Zealand cases, and its use in TB epidemiology, may enable:

- more focused contact investigations
- identification of the most highly infectious or pathogenic strains
- clarification of the epidemiology of transmission, in particular settings for transmission that may currently be undetected by conventional contact tracing techniques.

However DNA identification of organisms alone will not achieve the epidemiological objectives above if clear responsibility is not assigned for computer-assisted analysis of the data and appropriate action on the results.

There is no information on the quality of contact investigations for TB in New Zealand. Research or audit is needed. Standardised documentation should be adopted, as provided in Figures 6.3 and 6.4.

Responsibility should be assigned for co-ordinating investigation and reporting in multi-district outbreaks of TB.

The yield from doing an initial CXR on Mantoux-negative people aged over 60 years requires evaluation.
References


Chapter 7: Tuberculosis Control in People from Countries with a High Incidence of Tuberculosis

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Summary

The purpose of TB screening is to detect and treat imported TB disease early, minimise the severity of disease and reduce the risk of TB to others.

Epidemiology

- Sixty-nine percent of TB cases in New Zealand are foreign-born.
- Foreign-born people in New Zealand have a TB rate 10 times that of the New Zealand-born population.
- Almost all cases of TB in foreign-born people occur in the first five years after arrival (60% in the first year, 34% between one and five years).
- People from the following countries have rates of TB in New Zealand of over 1/1000: Somalia, Vietnam, India, Cambodia, Indonesia, Tokelau, Philippines and Thailand.
- The number of foreign-born students entering New Zealand is rising rapidly (up 73% to 73,325 visas and permits issued in 2001). Most of these are not screened before arrival and come from countries that have high rates of TB.

Current TB screening requirements

- All low TB prevalence countries have slightly different TB screening criteria and practices.
- The New Zealand Immigration Service (NZIS) requires all people aged 12 years and over (except those on Australian or New Zealand passports, which includes people of Cook Islands, Tokelauan and Niuean nationality) planning to enter and stay in New Zealand for more than 24 months to have a medical examination and a CXR before arrival. Other exceptions are quota refugees (who currently have an examination on arrival), and asylum seekers (at the time of residence application).
- Pregnant women are not required to have a CXR.

Advice to health professionals

- NZIS does not require TB screening in some foreign-born people. These are: people from the Cook Islands, Tokelau and Niue; overseas adoptions; pregnant women; children under the age of 12 years; and anyone travelling on a New Zealand or Australian passport. Some of these people may have a higher risk of TB than the New Zealand-born population.
- Health professionals need to be aware of the risk of TB in people from, or who have lived in, countries with a high incidence of TB, particularly in the first five years after arrival. History should include any recent overseas travel.
- HIV infection should be considered in all people diagnosed with TB, particularly if they are foreign-born.
- Drug resistance should be considered, and treatment altered accordingly.
- Interpreters should be employed when discussing the diagnosis and treatment of TB with people who have a poor understanding of English.
Foreign-born people entering New Zealand need to know the following.
- A normal CXR on NZIS screening does not mean they will not develop TB in future.
- TB is a treatable disease.
- They should seek medical advice if they suspect they have TB.
- The treatment of TB in New Zealand is free (Tuberculosis Act 1948).
- The greatest risk of TB is in the first five years after arrival in New Zealand.

Proposed changes

- All people intending to stay in New Zealand for six months or more should be required to undergo a CXR for TB.
- Reduce the minimum age at which CXR screening is required to 11 years.
- Investigate the introduction of a health undertaking in New Zealand (similar to the Australian health undertaking).
- Screen all quota refugees for TB offshore, where practicable, during 2002–03.
- Improve communication channels between New Zealand and Pacific nations with respect to mobile TB cases.
- Improve education and awareness of TB among new immigrants.
- Exempt people from low-incidence countries (by passport) from TB screening unless they have risk factors for TB.
Introduction

This chapter:

- reviews the epidemiology of TB in foreign-born people in New Zealand, comparing TB rates in the migrant country of origin with crude rates for foreign-born people in New Zealand, by country of birth
- examines current New Zealand border control practices with respect to TB, comparing these with other countries with low rates of TB, and reviews the role of New Zealand within the Pacific community
- outlines recommendations for the New Zealand Immigration Service (NZIS), the Ministry of Health, and primary and secondary health care providers working in this area.
7.1 Epidemiology

7.1.1 Within New Zealand

There were 230 foreign-born cases of TB in 2001, representing 68.7% of all cases for whom birthplace data were available. This is the highest percentage of foreign-born cases reported in New Zealand (see also Chapter 1: ‘Epidemiology and Surveillance’). Over the previous six years (1995–2000) the percentage of foreign-born cases fluctuated between 57.0% (1999) and 65.6% (1997). Over the period 1995–99 the geographical regions contributing the highest proportions of cases were:

- Asia (excluding South East Asia): 370 cases (36.8% of overseas-born cases)
- Pacific: 222 cases (22.1%)
- South East Asia: 145 cases (14.4%)
- Africa: 141 cases (14.0%).

While the type of visa or entry requirements for most of these cases (1995–99) is not known, we do know that 49 cases were in the National Refugee Health Screening Centre (NRHSC), Mangere, (and therefore quota refugees) or the Auckland Refugee Council hostel (and therefore asylum seekers) at the time of diagnosis. An Auckland study of 100 TB cases suggests that most foreign-born cases are New Zealand residents. The study found that of the 79 foreign-born cases, 59 were New Zealand residents, seven were seeking residence, seven were visitors, three were refugees, and three fell into other immigration categories.2

Using 2001 New Zealand Census data and ESR 2001 TB notification data:

- the crude rate of TB in people born overseas was 32.64 cases per 100,000 (228/698,628), compared with a rate of 3.63 per 100,000 (105/2,890,869) in New Zealand-born people
- a total of 60.0% (114/191) of overseas-born cases notified during 2001 for which arrival dates were recorded developed TB within the first year of arriving in New Zealand
- a further 34% developed TB between one and five years of arriving in New Zealand.

Using 1996 Census and five-year ESR data (1995–99),1 Pacific people born in New Zealand had an annual rate of 13.60 TB cases per 100,000 population (81/119208 x 1/5) compared with an annual rate of 46.65 per 100 000 (203/87035 x 1/5) in Pacific people born overseas but now living in New Zealand. This is higher than the rate of notified cases in Pacific nations.3

The epidemiology of TB cases in New Zealand appears to reflect that found in other developed countries in the following ways.

- The majority (over 50%) of TB cases are born overseas. This finding is also reported in Canada,4 5 6 Europe,7 Denmark13 14 and Australia.8
- The highest rates of TB in foreign-born people occur in the first five years after arrival in the country.9 4 25 10
Immigrants from countries with a relatively high prevalence of TB remain at risk for the disease for many years after they immigrate to low-prevalence countries. This risk decreases over time.\textsuperscript{25,11} (DNA testing of immigrants with TB in Israel\textsuperscript{12} and Denmark\textsuperscript{13} suggests that most immigrants who developed TB were likely to have been infected before their arrival, irrespective of the length of time they had been in Israel or Denmark. It is not known whether this is the case in New Zealand.)

The annual incidence of TB in foreign-born populations generally reflects the reported incidence of TB in their regions of birth.\textsuperscript{5,14} However, this does not apply to people from countries with limited access to diagnostic tests or incomplete notification records (see Table 7.1).

Table 7.1 summarises data on people from countries that have had 10 or more notified cases of TB in New Zealand over the 1995–99 period. The annual TB case rate has been calculated based on the New Zealand resident population from that country. This figure will be an overestimate of the true rate of TB in that population if there are high numbers of short-term visitors from that country in New Zealand. This is particularly so if the resident population is small.

Nevertheless, the table provides some evidence to suggest that notified rates of TB are higher in New Zealand than in the country of birth for many foreign-born populations in New Zealand. There are a number of possible explanations for this.

1. The most likely explanation is that New Zealand has better diagnostic and notification records than many of the countries listed in the table.

2. Some people may be coming to New Zealand seeking TB treatment, or there may be age or other characteristics that could bias the crude rate. There is some evidence to suggest self-selection by individuals in need of TB treatment – as it is often not available in developing countries. Individuals who would otherwise die of untreated TB or incur considerable health care costs in their own country may take substantial personal and financial risks to seek life-saving therapy in an industrialised country. This may include concealing illness at time of entry, or during interviews later.\textsuperscript{15}

3. Screening for permanent residence in those applying within New Zealand (as required by NZIS) may identify new cases.

4. The higher rate in some foreign-born people living in New Zealand may reflect a real difference in risk between the two populations. Possible explanations for this could be stress or socioeconomic conditions, particularly overcrowding in New Zealand, which may lead to increased exposure to TB, or reactivation of latent TB.

Table 7.1: Number of TB cases in foreign-born people, by country of birth, compared with TB rates in birth country

<table>
<thead>
<tr>
<th>Country of birth</th>
<th>Number of TB cases in NZ (1995–99)</th>
<th>NZ TB rate by birth country (per 100,000 people)\textsuperscript{a}</th>
<th>Birth country TB rate (per 100,000 people)\textsuperscript{b}</th>
<th>Rate ratio (NZ rate by birth country/rate in birth country)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somalia</td>
<td>86</td>
<td>1977.0</td>
<td>31</td>
<td>63.8</td>
</tr>
<tr>
<td>Vietnam</td>
<td>40</td>
<td>230.9</td>
<td>112.2\textsuperscript{3}</td>
<td>2.1</td>
</tr>
<tr>
<td>India</td>
<td>147</td>
<td>229.5</td>
<td>130</td>
<td>1.8</td>
</tr>
</tbody>
</table>

Guidelines for Tuberculosis Control in New Zealand 2003 – Chapter 7: Tuberculosis Control in People from Countries with a High Incidence of Tuberculosis
<table>
<thead>
<tr>
<th>Country</th>
<th>Annualised Rate</th>
<th>National TB Rate</th>
<th>Population Size</th>
<th>New Zeland TB Rate</th>
<th>Regional TB Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cambodia</td>
<td>29</td>
<td>157.8</td>
<td>142</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>Indonesia</td>
<td>19</td>
<td>140.0</td>
<td>16</td>
<td>8.8</td>
<td></td>
</tr>
<tr>
<td>Tokelau</td>
<td>10</td>
<td>132.8</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Philippines</td>
<td>46</td>
<td>131.4</td>
<td>198.1</td>
<td>0.7</td>
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</tr>
<tr>
<td>Thailand</td>
<td>22</td>
<td>131.4</td>
<td>77</td>
<td>1.7</td>
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<td>China</td>
<td>74</td>
<td>75.8</td>
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<td></td>
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<td>22</td>
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</tr>
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<td>Sri Lanka</td>
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<td>69.6</td>
<td>32</td>
<td>2.2</td>
<td></td>
</tr>
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<td>42</td>
<td>61.0</td>
<td>15</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Korea</td>
<td>36</td>
<td>59.1</td>
<td>51.5</td>
<td>1.2</td>
<td></td>
</tr>
<tr>
<td>Samoa</td>
<td>73</td>
<td>34.6</td>
<td>18</td>
<td>1.9</td>
<td></td>
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<td>Hong Kong</td>
<td>19</td>
<td>32.3</td>
<td>106.4</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Malaysia</td>
<td>14</td>
<td>23.5</td>
<td>68.1</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>Taiwan</td>
<td>12</td>
<td>22.0</td>
<td>Not available</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fiji</td>
<td>18</td>
<td>19.2</td>
<td>23</td>
<td>0.8</td>
<td></td>
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<tr>
<td>New Zealand</td>
<td>861</td>
<td>6.0</td>
<td>10.3</td>
<td>0.6</td>
<td></td>
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<tr>
<td>United Kingdom</td>
<td>43</td>
<td>3.7</td>
<td>11.2</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a) Annualised rate calculated by dividing number of cases (1995–99) by 5, then by the total number of people who identified themselves as being born in that country at the 1996 NZ Census, expressed as number of cases per 100,000 people.


### 7.1.2 TB rates in the Western Pacific region

The Western Pacific region encompasses Pacific Island nations together with Pacific Rim countries in Asia. In New Zealand, approximately 60% of all foreign-born cases are born in Western Pacific nations and territories.

The Western Pacific region, one of the six regions of the World Health Organization, is home to approximately 1.6 billion people, nearly one-third of the world’s population. It stretches over a vast area, from China in the north and west, to New Zealand in the south, and French Polynesia in the east. One of the most diverse of the WHO regions, the Western Pacific constitutes some of the world’s least developed countries as well as the most rapidly emerging economies. In 2000 there were about 2 million estimated cases of all types of TB in the region, of which only 41% were detected and notified. Figure 7.1 illustrates the countries of the Western Pacific region.
New Zealand has an interest in the control of TB in Pacific nations for the following reasons.

1. In 1996 there were more than 200,000\(^{16}\) Pacific people in New Zealand. Over the next 50 years this population is expected to grow at a faster pace than the total New Zealand population due to a higher birth rate. Pacific peoples’ share of the total population is expected to double from 6% at the 1996 Census to about 12% in 2051.

2. New Zealand is in relatively close proximity to its Pacific neighbours.

3. There are higher rates of TB cases in some Pacific nations (particularly Niue, Fiji, Tonga, Samoa and Cook Islands) than in New Zealand.

4. There were 222\(^1\) cases of TB reported in New Zealand between 1995 and 1999 in people born in Pacific nations (22.1% of the 1005 cases born overseas).

5. Pacific people are very mobile, with frequent air travel between Pacific nations and New Zealand.

The overall rate of notified cases in the Western Pacific Region in 1999 was 49.2 per 100,000 population.\(^{17}\) The New Zealand rate was 9.4 per 100,000. New Zealand receives a number of visitors, and permanent and long-term arrivals from countries within the Western Pacific Region that have high rates of TB. These include Hong Kong, Philippines, Vietnam, Malaysia, Korea, China and Japan. The notification rates of these countries should be interpreted with caution, as there are differing reporting systems and TB control policy between countries, changing definitions of a notifiable case, and possible under- or over-reporting. For example, while the notified rate of TB in China is 36.3 per 100,000, the estimated rate is 103 per 100,000.\(^{18}\)
7.1.3 Antibiotic-resistant TB

Antibiotic-resistant TB can be divided into the following categories.

- **Resistant to one or more antibiotics** – 31 of the 40 cases of antibiotic-resistant TB in 2001 were foreign-born. The birth countries contributing the greatest number of cases with drug resistance were China (five cases), Philippines (four) and India (three). At a regional level, 17 of the 31 cases were from the Western Pacific Region (see also Chapter 1: ‘Epidemiology and Surveillance’).

- **Resistant to two or more antibiotics** – in 2001 there were seven cases resistant to two or more antibiotics, down from a high of 14 in 1998. All of these cases were foreign-born.

- **Multi-drug-resistant TB** – there were no cases of multi-drug-resistant TB (MDR-TB) in 2001 (defined as resistant to at least isoniazid and rifampicin). New Zealand currently has a low rate of MDR-TB (0.0–1.1% of all new TB cases per year during 1995–2001). The number of cases of MDR-TB has remained between 0 and four per year since 1995.

The main reason for antibiotic-resistant TB in foreign-born people entering New Zealand is likely to be inadequate treatment regimens. This may be because treatment was not given for long enough (eg, three months instead of six months), compliance with treatment regimens has not been documented, or two drugs were used instead of the recommended three or four.

The introduction and expansion of DOTS (directly observed therapy short-course) coverage, particularly in the WHO Western Pacific Region, may help to prevent an increase in antibiotic-resistant TB. As almost all of those with antibiotic-resistant TB in New Zealand are foreign-born, New Zealand’s best way to prevent antibiotic resistance here is to ensure complete and efficient identification, appropriate treatment and contact tracing of TB, especially in people not born in New Zealand.

7.1.4 HIV / AIDS and TB co-infection

In 2001 there were six cases of AIDS/HIV with TB co-infection. All of these cases were in foreign-born people from Asia and Africa. The percentage of new TB cases that also had HIV/AIDS was 1.6% (2001 data) compared with a rate of 1.2% for the 1995–99 period.

While HIV/TB co-infection is low in New Zealand (1.6%) and in much of the Western Pacific region, the prevalence rate of HIV in new TB cases in some countries in the region is expected to rise in the next few years, particularly in Cambodia (7.9%), Malaysia (4.9%) and Fiji (3%). In some countries in sub-Saharan Africa more than 70% of patients with active TB are also HIV-seropositive. New Zealand could experience an increase in HIV/TB co-infection in future if the number of people migrating from countries with a high rate of HIV or HIV/TB co-infection increases.
It is not known how many TB cases in New Zealand are tested for HIV, or how many HIV patients are Mantoux tested. The WHO has called for improved collaboration between TB and HIV programmes with the ‘Promote HIV voluntary counselling and testing initiative’ (ProTEST). ProTEST aims to promote voluntary testing for HIV as a key to a more coherent response to TB in areas with a high prevalence of HIV. At present, new immigrants to New Zealand who are detained at the NRHSC, Mangere, are offered HIV testing. This service needs to be extended to all people who are diagnosed with active TB (see ‘Testing for HIV and other co-morbidities’, in Chapter 14: ‘Clinical Investigation and Assessment of Tuberculosis’). Screening must be accompanied by culturally appropriate counselling and support, but should remain voluntary. The issue of whether HIV screening should be part of the NZIS medical examination is beyond the scope of this chapter.

Currently there is no official regular matching of the TB notification database (held by ESR) and the HIV/AIDs database (held by the Department of Social and Preventive Medicine, University of Otago). See Chapter 18: ‘Tuberculosis and HIV’ for further discussion of surveillance of co-infection.

7.1.5 Immigration

New Zealand receives a large – and currently increasing – number of permanent and long-term arrivals, visitors, students and people on work visas each year. Permanent and long-term arrivals are those planning to stay in New Zealand for at least 12 months. For the year to October 2001 there were 76,700\(^{19}\) permanent and long-term arrivals to New Zealand. The largest proportion of these were born in Asia (36.0%). People from Pacific nations made up 6.6% of the total.

7.1.6 Temporary workers

NZIS issued 49,300 temporary work permits and visas in 2000, an increase of 3800 from 1999. Some of these were issued to refugee status claimants (asylum seekers) and some to people intending to apply for residence (eg, spouses of New Zealanders), but much of the increase resulted from New Zealand employers recruiting skilled people from offshore.

7.1.7 Foreign-born students

The number of foreign-born students in New Zealand is rising rapidly. In 2001 NZIS issued 73,325 student permits and visas, up 73% on the 42,387 issued in 2000. Chinese nationals accounted for 40% of these, with 28,739. A large number of student visas were also granted to nationals from South Korea (17%), Japan (8%), Thailand and Taiwan (4% each), and Hong Kong, Fiji and Malaysia (3% each). All of these countries have TB rates much higher than in New Zealand. Only those planning to stay for more than two years are screened prior to arrival.
In 2000 there were 22 new cases of TB notified in foreign-born students. Five of these had been in the country for less than one year and only two had been in the country over five years. The crude rate of new TB cases in foreign-born students within a year of arrival in New Zealand for the year 2000 was between 11.8 (5/42,400) and 16.9 (5/29,600) cases per 100,000 foreign-born students. A range is given, as it is not known in which year (2000 or 1999) the students obtained their permits or visas. Also, this is only an estimate, as the denominator does not include foreign students entering on a visitor’s visa.
7.2 Review of current screening practice

7.2.1 Purpose of TB screening

TB screening in people from countries with a high incidence of TB has personal health, public health and economic implications. At a personal health level, screening detects imported TB disease in those arriving from high TB incidence countries so that early, effective medical intervention can be offered.\(^{20}\)

From a public health perspective, screening reduces the risk of TB, particularly multi-drug-resistant TB, for people already residing in New Zealand. Ideally, those with TB would be identified and treated before arriving in New Zealand. From an economic perspective, screening reduces the burden of TB on New Zealand health services and reduces treatment costs by minimising the severity of disease, and the risk of infection in close contacts.

7.2.2 NZIS requirements

Medical and X-ray information

A new medical and X-ray certificate form was released by NZIS in February 2002 (see Table 7.2).

Table 7.2: Relevant questions on NZIS medical and X-ray certificate forms (February 2002)

<table>
<thead>
<tr>
<th>Section of form</th>
<th>Question asked</th>
</tr>
</thead>
</table>
| History         | Are you suffering from, or have you ever suffered from, any of the following: (a) TB (or have you had contact with a person who has had tuberculosis)? [no/yes]  
  Comment:** An interpreter should be used if the applicant cannot speak English sufficiently well. Also general medical history should be undertaken. |
| Examination of respiratory system | Any signs of abnormalities, including nose, lungs and chest disorders (if CXR is abnormal or shows signs of past TB, attach a respiratory physician’s (pulmonologist’s) report as to whether there is any active or chronic lung disease) [no/yes].  
  Comment: Lymph node groups should be examined. |
| Summary         | Is the applicant suffering from any infectious or communicable disease: [no/yes] |
| Chest X-ray (in those aged 12 years and over excluding pregnant women) | Is there any evidence of pulmonary tuberculosis (past or present)? [no/yes]  
  (CXR must be signed by radiologist, not just the report form.)  
  Comment: Always ask if previous films can be obtained for comparison if none are offered. If the person is asymptomatic, films taken 3-4 weeks earlier are satisfactory. Otherwise a repeat X-ray is needed. If chest or systemic symptoms of TB are present, the chest radiograph should not be more than about a week old. |

* For indications for detailed mycobacteriological testing, refer to Chapter 12.  
** Comments provided by Dr A Harrison, Respiratory Physician, Auckland DHB.  
* See Table 14.1, Chapter 14: ‘Clinical Investigation and Assessment of Tuberculosis’.

The Medical and X-ray Certificate Form must be completed by an approved NZIS panel doctor. Completed forms must not be more than three months old at the time the application is lodged, or the application will not be accepted for consideration, and the applicant would be required to undergo another examination and X-ray.

There is no requirement for applicants to have tuberculin skin tests because of:
a lack of standardisation of tuberculin skin tests done in different countries
a lack of ensuring quality control of testing materials and procedures in different countries
difficulty in interpreting the results in people from countries where BCG vaccine is used.

If an abnormality is detected on medical examination or X-ray, the results are forwarded to a doctor in New Zealand contracted by NZIS.

**New Zealand entry requirements**

Table 7.3 outlines the medical requirements for the various visas and permits for people entering New Zealand. In addition, NZIS reserves the right to ask any person applying for a visa to enter New Zealand to undertake a medical examination and CXR prior to visa issue, even if their stay is less than 24 months.

**Table 7.3:** Forms of New Zealand entry visa/permits and medical requirements, at March 2002

<table>
<thead>
<tr>
<th>Form of entry</th>
<th>Description</th>
<th>Permitted length of stay</th>
<th>Medical exam and X-ray²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visitor’s visa</td>
<td>Required for visits to New Zealand unless from a visa waiver country (see below)</td>
<td>Nine months in an 18-month period (may be extended for three extra months)</td>
<td>Required if intending to stay in New Zealand over 24 months³</td>
</tr>
<tr>
<td>Work permits and work visas</td>
<td>Required for those offered employment in New Zealand</td>
<td>Up to three years</td>
<td>Required if planning to stay in New Zealand over 24 months</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>Required if intended study course is 24 months or longer⁶</td>
</tr>
<tr>
<td>Residence</td>
<td>Required if wanting to live in New Zealand indefinitely</td>
<td>Indefinite</td>
<td>Required⁵</td>
</tr>
<tr>
<td>Limited purpose visa/permit</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>Not required⁴</td>
</tr>
<tr>
<td>Asylum seekers</td>
<td></td>
<td></td>
<td>Required on application for residence</td>
</tr>
<tr>
<td>Quota refugees (residence)</td>
<td></td>
<td></td>
<td>Required on arrival</td>
</tr>
<tr>
<td>Samoan quota (residence)</td>
<td></td>
<td></td>
<td>Required prior to arrival⁸</td>
</tr>
</tbody>
</table>

a Must be completed before arriving in New Zealand if stay is intended to be at least 24 months, and must be completed in New Zealand if stay is extended to longer than 24 months.

b Applicants must fulfil the following requirements:
- not likely to be a danger to public health
- not likely to be a burden on the health service
- fit for the purposes of entry.

New Zealand uses panel doctors in 108 countries. People who are applying for a New Zealand visa from these countries, and fit the criteria for a medical examination and X-ray, are required to have these carried out by one of the panel doctors.
New Zealand does not currently select any of its own panel doctors. NZIS uses the same panel doctors as the Department of Immigration and Multicultural and Indigenous Affairs (DIMIA), Australia, and therefore relies on DIMIA’s selection and review process for panel doctors. One of DIMIA’s selection criteria is that all panel doctors be able to communicate in English. DIMIA employs two regional medical directors, one in Bangkok and one in London. The current quality control measures are annual visits to all panel doctors in major centres, and visits to panel doctors in smaller centres once every three years. NZIS does not currently pay for these audit or liaison visits or have any influence on how they are carried out.

**Countries from which people are exempt visas**

Visa waiver agreements apply to the nationals of a specified list of countries (51 as at the beginning of 2002) who are visiting New Zealand for three months or less. Western Pacific countries on this list that have TB rates much higher than New Zealand include Malaysia, Kiribati, Hong Kong, Japan and Korea.

### 7.2.3 Other low-prevalence countries’ medical requirements

**Australia**

People seeking permanent residence in Australia or temporary residence for a period of more than 12 months (and in some instances for stays shorter than 12 months) must have medical and CXR examinations. From 25 March 2002 the minimum recommended age for X-ray screening for TB in Australia was reduced from 16 to 11 years. This was to bring Australia into line with Canada and the US, which will also be making the change in the next few months.

Changes on the CXR film are considered the principal indicator of past or current TB. A Mantoux test is not part of the routine examination for assessment of migrants, but may be requested. All migrants who are identified as having a history of TB and/or have an abnormal CXR film must sign an undertaking before leaving their country of origin that they will continue under surveillance in Australia (see also section 7.2.7, ‘Review of Australian health undertaking’). Those with a health undertaking need to report within a designated period – either one week or one month – of their arrival in Australia. A health undertaking is valid for only six months from the date of issue. If a migrant has not travelled to Australia in that time, he or she must have a further CXR examination and the case has to be cleared again by a medical officer.

Canada

A medical examination and X-ray are required for anyone planning to stay in Canada for over six months who is from a designated country/territory, irrespective of the reason for entry or visa type. No medical examination is required for those spending less than six months in Canada unless they are planning to work in a specified list of occupations or work sites, such as hospitals or schools.

Further information is available at: http://www.cic.gc.ca/english/visit/medexams-e.html

United States

A medical examination is required for all refugees going to the US and all applicants outside the US applying for an immigrant visa and aged 11 years and over. Aliens in the US who apply for adjustment of their immigration status to that of permanent resident also require a medical examination. Aliens applying for non-immigrant visas (temporary admission) may be required to undergo a medical examination at the discretion of the consular officer overseas or immigration officer at the US port of entry, if there is reason to suspect that an inadmissible health-related condition exists.23

United Kingdom

The UK does not routinely screen everyone, although:

- some screening is done prior to entry ‘at certain centres in a few countries’24
- nearly 100% of political asylum seekers are screened with a CXR at the port of arrival
- there is random CXR screening of (other) new immigrants
- new immigrants not screened on arrival are notified ‘to the Consultant in Communicable Disease Control for the eventual area of residence, who initiates investigation and follow-up at local chest clinics’.

Table 7.4: TB screening requirements for migrants to selected countries

<table>
<thead>
<tr>
<th>Country</th>
<th>Persons subject to screening</th>
<th>Age for CXR</th>
<th>Exemptions</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Zealand*</td>
<td>Persons wishing to stay longer than 24 months</td>
<td>12 years and over</td>
<td>Australia</td>
</tr>
<tr>
<td>Australia</td>
<td>Persons wishing to stay longer than 12 months</td>
<td>11 years and over</td>
<td>New Zealand</td>
</tr>
<tr>
<td>Canada</td>
<td>Persons wishing to stay longer than six months</td>
<td>11 years and over</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>Permanent immigration only</td>
<td>11 years and over</td>
<td>Temporary visitors, workers and students</td>
</tr>
<tr>
<td>UK</td>
<td>Screening on arrival for asylum seekers and those from TB-endemic countries</td>
<td>13 years and over</td>
<td></td>
</tr>
</tbody>
</table>

* Persons entitled to travel on New Zealand passports (and therefore enter New Zealand by right, without being subject to any immigration controls or health checks) include citizens of the Cook Islands, Tokelau and Niue, and overseas-born children to New Zealand parents (including children adopted overseas).
Table 7.4 outlines the current screening practices of selected English-speaking countries. In all countries pregnant women are exempt from a CXR. In Australia they are recalled postnatally for a CXR. If New Zealand were to adopt a health-undertaking scheme similar to Australia’s then it would be possible to recall women who were pregnant at the time of entry. Australia recently reduced the age at which applicants are required to undergo a CXR from 16 to 11 years and over, to bring it into line with other countries. While New Zealand’s current policy is 12 years and over, it would seem appropriate to lower the age of screening to those aged 11 years and over for consistency.

Some European and Scandinavian countries have different screening practices. Finland and Denmark have no mandatory screening, but may ask asylum seekers and refugees to be screened if symptomatic for TB. Norway only requires asylum seekers and refugees to be screened. The different screening policies and practices may reflect the perceived risk of TB in migrants to these countries, and the common source countries of migrants. Numerous articles have looked at the optimal screening practice of immigrants but no consensus has been reached. What is known is that foreign-born people living in developed countries have a higher rate of TB than native-born members of the population. An Australian study estimated that a 35-year-old refugee with a >15 mm tuberculin skin test reaction had a cumulative risk of TB to age 75 of 6.7%.

Weis et al do not recommend the use of CXRs to screen for TB in non-immigrant visitors, citing Canada’s findings of a low yield among new arrivals. They also report that 23% of people developing TB within one year of arrival to the US had a ‘normal’ CXR before their arrival. However, it is possible that there is a selection bias in the Canadian findings, where those who found they had TB on screening might not have submitted their application for admission. While the US results may be partly explained by fraudulent X-rays prior to entry, they are most likely to reflect the findings of other studies showing that new immigrants are most at risk of TB in the first year after arriving in a new country.

7.2.4 Cost effectiveness of immigrant screening for TB

No formal cost-effectiveness analysis has been carried out in New Zealand. However, a Canadian analysis of adult immigrant applicants found that while tuberculin skin testing detected the most active TB cases over a 20-year timeframe, it was considerably more expensive than CXR screening. Radiographic screening of immigrants at high risk of TB was found to be cost effective (preventing 4.3% of expected active TB cases at a cost of $3,943 CA per active case prevented [1997 dollars]). Tuberculin skin testing was considerably less cost effective relative than CXR screening ($32,601 CA per additional case prevented), and screening of immigrants from low-incidence countries was extremely costly for both interventions ($236,496 CA per case for radiographic screening and $68,799 CA per additional case prevented by tuberculin testing in the lowest risk group). This study only analysed the costs to third-party payers (federal and provincial government), and is based on Canadian Healthcare costs, so these figures do not include the cost to the individuals.

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* Source: Dr B Gushulak to Dr L Calder, personal communication, 23 October 1998.
Their high-risk group was a cohort where 50% were TB-infected and 10% had HIV. New Zealand does not currently define high risk. A rate of TB cases (applicable to other countries), over which any person applying for a visa to enter New Zealand is screened, needs to be set. A rate such as 20 per 100,000 may be appropriate. New Zealand should not require CXRs for the purpose of TB screening from immigrants of low-incidence countries, unless indicated on medical examination. The ideal would be to define risk by the country where the immigration applicant has resided for the last five years. However, this is not currently practical. A proxy is to determine a person’s risk in relation to the nationality stated in their passport.

While radiographic screening alone is the most cost-effective screening tool for TB, screening of close contacts is the most cost-effective population to screen. Screening of close contacts produces net savings of $815 CA for each prevalent case detected and treated, and $2186 CA for each future active case prevented. This emphasises the importance of contact tracing, especially in those screened within New Zealand.

### 7.2.5 Border control

Figure 7.1 outlines the three opportunities for screening people entering New Zealand: prior to arrival, on arrival, or at some later date (within two years of arriving in New Zealand).

**Figure 7.1:** Opportunities for screening migrants to New Zealand

![Diagram showing opportunities for screening migrants to New Zealand](image)

**Screening before arrival**

Screening prior to arrival in New Zealand applies to those who intend to reside in New Zealand for at least two years. It generally does not include students. In terms of reducing the burden of TB to those resident in New Zealand, screening prior to arrival would be the ideal, although it is not always practical as many people entering New Zealand extend their visit or wish to change their permit status while in New Zealand. The main problem with screening pre-arrival is ensuring the quality of screening. The use of foreign-trained doctors, language barriers and the opportunity for fraudulent screening or papers are problems that can only be addressed through quality control, audit, and evaluation processes.
**Screening on arrival**

Screening immediately on arrival in New Zealand occurs in only a small percentage of total arrivals, and mainly applies to quota refugees and those who claim asylum on arrival in New Zealand. People in this category are likely to be at high risk of being infected with TB through exposure in refugee camps and overcrowding. The current practice for people who ask for asylum at the border is to send them to the National Refugee Health Screening Centre (NRHSC), at the Mangere Refugee Reception Centre (MRRRC), or, in a few cases, to Mt Eden Prison.

If they can satisfactorily prove their identity (eg, by getting documents sent from overseas) then they are released on a work permit (only a small number satisfy this criterion). The 2002 Budget together with the passing of the Transnational Organised Crime Act 2002 mean that many refugee status seekers will be able to be released without a permit, but on conditions, to reside at an approved place (such as the Auckland Refugee Council hostel).

At present all or almost all people applying for asylum at New Zealand’s border have a full medical examination and screening before their application is decided. The presence or absence of TB or any other condition cannot affect the outcome of their refugee status application. The cost of screening of these groups is borne by the New Zealand government, as are all costs related to refugee status claimants. The refugee status claims are prioritised, with all being interviewed within two weeks of arriving at the MRRRC and determinations are made within a month of arrival.

Delays in this process do occur, particularly if there is legal involvement. If a claimant does not fulfil the definition of a refugee because they do not have a well-founded fear of persecution, they may appeal to the independent Refugee Status Appeal Authority. This can considerably lengthen the time before their claim is finally determined and they are either granted residence or required to leave New Zealand.

At this stage there is funding for all quota refugees, and for around 600 ‘other refugee’ (broadly defined) people to be fully medically screened annually. Around 1600 people currently claim refugee status in New Zealand per year, and around 20% of those claims are made at the border. Everyone who claims at the border receives information on screening and most or all appear to take up the offer of screening. However, there are insufficient resources to enable all claimants to be offered health screening. This means screening is carried out on most or all border claimants, but on few of those who apply after arrival.

Currently some people claiming asylum-seeker status from within New Zealand undergo two medical examinations: one on applying for asylum-seeker status (if they do so at the border) to satisfy health requirements, and another if their application is successful (fewer than 20% are successful) to satisfy immigration health requirements. A more efficient use of resources would be an initial TB screen in the form of a CXR for everyone, with no screening for other medical conditions. Asylum seekers would be entitled to the same level of health care as all New Zealanders while waiting for their application to be processed. This means they would be able to access free hospital care. If the application for asylum-seeker status is successful, a complete medical could then be undertaken.
There would be no need to repeat the TB screening unless indicated on medical examination.

This would bring asylum-seeker screening into line with that to be investigated for offshore visa applicants planning to enter New Zealand for more than six months. As less than 20% of asylum-seeker applicants are successful, it should reduce the cost of initial screening and substantially reduce duplication, while identifying at an early stage those with active TB so that treatment can be commenced. Mantoux testing with treatment of latent TB infection is most likely to be cost effective if done early after arrival. If this process were adopted, then it would be important for asylum-seeker applicants to be provided with information, advice and support on how to access health care in New Zealand.

**Screening some time after arrival**

Screening after arrival applies to those people who have arrived on a temporary visa (of less than two years’ duration) and who seek to extend their stay to more than two years. This covers a large number of people, and includes those on student visas who have satisfactorily completed at least one year of study and wish to further their studies. It also includes those wishing to apply for residence, extension of work visas, and some people seeking asylum. Those seeking asylum are required to have a CXR only if their application is successful.

### 7.2.6 Review of offshore screening of quota refugees

Three of the 10 countries that take quota refugees have adopted the practice of screening quota refugees for a range of diseases prior to arrival. They are Australia, the US and Canada.

NZIS have proposed screening quota refugees for TB in an approved offshore facility. The current plan is for screening to be focused on TB, with other conditions screened for as priorities and funding indicate. If refugees are found to have infectious TB, they will not be allowed to enter New Zealand on international flights until they have received treatment and are cleared for travel. Quota refugees would still be required to undergo medical examination and a CXR at NRHSC, Mangere, on arrival. This section looks at the advantages and disadvantages of this proposal for offshore screening of quota refugees from a New Zealand perspective, with particular emphasis on screening for TB.

Currently refugees arriving in New Zealand are sent to NRHSC, Mangere, where they undergo general screening and medical assessment. They are tested for TB, HIV infection, schistosomiasis, hepatitis B and C, syphilis, enteric parasites, typhoid and paratyphoid. They are also tested for iron deficiency, haemoglobinopathies, liver defects and urinary problems. Women are also screened for cervical cancer. Personal examination and assessment includes psychosocial assessment. Approximately 70% of refugees require referral to some secondary service for further management, and virtually every refugee requires some sort of intervention.
The goals of offshore screening, in those countries that undertake it, are to:

- diagnose and treat refugees prior to resettlement in another country
- reduce the risk of disease to those travelling on the same air flights
- reduce the importation of active disease such as TB
- reduce the risk of disease in nationals of the resettlement country
- in some cases, to refuse access to people with certain diseases or conditions.

The main advantage of screening quota refugees offshore in an approved facility is that diagnosis and treatment for those who require it is initiated at an earlier stage, reducing exposure to fellow refugees and enabling those identified with TB to complete treatment prior to travel and arrival in their new country. This also reduces the potential risk of TB to those travelling in the same aircraft or living in the destination country. There is some evidence that transmission of *M. tuberculosis* may occur during long (more than eight hours) flights, from an infectious source (a passenger or crew member) to other passengers or crew members. Screening and treatment prior to embarkation would help reduce the potential risk to fellow travellers.

The quality of screening that can be offered in refugee camps or settlements is the main concern with offshore screening of TB in quota refugees. This includes ensuring that:

- an X-ray belongs to a particular individual
- the quality of the film is sufficient to interpret
- laboratory facilities are adequate
- antibiotic sensitivity is tested for in those who are diagnosed with active TB
- antibiotics are stored correctly and are not past their expiry date
- there is full adherence with daily treatment.

On arrival in New Zealand refugees would still need to be reviewed by a chest physician in addition to undergoing a complete medical examination for TB and other health concerns.

From an economic perspective it is unlikely that offshore screening for TB alone would be cost effective, unless it could be shown that the risk to fellow travellers was reduced significantly. All refugees would still require a full medical examination, CXR and other screening tests on arrival. There is also the risk that refugees identified with TB offshore may receive inadequate treatment or be non-compliant with treatment, resulting in the development of antibiotic-resistant TB.

New Zealand is a small country that lacks the resources to establish its own dedicated clinics for screening refugees offshore. It would therefore have to rely on medical staff from other countries to carry out screening. This may lead to differences in the management of TB cases, or misunderstandings over information transfer. The decision to screen quota refugees for TB offshore therefore depends on the quality of screening available. To monitor the quality of screening, quota refugees should be given their X-ray films and treatment notes to be passed on to NRHSC medical staff. This will also enable continuation of treatment on arrival.
7.2.7 Review of Australian health undertaking

The Australian health undertaking is a requirement for all migrants who are identified as having a history of TB, and/or who have an abnormal CXR film.

- They must sign an undertaking before leaving their country of origin that they will continue under surveillance in Australia.
- Those with a health undertaking need to report within a designated period – either one week or one month – of their arrival in Australia.
- A health undertaking is valid for only six months from the date of issue. If a migrant has not travelled to Australia in that time, he or she has to have a further CXR examination and the case has to be cleared again by a medical officer.
- Although the Migration Regulations may require an individual to sign a health undertaking, there are no penalties for failure to comply.
- Follow-up and treatment for TB through a health undertaking are paid for by the individual states with money from the Australian government. Students and temporary residents who have offshore insurance may be required to seek payment from their insurer.

A prospective study by King et al in Victoria, Australia, in 1993 found that overall 58% of the 1660 migrants with a health undertaking made contact with the appropriate authorities. Of those who made contact, 89% were compliant with their undertakings. Factors associated with compliance were recent active TB or extensive bilateral tuberculous lesions on CXR (94% compliant), and country of origin. Changes to the undertakings system as a result of the study, together with the implementation of a tracing system using Medicare address information, have increased the final compliance rate to around 75%. Holders of temporary protection visas are now required to notify DIMIA of their current addresses, a change that should further increase compliance with health undertakings.

Compliance is just one way to evaluate the health undertaking. Pang et al, in a retrospective analysis of the records of immigrants to Western Australia in 1994 and 1995, assessed the effectiveness and efficiency of the health undertaking. As a result of pre-migration medical examination, 69 of the 1344 immigrants (5%) were diagnosed with active TB requiring full treatment; 65 (94%) of these were Asian. A total of 373 people (28%) required ongoing surveillance as they had radiological changes consistent with inactive TB, with seven more cases of active TB identified during reassessment and follow-up over a two-year period after arrival. All but one of the seven came from Asia.

All of the 1344 in this study attended their initial examinations. The authors identified three reasons for the high compliance rate:

- the early receipt of the pre-migration documents and CXRs in the study period resulted in sufficient time to remind the new immigrants before they moved
- no prior appointment was required to attend the chest clinic
- there was only one clinic in the state they could contact or attend.
The authors found that the efficiency of the surveillance programme was unsatisfactory, because almost 13% of the immigrants were put on health undertakings due to repeated poor-quality chest films, the majority of which were subsequently found to be normal. Rather than being an inefficiency of the health undertakings, this appears to be an inefficiency of pre-migration screening where quality control is not adequate. The second reason given was that nearly 50% were considered to have non-TB conditions that were obvious from the past medical history and/or further examinations. If these conditions only became obvious on further examinations then it would seem wrong to label them as inefficiencies of the system. It was reported that these ‘inefficiencies’ placed an increased burden and stress on both the immigrants and the chest clinic.

While health undertakings may be effective, an historical cohort study among 24,610 predominantly South East Asian refugees in Australia found that over a 10-year follow-up period the crude annual incidence of TB was 74.9 per 100,000 person-years. Only 29.6% of these were diagnosed as a result of routine follow-up procedures (at six months and 18 months after initial post-arrival screening). This suggests that 70% of cases in this cohort were not identified through the follow-up screening (similar to a health undertaking), raising awareness that those not followed up may still be at risk of TB for years after arrival.

Review of the Australian Health Undertaking Scheme has identified a number of factors that should be borne in mind if the scheme is adopted in New Zealand.

* Comply with ensuring rapid contact with immigrants on arrival (within four weeks). This would require immigrants with an undertaking to ring a toll-free number giving contact details.

* Pang et al suggested that appointment-less visits at the chest clinic improved the effectiveness of the service. Adoption of appointment-less visits in New Zealand would depend on the number of health undertakings issued (demand), and the number of chest clinics offering the service and competing demands for their services (supply). Before a scheme is introduced into New Zealand it would be important to have an estimate of both of these.

* An efficient scheme requires good-quality screening prior to migration. Currently New Zealand uses overseas doctors contracted to provide screening to those travelling to Australia, and relies on DIMIA to ensure that quality and audit checks are carried out. It would be better if New Zealand could acknowledge the service that DIMIA provides and work with DIMIA to establish a system for addressing any concerns that New Zealand doctors or applicants may have about the panel doctors. This would require migrants to pay, through their fees, for auditing and monitoring.

In terms of the screening process, both Australia and Canada have forms of follow-up or health undertakings for those with a known history of TB disease or changes on CXR. The success of these has been evaluated and suggests that while compliance is an issue, those most at risk of TB disease – new or reactivation – tend to comply with the undertaking.
The Ministry of Health and NZIS should investigate the feasibility and practicality of introducing a health undertaking scheme in New Zealand. The purpose of the scheme would be to follow up immigrants to New Zealand who have been identified as having abnormal X-rays on TB screening, or with a past history of TB. The Australian Health Undertaking Scheme should be used as a starting point, taking into account their experience and lessons learnt.

The key factors for New Zealand would be:

- ensuring the quality of offshore screening
- determining whether New Zealand has enough resources in terms of chest clinics, time and staff to ensure an effective system
- developing a way of tracing and communicating with immigrants on arrival.

The cost of implementing and maintaining a health undertaking scheme in New Zealand must also be considered. Trends in immigrant arrivals, particularly flow from high-risk regions, will be important when deciding whether there is a need for a health undertaking scheme in New Zealand.

### 7.2.8 Duration of stay and screening requirement

The length of stay permitted in New Zealand before which TB screening is required is currently 24 months. Other ‘peer’ countries have lower thresholds (eg, Canada has six months). If New Zealand adopted a period of six months, students intending to study for one or more academic years would require TB screening before arrival. What we do not know is whether people arriving from high-risk countries on student or work visas are representative of the general population in that country, and what effect if any a change in screening time would have on the incidence of TB in New Zealand.

The current crude rate of new TB cases in foreign-born students in New Zealand of 11.8 per 100,000 within a year of arrival is not too dissimilar to the New Zealand population rate. An American review of screening in students\(^3\)\(^6\) suggests that the epidemiology of TB in foreign-born students is changing, with more students developing the disease.

A reduction in the length of stay in New Zealand without screening could have a number of effects.

- There would be a sharp increase in the number of radiographic screens required by the NZIS.
- The inconvenience and cost of screening could act as a significant barrier to entry. There may also be a possible negative reaction from the education sector if the Export Education strategy was negatively impacted by such changes.
There would be some pressure on existing screening facilities if demand increased suddenly by several hundred percent, even if that demand was all self-funded. This implies that careful planning for implementation, with considerable communication with service providers, would be necessary.

NZIS is moving towards electronic and on-line mechanisms for renewing permits, but does not yet have the direct links to chest physicians or medical laboratories that a change in TB screening policy would require.

People from countries with a low incidence of TB are currently required to undergo TB screening if they are planning to stay in New Zealand for more than 24 months. As they are at low risk of TB, increasing screening (to all those planning to stay more than six months) in this group is not required unless there are risk factors for TB (such as signs or symptoms of TB, recent close contact, or a past history of TB).

Another issue is whether screening on initial entry is adequate. Individuals often return to their homeland for prolonged periods. As reported by Weis et al, 23% of all foreign-born individuals had travelled to TB endemic areas within the preceding two-years – for a median of 42 days (see Chapter 10: ‘TB Control in Non-Clinical Settings’). The question is, should they be screened at each re-entry? Doing so would consume a large amount of resources and be difficult to enforce. A better way to address the potential TB risk to foreign-born immigrants when revisiting their homeland might be to inform them of the symptoms of TB and treatment availability through a pamphlet or in-flight video.

### 7.2.9 Risk communication

Risk communication is important because of the ethnic and cultural diversity of migrants and evidence that the risk of TB remains for years after arrival in a Western country. Migrants need to be made aware of:

- the symptoms of TB
- the continued risk of TB even if there was no evidence of TB on the immigration medical examination (in many countries there is a stigma attached to TB because of its infectivity and often-inadequate treatment, and this may act as a barrier to migrants seeking medical advice)
- the fact that that TB is treatable and that it is important to seek medical help as soon as TB is suspected: this can reduce the risk to family and friends.

Health professionals in primary care should be aware of the continued risk of TB in migrants to New Zealand even if the migrants have been in the country for a number of years.
7.2.10 Pacific regional infrastructure for TB control

**Communication**

Communication between health care providers in different countries – particularly between New Zealand and Pacific nations and territories – is important in the control of TB in the region. Communication is important to ensure that supervision and medication supply are maintained for those diagnosed with active TB.

An informal arrangement currently operates. When a person receiving treatment for TB travels between New Zealand and a Pacific nation, the local public health service informs the New Zealand Ministry of Health, which in turn informs the Ministry of Health in the destination country. The destination Ministry then informs the local public health service of the person’s arrival. This arrangement does not appear to be working well at present* due to inaccurate overseas address lists, and possibly a lack of awareness of the arrangement.

**Measures needed to improve communication**

- Communication between New Zealand and Pacific nations with respect to TB case travel should continue to be between the relevant health bodies in each country rather than via customs or immigration. However, direct communication between those providing the treatment (local public health services) in each country is preferred.
- Efforts should be made to update contact lists and emphasise the importance of communication to ensure that treatment is continued, reducing the risk of reactivation, development of resistance and risk to close contacts. The responsibility of maintaining an updated list and communicating information should rest with one person within the Ministry of Health.
- Better use could also be made of PACNET – an email and telefax supported communication network for health professionals from the Pacific Islands and the Pacific Rim (part of the Pacific Public Health Surveillance Network established by the Secretariat of the Pacific Community – see below).

7.2.11 Key agencies involved in TB control in the Pacific region

**Secretariat of the Pacific Community (SPC)**

Established in 1947, this was formally known as the South Pacific Commission. All 22 island countries and territories are now full members. SPC is a technical and development organisation with work programmes in a number of areas, of which health is just one.

* Dr L Calder, Medical Officer of Health, ADHB, personal communication, 12/3/02.
WHO–WPR is one of six WHO regions. It has a population of 1.6 billion and covers the area from China to New Zealand and French Polynesia (see Figure 7.1). In September 1999 the Regional Committee for the Western Pacific declared a TB crisis in the region and urged member states to give high priority and to allocate sufficient resources to strengthen TB control. ‘Stop TB in the Western Pacific Region’ was also endorsed as a special project of WHO by the Western Pacific Regional Committee. The Stop TB special project aims to reduce the morbidity and mortality due to TB in the region by half within 10 years.

As part of the Stop TB project the Committee has outlined four key areas:

- directly observed therapy short course (DOTS) implementation
- health sector development
- drug supply and quality
- monitoring and evaluation.

They have set targets of an 85% cure rate and 70% case detection rate in the region, and co-ordinate data on new cases and incidence rates. WHO-WPR has also produced guidelines for the control of TB through DOTS strategy in Pacific countries.

NZAID is a semi-autonomous agency of the Ministry of Foreign Affairs and Trade superseding New Zealand’s Official Development Assistance Programme (NZODA). NZAID’s purpose is to secure lasting improvements in the living conditions of poorer people in developing countries. New Zealand’s support is concentrated on Pacific nations and the poorer East and South East Asian countries. Currently, just under half of NZAID is directed to the Pacific.

Further information is available at: http://www.nzaid.govt.nz

### 7.2.12 The Pacific Regional TB Control Project

This is a joint project between SPC and WHO-WPR, with some funding from NZAID. Phase one involved introducing DOTS (see Chapter 5: ‘DOT’) to Kiribati, Samoa, Tonga and the Cook Islands. The goal of phase two of the project is to control TB through extending DOTS in Pacific Island countries and territories (PICT), with a focus on the countries involved in phase one together with Niue, Tokelau and Wallis and Futuna. This phase is due to run for three years, from November 2001 to October 2004.

The five components of phase two are:

1. introduce DOTS to Niue, Tokelau, Wallis and Futuna (the Pacific Regional TB Control Project will conduct baseline studies and assist in the design and implementation of country-specific DOTS strategies)
2. strengthen DOTS strategies in the Cook Islands, Kiribati, Samoa, and Tonga (ie, build on the recently introduced programmes in these areas)
3. provide laboratory staff training and systems development, including the establishment of quality assurance systems (this will be done through an Australian non-government organisation (CHATA), which the SPC helped to develop)

4. support the development of strategies to address TB/HIV co-infection (to be piloted in Kiribati), and help conduct a pre-feasibility study as a first step towards a comprehensive study of TB prevalence in the Pacific

5. recognise the work of SPC and WHO in the area of TB control and DOTS programmes in the Pacific.
7.3 Future developments

As a result of discussions between NZIS and the Ministry of Health, a number of changes to TB screening of foreign-born migrants have been proposed, either for direct implementation or for investigation with a view to implementing.

7.3.1 Who to screen

- All people 11 years of age and over from countries with a high incidence of TB planning to stay in New Zealand for more than six months in any three-year period (to exclude re-screening) should be required to undergo TB screening by CXR prior to arrival.
- Immigrants from a low-incidence country (determined by nationality listed in their passport) will not be required to undergo TB screening unless indicated on medical examination. Low-incidence countries will be specifically identified in a list format.
- The term ‘high incidence of TB’ should refer to all countries not specifically listed as a low-incidence country. In practice the term would be used to refer to countries with TB rates of over approximately 20 cases per 100,000. ‘High-incidence’ countries should also include countries where the notification rate is likely to be inaccurately low due to poor diagnosis and notification.
- The government has invested resources into the refugee status determination process so that people claiming asylum in New Zealand now wait no more than six months from the time of application to the time of ultimate acceptance or rejection (down from over two years four years ago). These people will only be screened if their application is successful – unless symptoms warrant earlier investigation.
- Women who are pregnant at the time of their NZIS medical examination (and are therefore currently exempt a CXR) should be required to undergo a CXR after the birth of their child. This could be done by inserting an alert in the medical warning system section of the National Health Index (NHI) number of the woman. The Ministry of Health would need to develop a way to insert the alert when a pregnant woman from a high-incidence country first seeks medical attention (and obtains an NHI number).

7.3.2 Where to screen

- NRHSC at the Mangere Refugee Reception Centre should continue to be responsible for full medical examinations and TB screening of quota refugees entering New Zealand.
- Quota refugees will be screened for TB in an approved offshore facility within three months before embarkation to New Zealand. Refugees diagnosed with active TB would be required to undergo treatment prior to travel. The X-ray and treatment notes should accompany refugees to New Zealand to ensure continuation of care and to provide quality review. Refugees will still be required to undergo a full medical examination, and TB screening on arrival in New Zealand. The repeat CXR will provide an audit of the quality of offshore screening, and may not be required once quality is assured.
7.3.3 Quality

- There need to be clear guidelines for NZIS consultant doctors as to what is acceptable on a CXR and what is not.

- All abnormal NZIS CXRs (and their reports) from applicants applying from within New Zealand (even if they are reported as inactive or old TB) should be immediately referred by NZIS, via the Ministry of Health, to the local medical officer of health for follow-up.

- It is important that New Zealand have effective immigration procedures to identify those with active TB at the earliest possible time. Audit and monitoring procedures need to be established to ensure that overseas panel doctors undertake appropriate medical examinations.

7.3.4 Monitoring and review

- Surveillance of HIV/TB co-infection needs improvement (see Chapter 18: ‘Tuberculosis and HIV’).

- TB notification forms to ESR need to be completed, particularly the sections on birth country and length of time since arrival. Additional information such as residency status, type of entry (eg, general skills, Samoan quota, family, quota refugee) and a list of all the countries that the person has lived in for more than one year would be useful for monitoring current screening practice and identifying at-risk groups.

- A review of TB trends and data similar to the one carried for the period 1995–99\(^1\) should be undertaken for the period 2000–04, especially if the screening period is reduced from 24 months to six months. Particular attention should be paid to the country of birth and for how long cases have been in New Zealand.

7.3.5 Resources

- NZIS should investigate increasing their health operations resources. This should include more medical consultants and operations staff as immigration numbers increase.

- The Ministry of Health needs to ensure that there are sufficient funds and resources to cover any increase in screening generated by a change in screening policy.

- Provision should be made for increasing staff levels, space and access to X-ray facilities if a New Zealand Health Undertaking Scheme is introduced. The increased number of people arriving from countries with a high incidence of TB would increase demand on chest clinics, particularly in Auckland but also in Wellington and Christchurch.
The distribution of overseas panel doctors currently contracted to undertake NZIS medical examinations and X-rays should be reviewed in response to demand.

7.3.6 Communication and support

- Primary and secondary health providers need to be informed of TB rates in different countries so that they can be alert to the risk of TB when seeing people who were born in or have resided in countries with a high incidence of TB, especially if there has been recent travel to that country.

- Communication to migrants is the responsibility of NZIS, Ministry of Health, the Office of Ethnic Affairs, and health workers. They need to ensure that the relevant information about TB is supplied to new migrants. The key information that needs to be disseminated is that, if arriving from a country with a high incidence of TB, even if the individual is not found to have TB on CXR screening, this does not mean they will not develop TB later. The symptoms of TB need to be made known, as well as what to do, and that full treatment is available and works, to enable early recognition and treatment.

- The stress associated with moving to a new country coupled with overcrowding can contribute to active TB. New Zealand has improved the settlement process, including provision of adequate housing, education, and access to local cultural and support groups. Ways to support and assist new immigrants should continue to be developed and improved.

7.3.7 Pacific Island region

- The most effective long-term strategy for control of TB in Pacific populations is through control (diagnosis, management, treatment, follow-up and contact tracing) of TB in Pacific countries. This is because Pacific-born people travel frequently between New Zealand and their homeland, and many of New Zealand’s notified TB cases occur in Pacific-born people. Increasing awareness of TB treatment combined with the currently low rate of MDR-TB and HIV infection in most Pacific nations creates an opportune time for action; in particular, DOT, treatment of smear-negative cases, contact tracing and treatment of latent TB infection.

- New Zealand should take a more active role in WHO and SPC programmes for TB control in the Pacific. The specific type of support would need to be determined through discussion with those involved in these programmes, but it may be in the form of training, equipment, etc.

- There needs to be a clearer line of communication between public health units in the different countries with respect to the management of mobile TB cases and contact tracing.

- Education and information about TB needs to be provided in an appropriate format to Pacific peoples living in New Zealand (particularly those living in urban centres) about the lifelong risk of TB, signs and symptoms, and (most importantly) seeing a doctor for treatment, as TB is a treatable disease.
7.3.8 Health undertaking

A feasibility study into the introduction of a health undertaking scheme for TB should be undertaken. This will examine current resources, the projected number of undertakings issued and the distribution of these immigrants, together with a strategy to ensure that immigrants contact the service.

7.3.9 General conclusions

We need to improve TB screening policy and practice because the number of people entering New Zealand from countries with a high incidence of TB is increasing, as is the number of TB cases in foreign-born people in New Zealand. Suggested changes to screening include:

- reducing the age and duration of stay at which screening occurs
- limiting screening to those from high-incidence countries
- improving communication at all levels (this means communicating the reasons for screening to those applying for entry to New Zealand, communicating the importance of adhering to treatment if TB is diagnosed, the importance of identifying close contacts and communicating the risk to them, communicating to primary care providers and immigrants the long-term risk of TB if from a high-incidence country, and communication between countries, particularly Pacific nations when a person with TB is intending to travel).

If the length of stay allowed in the country without screening is reduced from 24 months to six months, this will increase the number of TB screening tests performed offshore. It will become vital for the NZIS and the Ministry of Health to ensure that quality screening occurs. While some steps have been recently introduced, such as radiologists signing the X-rays, quality can only be assured through audit and review.
References


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Chapter 8: BCG Vaccination

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Summary

This chapter provides recommendations for the use of Bacille Calmette-Guérin (BCG) vaccination. It should be read in conjunction with the *Immunisation Handbook 2002.*

The use of BCG vaccination to protect against TB is controversial because studies have shown variable efficacy. BCG’s principal value lies in preventing severe disease, including disseminated and meningitis in young children. It continues to have a role as a neonatal vaccine.

There remain many unanswered questions regarding BCG efficacy in other age groups, but it seems that until better vaccines become available BCG use should be considered only in high-risk adult groups. BCG vaccination has only a small role in reducing the population incidence and transmission of TB.

Neonatal BCG

Neonatal BCG should be offered to infants at increased risk of TB, defined as those who:
- will be living in a house or whānau with a person with either current TB or a past history of TB
- have one or both parents who identify as being Pacific people
- have parents or household members who have lived for a period of six months or longer within the last five years in countries where there is a high incidence of TB*
- during their first five years will be living for three months or longer in a high-incidence country.*

A caregiver’s request should not in itself be accepted as an indication for vaccination: caregivers of infants should be referred to a medical practitioner or the local medical officer of health if BCG is sought and the baby does not meet the above criteria.

BCG can be administered safely with other childhood vaccines.

Medical officers of health and other health care providers should liaise to ensure that:
- neonates at risk are identified and vaccinated
- documentation of vaccinations is sent to the medical officer of health
- documentation of side-effects is sent to the medical officer of health.

If vaccination is not done in hospital, it should be arranged through the local medical officer of health. Children who have missed vaccination at birth should be vaccinated at any time up to the age of five years. Mantoux testing before vaccination is necessary for all children over the age of 12 weeks to detect whether they have already been infected.

BCG for other groups

BCG vaccination should be considered for:
- contacts aged less than five years of active TB cases
- immigrants aged less than five years from high-incidence countries
- health care workers at high risk of TB exposure.

Vaccination is recommended only for those who:
- work in a clinical capacity with known TB patients

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* All countries except Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Holland, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, New Zealand, Norway, Slovakia, Sweden, Switzerland, United Kingdom and the United States of America.
- work in a mycobacteriology laboratory
- work in an adult general medical inpatient facility in areas with a relatively high incidence (eg, Auckland), or other centres where there may be an outbreak
- are planning to travel to work in health care facilities in high-incidence countries
- are likely to be exposed to multi-drug-resistant TB.

BCG vaccination is unnecessary in most travellers. It is more useful to ensure that a pre- and post-travel Mantoux test is documented, and to carry out investigations and treatment for disease or latent TB infection in the event of Mantoux conversion.

**Adverse reactions / contraindications**

- Localised adverse reactions are common, but serious long-term complications are rare.
- The risk of suppurative lymphadenitis is more common among newborns than in older infants and children.
- The most serious complication of BCG vaccination is disseminated BCG infection. Nearly all reported cases have been in immuno-compromised patients.
- Adverse reactions will usually resolve spontaneously.
- BCG is contraindicated in people receiving immunosuppressive drugs or have immunosuppressive conditions, including HIV.
Introduction

This chapter provides recommendations for the use of Bacille Calmette-Guérin (BCG) vaccination. It also examines the information that led to different policies being used in various countries. The evidence for recommending continuation of limited BCG vaccination in New Zealand is also reviewed, and new guidelines for the use of BCG in New Zealand are presented.

Vaccinators and all health care workers who advise people about BCG vaccination should be familiar with the chapter on TB in the *Immunisation Handbook 2002*.\(^1\)

Details for administering the vaccine may be found in the *Technical Guidelines for Tuberculin Testing and BCG Vaccination 1996*.\(^2\) Only trained vaccinators who have been gazetted by the Director-General of Health (Tuberculosis Regulations 1951) are permitted to perform BCG vaccination. Vaccination for the purpose of preventing TB may not be performed by others. Application for gazetting is made through the local medical officer of health.
8.1 Background

BCG vaccine was developed by two French researchers in the early 1900s, who used a strain of *Mycobacterium bovis* and attenuated it. By 1915 the attenuated strain had been given to cows and protection from TB had been demonstrated. Over the next 13 years the vaccine was tested in multiple different animal species. No evidence of reversion to virulence was detected, and the vaccine was found to confer resistance to challenge with virulent tubercle bacilli.

The BCG vaccine was first given to a human in 1921. Since that time more people have received BCG vaccine than any other vaccine. Approximately 100 million children receive this vaccine each year. In the 1950s major trials using different vaccine strains were set up by the British Medical Research Council and the United States Public Health Service to determine evidence of efficacy of BCG vaccine. High efficacy against TB was seen in the trials organised by the British Medical Research Council with BCG vaccination given to tuberculin-negative adolescents. However, this was not the case in the US, where BCG vaccination was given to tuberculin-negative people of all ages and found to provide very little protection. The UK proceeded to recommend routine vaccination in adolescents. The US restricted the use of BCG vaccination to high-risk groups.

Since that time BCG has been taken up by most countries. BCG was incorporated into the WHO Expanded Programme of Immunization (EPI) infant vaccination schedule in 1974.
8.2 Immunisation policies

8.2.1 Examples of policies in different parts of the world

BCG vaccination policies differ greatly between different countries. Details of some of the policies currently implemented worldwide include:\(^5\)

- BCG only at birth – this is currently recommended by the WHO EPI and the WHO Global Tuberculosis Programme, and is the policy in most of the world, particularly developing countries
- BCG once in childhood – this policy has been in use in the UK for many years, along with selective vaccination of tuberculin-negative adolescents
- repeated/booster BCG – in Eastern Europe BCG is recommended up to five times in some countries (the criteria for revaccination differs between countries)
- no routine BCG – this has always been a policy in the US and the Netherlands, but a number of other countries have also been moving to this in recent years. BCG is still recommended in high-risk groups.

Implementation of these policies varies across countries, based on regional differences in TB, differences in health systems, and local history.

8.2.2 Discontinuation of population-based BCG vaccination

The International Union against Tuberculosis and Lung Disease (IUATLD) has suggested criteria under which it may be reasonable for a country to shift from routine BCG vaccination to selective vaccination of high-risk groups.\(^5\) The IUATLD recommends that BCG be discontinued only if:

- an efficient notification system is in place, and either
  - the average annual notification rate of smear-positive pulmonary TB is less than 5 per 100,000, or
  - the average annual notification rate of TB meningitis in children under five years of age is less than 1 per 10 million population over the previous five years, or
  - the average annual risk of TB infection is less than 0.1%.

8.2.3 Mass neonatal BCG immunisation programmes

These have been implemented in many countries. Several countries have modified their original mass neonatal BCG vaccination programmes, with varying results.

A recent study from Spain, where BCG vaccination was discontinued in 1987, found little subsequent effect on childhood TB.\(^9\) Sweden discontinued mass BCG vaccination in 1975 but continued a selective BCG programme for high-risk neonates. This selective programme was initially implemented poorly but was later improved. For children born to Swedish parents the rate of TB remained low. However, there was a large increase in TB incidence in children born to foreign parents (from 2.6/100,000 to 39.4/100,000 children),
particularly in the years when the selective immunisation programme was poorly instituted.\textsuperscript{10}

A similar change in BCG programme occurred in the Czech Republic in 1986. A review of this change after six years concluded that continuation of a selective BCG programme is required for high-risk infants.\textsuperscript{11}
8.3 Efficacy of BCG

BCG does not prevent infection, but may prevent or modify the development of disease, offering protection against severe or disseminated forms of TB. The efficacy of BCG vaccination against TB is controversial. There have been many studies, controlled trials, case control and cohort studies evaluating the protective efficacy of BCG in different populations throughout the world over many years. Variable efficacy has been found. However, the results consistently demonstrate BCG’s ability to protect against severe childhood TB.

8.3.1 Childhood TB

The efficacy of neonatal BCG was established in the 1950s in two large randomised controlled trials (RCTs) demonstrating a 68–75% reduction in morbidity. A Harvard meta-analysis of published literature of the efficacy of BCG in newborns and infants demonstrated a protective efficacy of vaccination against the development of TB at all sites of 74% (95% CI, 0.62–0.83) for RCTs, but only 52% (95% CI, 0.38–0.64) when estimated from case control studies. However, there was greater protective efficacy demonstrated for death of 65% (95% CI, 0.12–0.86), for meningeal TB of 64% (95% CI, 0.30–0.82) and for disseminated TB of 78% (95% CI, 0.58–0.88).

Two further meta-analyses that evaluated all studies regardless of age also found a protective effect against meningeal and disseminated disease as well as death. It is well recognised that meningeal and miliary disease are more common in infants than in adults. Evidence of protection against pulmonary disease in children is less consistent.

It is now generally considered that BCG’s principal value lies in preventing severe disease in young children, and that it has had little effect in reducing the population incidence and transmission of TB.

8.3.2 Adult pulmonary TB

Many trials evaluating BCG efficacy for adults were conducted from the 1930s through to the 1980s. All had differences in eligibility criteria, methods of disease surveillance, diagnostic criteria, vaccine strain and administration and environmental factors. A wide range of efficacies was found, ranging from 0 to 80%. The majority of these trials evaluated protective efficacy against pulmonary TB. A variety of reasons for these differences in efficacy have been proposed and there have been a number of in-depth evaluations of these results as well as one comprehensive meta-analysis. This Harvard meta-analysis determined a protective efficacy of 51% in the trials and 50% protective effect from the case-controlled studies.

Overall, there remain many unanswered questions regarding BCG efficacy, but it seems that until better vaccines become available BCG use should be considered only in high-risk adult groups. These criteria are discussed in detail later.
8.3.3 Duration of protection provided by BCG

The length of duration of protection after BCG vaccination is unclear. The evidence appears to suggest that BCG provides protection for 10 years, but studies evaluating protection after this time period find differing results. Al Kassimi et al, who evaluated 537 cases and 5756 controls, found waning immunity at 20 years (Table 8.1).\(^\text{19}\) The protective effect at 25–34 years post-vaccination dropped to 20\% and the vaccine ceased to provide any protection 25 years post-vaccination. However, in a review of a number of trials with observation periods up to 15 years, in seven of nine controlled trials the efficacy did not change over that time period.\(^\text{20}\) It is speculated that immunity declines over time and is markedly reduced by 10–20 years after vaccination.\(^\text{3}\)

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<tr>
<th>Years since vaccination</th>
<th>Relative risk (confidence intervals)</th>
<th>Protection (confidence intervals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5–14</td>
<td>0.174 (0.069–0.44)</td>
<td>82 (55,93)</td>
</tr>
<tr>
<td>15–24</td>
<td>0.327 (0.174–0.612)</td>
<td>67 (55,77)</td>
</tr>
<tr>
<td>25–34</td>
<td>0.798 (0.395–1.023)</td>
<td>20 (-6.37)</td>
</tr>
</tbody>
</table>

Source: Al Kassimi\(^\text{19}\)

8.3.4 Can the efficacy of vaccination be assessed for individuals?

The answer to this question is ‘no’, for all practical purposes. Special immunological testing might, in theory, give some idea. However, the tuberculin (Mantoux) skin-test response does not show whether protective immunity has been stimulated or not (see Chapter 2: ‘Mantoux Testing’). The development of a local infection and subsequent scarring merely shows that tissue infection (or possibly an allergic reaction to the vaccinating material) has occurred.

Nevertheless, the literature on efficacy discussed earlier shows that protective immunity after BCG vaccination of neonates and small children is expected in a majority, despite the fact that there is no test available to assess the level of individual protection.

8.3.5 Are repeat BCG vaccinations ever required?

No boosters are recommended in New Zealand. In some countries there has been widespread use of boosters, but there is little evidence to support this.\(^\text{5}\) A case control trial in Chile\(^\text{21}\) evaluated the role of repeated BCG vaccination in increasing protective efficacy among 68 15–35-year-old patients with TB. The authors found no evidence for increased protection with increased number of BCG scars. A controlled trial in Malawi evaluating a second dose of BCG vaccine found no evidence of increased protection against TB.\(^\text{22}\) On the basis of this and other data,\(^\text{23,24}\) the WHO\(^\text{25}\) state that ‘The effectiveness of repeat vaccination is unknown so no more than one vaccination should be given in a lifetime’. The Tuberculosis Working Group support this recommendation.
Often it is uncertain whether an individual has been previously vaccinated or not. Previous BCG vaccination is defined as documented evidence of a BCG vaccination (including date), or history of BCG vaccination supported by a compatible scar. A compatible scar is considered to be one of at least 4 mm diameter at a likely site. The scar is usually at the insertion of the deltoid, but it may be elsewhere, such as scapula, thigh or buttock. Persons not meeting these criteria may be offered a vaccination. Inadvertent repeat vaccination is not harmful.
8.4 Neonatal BCG Vaccination

8.4.1 The need for continuing selective vaccination of neonates

BCG immunisation was first introduced to New Zealand in 1948 and was later extended to all adolescents. With declining population incidence of TB, the adolescent BCG programme was discontinued in the South Island in 1963 and phased out in the North Island by 1990. A neonatal BCG programme was initiated in New Zealand in 1976, initially in high-risk districts, and later extended to targeted populations. This programme has been variably implemented.

There has been no decline in the total population rate of TB in New Zealand in the last 20 years, and it is still one of the most common notifiable infectious diseases. There has been a decline in incidence of TB in the Māori population, and a corresponding rise in TB in ‘Other’ ethnic groups (particularly Asian and African), whose numbers in New Zealand have increased over recent years (see Chapter 1: ‘Epidemiology and Surveillance’).

Over the last decade there has been little change in the incidence of TB in those under 15 years, apart from a rise in 1998–99. There has also been little reduction in meningeal and miliary disease in children over this last decade (see Figure 8.1). Pacific, African and Asian children are disproportionately affected. Furthermore, New Zealand does not meet IUATLD criteria for discontinuing BCG vaccination.

These observations suggest there is still a need for an infant BCG programme targeted at high-risk groups in New Zealand.
8.4.2 Eligibility criteria for neonatal BCG vaccination in New Zealand

Neonatal BCG should be offered to infants at increased risk of TB, defined as those who:

- will be living in a house or whānau with a person with either current TB or a past history of TB
- have one or both parents who identify as being Pacific people
- have parents or household members who have lived for a period of six months or longer within the last five years in countries where there is a high incidence of TB
- during their first five years will be living for three months or longer in a high-incidence country.

High-incidence countries are all countries except Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Holland, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, New Zealand, Norway, Slovakia, Sweden, Switzerland, UK and the US.
Vaccination is usually advisable if the parent or household member is foreign-born and has spent at least six months in a high-incidence country within the past five years. The decision is not so clear-cut when the adult is a New Zealand resident who has travelled to a high-incidence country. The vaccinator must assess the adult’s actual risk of exposure to TB during the past five years. For example, it is reasonable not to vaccinate the baby of a business person who has spent a year in a Hong Kong bank with a low risk of TB exposure. On the other hand, a baby living with a person who has returned recently from six months’ volunteer work in a poor rural Indian community should be vaccinated.

Vaccination may even be appropriate for a baby living with an adult who has travelled to a high-risk setting (eg, providing patient care in a hospital in a high-incidence country) for less than six months in the past five years. In cases where there is difficulty assessing the level of risk, advice should be sought from the medical officer of health. Mantoux testing the adult concerned may help to clarify the risk to the baby.

The low-incidence countries listed above have been selected because their national rate reported to WHO is less than New Zealand’s rate of 10.3 per 100,000.

8.4.3 Caregiver’s request
This in itself should not be accepted as an indication for vaccination. Caregivers of infants who do not meet the above criteria should be referred to a medical practitioner or the local medical officer of health to discuss the risks and benefits of vaccination before a final decision is made.

8.4.4 Practical considerations with neonatal BCG vaccination
BCG can be administered safely with other childhood vaccines. There is no evidence to suggest that an interval of three weeks is needed between the administration of BCG vaccination and any other live vaccines not given concurrently. BCG does not appear to adversely affect the immune response to other childhood vaccinations given simultaneously, although this is based on data from one study only. This study in Zaire evaluated responses to DTP and polio in HIV-infected children given BCG vaccination, and found no decrease in immune response to these immunisations.

8.4.5 Unvaccinated baby exposed to TB
If a baby has not been vaccinated before leaving hospital and there is a history of current TB in someone who has contact with the baby, do not vaccinate immediately. Withhold vaccination, conduct Mantoux testing, seek paediatric advice and vaccinate only after the possibility of infection in the baby has been excluded. Vaccination of an infected baby:
- may not protect the baby from incubating disease
- may prevent the Mantoux test from assisting with diagnosis of the disease.
8.4.6 Delayed vaccination of premature infants

Infants born prematurely (prior to 34 weeks’ gestation) should have their BCG vaccination delayed until 34 weeks post-conceptional age. Babies born after this age or with low birthweight appear to produce an adequate response based on tuberculin skin-test responses. These studies are all limited by the fact that the tuberculin skin test is an unsatisfactory measure of protection afforded by BCG. There are no studies in premature infants of vaccine efficacy using disease as outcome.

8.4.7 Vaccination in hospital or the community?

Neonates at risk should be identified antenatally by GPs and lead maternity carers (LMCs). The advantages and disadvantages of in-hospital versus community vaccination are summarised in Table 8.2.

Table 8.2: In-hospital versus community vaccination

<table>
<thead>
<tr>
<th>Hospital service</th>
<th>Community clinic service</th>
</tr>
</thead>
<tbody>
<tr>
<td>Captive baby: potentially higher coverage</td>
<td>Lower cost per vaccination</td>
</tr>
<tr>
<td>Protection at the earliest possible time</td>
<td>Public health office history of provision</td>
</tr>
<tr>
<td>Can access unmotivated new mothers (and their babies)</td>
<td>Difficult access for clients</td>
</tr>
<tr>
<td>LMC providers do not assess eligibility reliably, and do not provide vaccination reliably</td>
<td>Delay may result in need for pre-vaccinal Mantoux testing and delayed protection</td>
</tr>
<tr>
<td>High vaccinator turnover if midwives, not public health, are the vaccinators</td>
<td>Lower coverage and high non-attendance rate</td>
</tr>
<tr>
<td>Higher cost than community clinic vaccination</td>
<td>Stressful time for mother to give consent</td>
</tr>
<tr>
<td>Stressful time for mother to give consent</td>
<td></td>
</tr>
</tbody>
</table>

On balance, vaccination in hospital is recommended as preferable.

A pilot programme of in-hospital BCG administration was trialed at Middlemore Hospital under the supervision of public health. It required intensive staff commitment, but achieved excellent results, with risk assessment of 83% of babies targeted and vaccination of 88% of those considered eligible. LMCs were encouraged to take over the responsibility of assessing the baby’s TB risk. This report concluded that the programme could operate successfully if LMCs carry out risk assessment, and a regional provider of vaccination services delivers the actual vaccination. However, it is limited by higher costs than provision of BCG vaccination in community clinics or by GPs, and requires close monitoring.
If vaccination is not done in hospital, it should be arranged through the local medical officer of health. Children who have missed vaccination at birth should be vaccinated at any time up to the age of five years. Mantoux testing before vaccination is necessary for all children over the age of 12 weeks to detect whether they have already been infected.

### 8.4.8 Data collection and surveillance

The steps involved in neonatal BCG vaccination, data collection and monitoring are shown in Figure 8.2.

Medical officers of health and other health care providers should liaise to ensure that:

- neonates at risk are identified and vaccinated
- documentation of vaccinations is sent to the local medical officer of health
- documentation of side-effects is sent to the local medical officer of health.

An adequate immunisation coverage measurement requires the numbers of infants meeting the above criteria to be recorded, as well as the numbers actually receiving vaccine. Each district should establish such a system, with results collated at a national level. The documentation of numbers of vaccinations given in each district will also facilitate the monitoring of `adverse events`, which is an essential part of the programme. This has not been achieved in most districts.

Ideally there should also be surveillance of the number of babies (by ethnic group) not meeting the criteria. Periodic review of the proportions of each ethnic group that meet the criteria will give some insights into the extent to which the criteria are being correctly applied in each health district (see Figure 8.2).
**Figure 8.2:** Framework for monitoring neonatal BCG programme

- **Antenatal interview**
  - Will baby meet criteria?
    - Yes
      - Mother consents to vaccination
        - Yes
        - BCG delivered in maternity unit
          - Yes
          - Consent form sent for adverse events surveillance and coverage monitoring
          - Total no. of BCGs given is collected
            - Numerator
            - Adverse event rate
          - Denominator
          - Adverse event rate
        - No
          - Consent form sent to medical officer of health for coverage monitoring
          - Consent form sent for community vaccination
        - No
          - BCG delivered in community
        - Yes
      - No
    - No
  - Count the numbers by ethnic group and calculate rates of babies not meeting the criteria

- **Postnatal vaccination**
  - Yes
  - Consent form sent for adverse events surveillance and coverage monitoring
  - No
  - Consent form sent to medical officer of health for coverage monitoring

- **Community follow-up**
  - Adverse event reports directly from medical practitioners or via CARM* (Dunedin)
  - Yes
  - Consent form sent for adverse events surveillance and coverage monitoring
  - No
  - BCG delivered in community
  - Yes
  - Consent form sent to medical officer of health for coverage monitoring
  - No
  - Consent form sent for community vaccination

---

**8.4.9 The cost-effectiveness of neonatal BCG**

There is little published work on the cost-effectiveness of BCG vaccination. A recent economic evaluation from Japan of universal neonatal BCG found that the costs were heavily dependent on estimated vaccine efficacy used.\(^{34}\) There are no published cost–benefit analyses on selected BCG vaccination programmes targeted at high-risk groups. A cost–benefit assessment of selective vaccination policy in New Zealand would be very useful.
8.5 Other groups eligible for BCG vaccination

BCG vaccination may be considered in groups other than neonates, as shown below.

8.5.1 Indications for BCG vaccination in people other than neonates

BCG should be offered to the following persons at risk if they have not had a previous BCG vaccination and if a pre-vaccination STU Mantoux reaction is negative (less than 5 mm).

1 Contacts aged less than five years of active TB cases

Note that a contact exposed to TB in the preceding three months will need two negative Mantoux tests, in order to test for conversion before vaccination. The second Mantoux test should be placed no earlier than eight weeks after the date of the last exposure to the untreated source case.

2 Immigrants aged less than five years from high-incidence countries

3 Health care workers at high risk of TB exposure

A baseline two-step Mantoux test is essential before health care workers have contact with patients or infectious materials (see Chapter 2: ‘Mantoux Testing’). Vaccination is recommended only for those who:

- work in a clinical capacity with known TB patients
- work in a mycobacteriology laboratory
- work in an adult general medical inpatient facility in areas with a relatively high incidence (eg, Auckland), or other centres where there may be an outbreak
- are planning to travel to work in health care facilities in high-incidence countries
- are likely to be exposed to multi-drug-resistant TB.

4 Specific populations with high risk

The medical officer of health may recommend vaccination programmes for specific populations with high risk of TB, depending on local epidemiology. Staff and residents of rest homes, prisons and other closed populations may be recommended to have vaccination, from time to time, depending on local epidemiology and in consultation with the medical officer of health.

* BCG should be given as soon as pre-vaccinal Mantoux testing is completed and found to be negative (<5 mm). If it is not given within four weeks of the negative tuberculin test, then tuberculin testing should be repeated.
8.5.2 Age cut-off for BCG vaccination

The relationship between vaccine efficacy and age at vaccination remains unclear. The age at vaccination did not appear to explain much of the variation in vaccine efficacy in the Harvard meta-analysis. Among the seven prospective trials that enrolled patients randomly, the estimated protective efficacy was 85% for BCG vaccination at birth, 73% for vaccination at age 10 years, and 50% for vaccination at age 20. However, for the entire meta-analysis, mean age at vaccination accounted for only 6% of between-study variance. Fifteen-year follow-up from the very large BCG field trial co-sponsored by the Indian Council of Medical Research, the WHO and the US Public Health Service (commonly known as the Chingleput trial) has demonstrated that in the older age group, risk of disease was greater among the recipients of the BCG vaccine compared with controls.

The value of vaccinating older children and adults remains unclear. For this reason the Ministry of Health’s Tuberculosis Working Party has elected to reduce the age cut-off for BCG vaccination from 35 years (in the 1996 Guidelines for Tuberculosis Control in New Zealand) to five years, with the exceptions discussed above in 8.5.1.

8.5.3 BCG in health care workers

Assessment of the efficacy of BCG in specific risk groups has been limited. A review article on risk of transmission of TB to health care workers concludes that the current risk varies among health care workers and within institutions (see Chapter 9: ‘Infection Control’).

What is the best policy to reduce risks for health care workers? The alternatives are regular tuberculin skin testing (with treatment for latent TB infection (LTBI) in reactors) or BCG vaccination. Efficacy of BCG in health care workers was reviewed in the Harvard meta-analysis. The authors concluded that all the studies evaluating this had limitations, particularly methodological problems, and the studies were unable to be analysed together. Despite these limitations, the cohort studies they reviewed indicated that the rates of TB had been substantially lower among health care workers receiving BCG than among unvaccinated health care workers with negative tuberculin test.

Overall the papers reviewed suggest that vaccination with BCG may be protective in health care workers whose tuberculin tests are negative. US investigators performed a decision analysis to determine the optimal strategy to prevent TB in health care workers with a negative tuberculin test. They compared BCG vaccination or annual tuberculin skin tests (with treatment for LTBI in reactors) in skin-test-negative health care workers, and evaluated outcome measures of number of cases and deaths from TB and BCG and/or isoniazid adverse reactions over 10 years. They found that measures flowing on from annual tuberculin testing decreased the number of TB cases by 9% and BCG vaccination decreased the number by 49% relative to no prevention intervention. This is based on a number of assumptions, including a workplace incidence of Mycobacterium tuberculosis infection greater than 0.06% per year.
An earlier study using decision analysis evaluated the role of BCG in tuberculin-negative house staff and medical students.\textsuperscript{40} It concluded that if BCG has an efficacy rate of at least 13.1%, BCG should be considered for this group of health care workers working in high-risk areas.

The reasons put forward against BCG vaccine include:

- incomplete protection – variations in vaccine efficacy have been widely documented in adults (as discussed previously) and are a significant limitation to the use of this vaccine
- side-effects of vaccination – see below under 8.7: ‘Adverse reactions to BCG vaccination’
- difficulty interpreting the tuberculin test (and consequent difficulty in diagnosing new infections) after vaccination.\textsuperscript{41}

The role of BCG in protecting health care workers remains unclear, but it seems that it should be considered in the health care worker at higher risk of TB exposure, as described in 8.5.1. All other personnel should have the risks and benefits fully discussed before considering vaccination. Two-step baseline Mantoux testing and serial follow-up Mantoux testing may be more appropriate than vaccination for most health care workers.

### 8.5.4 BCG in travellers

BCG vaccination is unnecessary in most travellers. Vaccination for overseas travel, even prolonged travel in high-incidence areas (eg, exchange students), should be discouraged (see Chapter 10: ‘TB Control in Non-clinical Settings’). It is more useful to ensure that a pre- and post-travel Mantoux test is documented, and to carry out investigations and treatment for disease or LTBI in the event of Mantoux conversion.

Vaccination should, however, be considered in:

- a child aged less than five years travelling for three months or longer to a high-incidence country
- an unvaccinated health care worker (regardless of age) who is going to work in a health care facility in a high-incidence country
- travellers to areas with a high incidence of multi-drug-resistant TB.

### 8.5.5 BCG for occupational groups other than health care workers

BCG is not recommended for any other occupational groups. For occupational groups at risk of TB, Mantoux surveillance without vaccination is recommended (see Chapter 10: ‘TB Control in Non-clinical Settings’).
8.6 Follow-up after BCG vaccination

BCG vaccination will almost invariably result in tuberculin conversion, with a positive skin test developing after vaccination. These tuberculin reactions will then wane, more rapidly in individuals given the vaccine in the neonatal period.20 However, as there is no evidence relating the degree of protection to either the size of any subsequent Mantoux reaction or to the presence or absence of any scar formation,42 follow-up tuberculin testing after vaccination is not recommended.19 Once an individual has been vaccinated, there is no reliable way to distinguish tuberculin reactions caused by BCG from those caused by natural infection.43
8.7 Adverse reactions to BCG vaccination

8.7.1 Incidence of adverse reactions

Localised adverse reactions are common, but serious long-term complications are rare. Side-effects are reported to occur in 1–10% of vaccinated people. Reactions expected after vaccination include axillary or cervical adenopathy and induration, and pustule formation at the injection site. These can persist for three months after vaccination and usually occur within a few weeks to months after vaccination, but symptoms may rarely be delayed for months in the immunologically normal patient, and years in the immuno-compromised patient.

Local ulceration and regional lymphadenitis are the most common complications. A minor degree of adenitis in the weeks following vaccination should not be regarded as a complication. More severe local reactions include ulceration, caseous lesions or drainage at the vaccination site, and regional suppurative lymphadenitis with draining sinuses.

Adverse reactions seem more frequent and severe in adults. One widely quoted study evaluated 20 adult patients receiving BCG, all of whom developed local effects of erythema, induration and tenderness at the site of vaccination. Local ulceration with drainage occurred in 14.

The risk of suppurative lymphadenitis is more common among newborns than in older infants and children (Table 8.3). Severe injection site reactions, large ulcers and abscesses are more common after inadvertent subcutaneous injection. Vaccination of individuals who are tuberculin-positive may also give rise to such reactions. Individuals with LTBI may have an accelerated response to BCG vaccine, characterised by induration within one to two days, scab formation, and healing within 10 to 15 days.

Table 8.3: Age-specific estimated risks for complications after administration of BCG vaccine

<table>
<thead>
<tr>
<th>Complication</th>
<th>Incidence per million vaccinations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age &lt; 1 year</td>
</tr>
<tr>
<td>Local subcutaneous abscess, regional lymphadenopathy</td>
<td>387</td>
</tr>
<tr>
<td>Musculoskeletal lesions</td>
<td>0.39–0.89</td>
</tr>
<tr>
<td>Multiple lymphadenitis, non-fatal disseminated lesions</td>
<td>0.31–0.39</td>
</tr>
<tr>
<td>Fatal disseminated lesions</td>
<td>0.19–1.56</td>
</tr>
</tbody>
</table>

Source: Lotte

Keloid scars at the injection site, although not uncommon, are largely avoidable. Some sites are more prone to keloid formation than others, and vaccinators should adhere to the site recommended (mid-upper arm). Most experience has been with the upper arm site and it is known that the risk of keloid formation increases greatly if the injection is given higher than the insertion of the deltoid muscle into the humerus.
Rarely, osteitis and osteomyelitis, lupoid and other types of skin disorders and neurological disorders have been reported following BCG vaccination.\textsuperscript{144}

The most serious complication of BCG vaccination is disseminated BCG infection. Nearly all reported cases have been in immuno-compromised patients. Fatal disseminated BCG disease is rare (Table 8.3).

The incidence of adverse reactions to BCG vaccination in New Zealand is probably under-reported because it is subject to passive surveillance only. Between 1965 and 2001, in New Zealand, the Centres for Adverse Reactions Monitoring has recorded 124 adverse events (91 cases) following BCG vaccination. These include injection site reactions (including abscess), lymphadenopathy, skin reactions, alimentary, anaphylaxis, and other reactions.

A recent prospective study of BCG adverse events in Australia evaluated 918 subjects (545 children) and found adverse reactions reported in 45 vaccinees (5%).\textsuperscript{47} There were 53 adverse reactions reported in these patients, which included 23 injection site abscesses (2.5%), 14 severe local reactions (1.5%), and lymphadenitis in 10 (1%). No severe adverse reactions were seen, with only 1% requiring medical attention. Injection site abscess and local reactions were more common in older vaccinees. This study also found significant under-reporting to the passive surveillance system during this study period. There were only 20 reports of adverse events in the same time period.

**8.7.2 Management of adverse reactions**

Adverse reactions will usually resolve spontaneously. Every effort should be made to identify the causative organism from any lesion constituting a serious complication. Treatment recommendations for local abscess formation and suppurative lymphadenitis remain controversial.\textsuperscript{48} Medical therapy offers no more than observation, but there may rarely be a role for surgical drainage. For persistent reactions with fever, marked regional adenopathy and local disease, specialist advice should be sought before considering whether to treat what is, in effect, BCG disease, with rifampicin and isoniazid. It is important that all complications are recorded and serious cases referred to a physician.

**8.7.3 Reporting of adverse reactions**

Abscesses and more serious complications should be reported to the local medical officer of health, in the interests of quality control of BCG vaccine and vaccination technique. This is particularly important as side-effects are recognised as varying by vaccine strain.

Adverse events should also be reported to:

- The Medical Assessor
- Centre for Adverse Reactions Monitoring
- PO Box 913 (Freepost No. 112002)
- Dunedin

on reply-paid postcard H1574, with the patient’s/guardian’s consent. If the patient or guardian does not consent, the report should be made without personal identification.
8.8 Contraindications to BCG vaccination

BCG vaccine should not be given to those people:\(^\text{13.5}\)

- whose immunological responses have been suppressed by corticosteroids, other immunosuppressive treatment, or radiotherapy
- whose immunological responses are impaired by generalised malignant conditions, lymphoma, leukaemia, HIV infection (see Chapter 18: ‘Tuberculosis and HIV’), congenital or acquired immune deficiency
- with a past history of TB
- with a Mantoux reaction \(^\text{2} \ 5\) mm
- with significant fever
- with generalised septic skin conditions (in the case of eczema, a vaccination site free of skin lesions should be chosen)
- in groups at high risk of HIV infection (e.g., neonate born to a mother known to be HIV infected: BCG should be withheld until HIV status is determined – see Chapter 18: ‘Tuberculosis and HIV’)
- who are neonates in a household where an active TB case is suspected or confirmed (see 8.4.5: ‘Unvaccinated baby exposed to TB’).

Vaccination may be deferred in pregnancy – BCG vaccination is never an urgent measure. (This is a precaution only, as no harmful effects to the foetus have been observed following vaccination during pregnancy).
8.9 Other roles for BCG vaccine

BCG has also been found to be protective against leprosy.\textsuperscript{5} This has been confirmed in a number of controlled and observational studies.

Other uses for BCG vaccination as a form of immunotherapy have been evaluated over the last decade, with varying success. One highly successful use was in intravesical administration of BCG against superficial bladder carcinoma recurrences or against carcinoma \textit{in situ}.\textsuperscript{49} Immunotherapy with intravesical BCG provides an effective alternative approach to chemotherapy, with reduction in recurrences, and in some cases improves outcome.

An alternative use evaluated for BCG was in prevention of atopy. The observation that the incidence of atopy increased as infectious diseases declined suggested the hypothesis that infections suppress allergic diseases. A number of observational studies evaluating this hypothesis using BCG as a potent adjuvant of induction of cell-mediated immunity and modulator of immune response seemed to support this. A recent careful case-control study from Sweden evaluating this found that early BCG does not affect the development of atopy.\textsuperscript{50} At this time there seems no role for the use of BCG for this purpose.
8.10 Future directions

8.10.1 Future vaccines for TB

The limitations of BCG vaccine have been recognised for many years, but an alternative effective vaccine has not been found. There have been many difficulties developing an effective vaccine against TB due to the antigenic complexity of the Mycobacterium tuberculosis organism, limitations in knowledge of determinants and markers of protective immunity against TB, and the optimal way to deliver vaccine.⁴ ⁵ There is an urgent need to identify some correlate of natural and vaccine-derived protective immunity.

New approaches to developing an alternative TB vaccination tried in recent years include:

- plasmid DNA vector-based vaccines
- recombinant and mutant BCG vaccines that use BCG as the vector itself
- sub-unit vaccines created from cell-wall antigens
- live attenuated Mycobacterium tuberculosis.

The design of immunogenicity and feasibility studies, and eventually controlled trials, will need careful planning and implementation to avoid difficulties experienced in the past.⁵¹

8.10.2 Data collection

There is a need for accurate data collection on implementation of the selective neonatal BCG programme, with collection of numerator (those receiving BCG) and denominator (those eligible for vaccination) data in all regions. This data, along with incidence data, is essential to evaluate the usefulness of this programme. There is a lack of cost–benefit data on implementation of this selective neonatal BCG vaccination policy and consideration should be given to initiating such a study.

There needs to be active collection of adverse events secondary to BCG vaccination if an increase in adverse events is noted through the current passive surveillance system. This may occur particularly if the vaccine strain is changed.

8.10.3 Quality control

The only quality control of BCG vaccination is in the Tuberculosis Regulations 1951. These are out of date and will be reviewed in conjunction with all other regulations which come under the Health Act 1956 and Tuberculosis Act 1948. It is envisaged that these Acts will be revoked and replaced by a revised Public Health Bill/Act. The level of initial training required to become a gazetted vaccinator is less intensive than the standard expected for approval (under the fifth amendment of the Medicines Act by the medical officer of health) of non-medical vaccinators who use other vaccines. There is no ongoing monitoring of vaccinator performance or up-to-date register of vaccinators. Mantoux testing and BCG vaccinator standards should both be covered by the medical officer of health approval which is applied to other vaccines.
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Chapter 9: Infection Control in Tuberculosis

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Further reading
Summary

- TB is a communicable disease which poses a risk to health care workers.
- Patients on treatment may continue to be smear-positive for prolonged periods. Most evidence suggests that patients have significantly reduced infectivity on appropriate treatment, even if they continue to be smear-positive. The major risk for contacts lies in exposure to the infectious case before diagnosis.
- Children under the age of 12 years are rarely infectious. If children are sputum smear-positive, however, they need to be treated with the same precautions as adults.

Isolation of infectious TB

- Isolation of infectious TB is an important public health protection measure. Isolation may take place in hospital or in the community.
- Infectious patients should be isolated in hospital if, in the opinion of hospital or public health staff:
  - they will not comply with the community infection control precautions described below, or
  - they are sufficiently unwell to warrant admission to hospital.
- If the patient is not acutely ill, home isolation and treatment will often be the preferred option. A public health nurse should visit the home within 24 hours of diagnosis and start of treatment, and educate the patient and family about taking precautions to reduce the chance of infecting others.
- Patients with smear-positive pulmonary TB may be removed from isolation if both of the following have been met:
  - there has been a minimum of two weeks’ effective chemotherapy
  - at least two sputum specimens are smear-negative.
- Many patients will have ceased to produce sputum after two weeks’ treatment. They are unlikely to be infectious.

Hospital isolation policy to prevent nosocomial TB

- People who are in hospital should be isolated if pulmonary TB is suspected or has been diagnosed.
- Isolation rooms need negative-pressure ventilation systems.
- Acid-fast bacilli (AFB) smear results should be available within 24 hours, enabling the removal from isolation of those in whom active disease is not confirmed.
- HIV-infected patients should be nursed in separate wards from TB patients.
- Any patient hospitalised with suspected or known infectious pulmonary multi-drug-resistant disease must be transferred to a facility with a negative-pressure ventilation system.
- Infectious TB patients should wear masks when they leave the isolation room for investigations in other parts of the hospital.
- Universal precautions will protect against the (unlikely) possibility of cutaneous transmission of TB from body substances containing Mycobacterium tuberculosis.
- TB wound care requires the wearing of particulate respirators and gloves.
Personal protective equipment

- Health care workers must wear NIOSH-approved (N95) particulate respirators when providing care for adult patients with known or suspected infectious pulmonary TB.

Hospital engineering controls

- Isolation areas require adequate ventilation with direct engineering controls that dilute airborne droplet nuclei containing TB bacilli. Negative-pressure ventilation extracts air and lowers the pressure in the isolation room. This ensures that contaminated air does not flow from the isolation room to clear areas.
- High-efficiency particulate attenuation (HEPA) filtration is essential if air is recirculated within a room used for isolation. Self-contained portable HEPA filtration units are available, but they are prone to short-circuiting of the air flow and are not recommended.
- Ultra-violet germicidal irradiation is used only as a supplement to other dilution systems. However its role remains unclear.
- A programme of regular testing is necessary to ensure that engineering controls of air quality are effective. This should include:
  - monthly smoke tests (these ensure that air-flow direction is as intended)
  - checks that negative-pressure gauges are functioning correctly
  - regular review and replacement of HEPA filters.
- For more information, refer to the Centers for Disease Control web site: http://www.cdc.gov/nchstp/tb/notes/TBN_2_00/training.htm.

Diagnostic procedures with transmission potential

- Aerosol-generating procedures such as bronchoscopy and sputum induction on patients with TB (and certain other infections) should be carried out in respiratory isolation conditions. Particulate respirators should be worn when TB is a possible diagnosis.
- Instruments, such as bronchoscopes and nebulisers, when used for patients with TB and other mycobacterial diseases, should be cleaned and sterilised. Monthly mycobacterial cultures from bronchoscopes are recommended.

Staff screening

Pre-employment

- Health care staff and students should receive pre-employment screening (this is unnecessary in rest homes). Pre-employment screening consists of a pre-employment questionnaire, Mantoux testing and, if appropriate, a CXR.
- Universal use of BCG for staff and students cannot be supported in New Zealand at present because of the comparatively low risk of occupationally acquired TB for most workers. It also has low efficacy in adults and makes the further use of the Mantoux as a diagnostic tool more difficult (see Chapter 8: 'BCG Vaccination').
- However, where the risk is higher than usual, as in those working in units where unsuspected cases of infectious TB occur frequently, the advantages and disadvantages of BCG should be discussed with a prospective worker and vaccination provided if the worker decides to have it.
During employment

- Surveillance can consist of regular TB symptom questionnaires, Mantoux tests and CXRs. Staff at high risk of TB exposure should have an annual questionnaire about TB symptoms and recent exposure, and a Mantoux test (if they are Mantoux negative).
- Staff working in lower-risk areas require no routine surveillance during employment. Staff working with immunosuppressed patients should have a low threshold for reporting TB symptoms.
- Routine, periodic CXR screening is no longer recommended for health care workers.
- Well-designed sample studies of Mantoux conversion rates should be conducted in hospital settings where unsuspected TB cases are more likely to occur, such as in wards caring for large numbers of people from Pacific, Asian and African populations.
**Introduction**

Health care workers face unavoidable hazards, including exposure to patients with infectious TB. The risks posed by this hazard cannot be eliminated, but they can be reduced.

Systematic measurement of infection of health care workers and assessment of risk are largely undeveloped in New Zealand. Although there are occupational TB screening programmes in some hospitals, published accounts of the epidemiology of latent TB infection and TB disease among New Zealand health care workers are rare.\(^1\) There are reports of tuberculin conversion among staff in US hospitals\(^2\) and among medical students and new graduates in New Zealand.\(^3\) There are also reports of increased rates of TB disease among health care workers in the UK\(^4\) and the US.\(^5\)

The global increase in TB has been reflected in New Zealand, where notification rates increased during the 1980s and have not fallen. The emergence of multi-drug-resistant strains has been a problem in many countries. So far there have been few patients in this country with multi-drug-resistant organisms, but protection of health care workers must take into account the probability that these numbers will increase, especially in immigrants.
9.1 Infectivity of patients with TB

9.1.1 What happens to sputum status with treatment?

Telzak et al. found a mean of 33 days and a median of 23 days after starting treatment before three consecutive negative sputum smears were obtained in cases of smear-positive pulmonary TB. In British Columbia patients, after four weeks of treatment 80% of smear-positive specimens were culture-positive. It was not until 12 weeks of therapy that a majority of smear-positive specimens were culture-negative. Telzak et al. found a mean of 33 days and a median of 23 days after starting treatment before three consecutive negative sputum smears were obtained in cases of smear-positive pulmonary TB. In British Columbia patients, after four weeks of treatment 80% of smear-positive specimens were culture-positive. It was not until 12 weeks of therapy that a majority of smear-positive specimens were culture-negative.

Analysis of smear and culture results from the mycobacteriology laboratory at Auckland Hospital revealed that:

- 95% of (pre-treatment) specimens with 0-1 acid-fast bacilli (AFB) per high-power field (HPF) on microscopy are culture-positive
- Cultures from patients with smear-negative pulmonary TB take a mean of 14 days to become culture-positive
- Cultures from patients with 10 AFB/HPF prior to TB treatment take a mean of four days to become culture-positive
- Cultures from patients with 10 AFB/HPF who have received 14 days treatment take a mean of 10 days to become culture-positive.

These Auckland data 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. Currently this is speculative and cannot be included in practical guidelines for the release of smear-positive patients from isolation. This topic is discussed below.

9.1.2 What is the infectivity of patients who remain smear-positive on treatment?

The above data show that patients on treatment may continue to be smear-positive for prolonged periods. The infectivity of these people is unclear. Most evidence suggests that patients have significantly reduced infectivity on appropriate treatment, even if they continue to be smear-positive.

Experimental exposure of guinea pigs to sputum smear-positive human patients has demonstrated that the infectiousness of the 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.

In Madras, patients were randomised to home treatment and sanatorium treatment. After five years of follow-up the incidence of active TB, TB infection and death from TB was no greater in the contacts of patients treated at home than in the contacts of patients treated in a sanatorium. This indicated that the major risk for contacts lies in exposure to the infectious case before diagnosis.
This finding was supported by a retrospective study of skin-test positivity rates among household contacts. No significant difference in rates was found between contacts of cases who were discharged while smear- and culture-positive and cases who were not discharged until smear- and culture-negative.\textsuperscript{13} Similarly, none of 74 contacts who were tuberculin-negative when their index cases were discharged after two weeks’ treatment had skin-test conversions on subsequent retesting; 31\% of them were on isoniazid chemoprophylaxis, however.\textsuperscript{14} None of 13 young contacts who were tuberculin-negative when their index cases were discharged after four weeks’ treatment had skin test conversions on subsequent retesting. Nine of them were on isoniazid chemoprophylaxis.\textsuperscript{15}

On the other hand, Riley and Moodie demonstrated that 7 of 70 contacts who were tuberculin-negative initially went on to convert their skin tests after the index case had received 6–20 weeks of treatment.\textsuperscript{16}

Treatment leads to a sharp decline in cough frequency, which is associated with a decline in infectivity. Cough frequency is a less statistically significant indicator of infectivity than extent of disease or bacteriologic status.\textsuperscript{17}

9.1.3 What is the infectivity of children?

Children under the age of 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 sufficient strength to expel significant numbers of TB bacilli. Some, however, 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 treated with the same precautions as adults.
9.2 Isolation of infectious TB

Isolation of infectious TB is an important public health protection measure. Isolation may take place in hospital or in the community.

9.2.1 Isolation of infectious cases in hospital

Infectious patients should be isolated in hospital if, in the opinion of hospital or public health staff:

- they will not comply with the community infection control precautions described below, or
- they are sufficiently unwell to warrant admission to hospital.

9.2.2 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 will often be the preferred option. This avoids the possible exposure of previously unexposed people, which may happen in a hospital. A public health nurse experienced in TB control should visit the home within 24 hours of diagnosis and start of treatment, and educate the patient and family about the following.

The infectious patient must:

- stay at home and not go to places where there will be previously unexposed people or casually exposed people
- minimise the duration and number of visits by previously unexposed people or casually exposed people (this is especially important if the visitors are children – all visiting by children should be strongly discouraged until the patient is smear-negative)
- not allow previously unexposed people to come to live with them until sputum converts to negative
- wear a mask during visits to the household by previously unexposed people or casually exposed people (including public health nurse visits)
- cover their mouth when sneezing or coughing
- be educated about disease transmission and disease control
- comply with adherence and medication side-effect monitoring.

9.2.3 Criteria for ending isolation

In the past a good clinical response after two weeks’ treatment was taken as indicating low infective risk. Following reports of transmission of multi-drug-resistant TB in hospitals, three negative sputum smears became the standard US recommendation before a patient should come out of respiratory isolation. However, this is generally believed to be excessively strict. Waiting for three negative smears before releasing a person from respiratory isolation when they have responded well to treatment is not recommended.
Patients with smear-positive pulmonary TB may be removed from isolation if all of the following have been met. The patient has:

- received a minimum of two weeks’ effective chemotherapy.
- stopped coughing
- a susceptible strain of *M. tuberculosis*
- responded well to treatment
- provided at least two sputum specimens that are smear-negative.

Many patients will have ceased to produce sputum after two weeks’ treatment. They are unlikely to be infectious. If spontaneous sputum specimens cannot be obtained, supervising nursing staff must be sure that the patient is no longer coughing before the decision is made to end isolation.

### 9.2.4 Hospital isolation policy to prevent nosocomial TB

A number of important measures need to be implemented when a person with suspected or known infectious TB is admitted.

- People who are in hospital should be isolated (in a single room) if pulmonary TB is suspected (see Chapter 14: ‘Clinical Investigation and Assessment of Tuberculosis’) or has been diagnosed.
- Isolation rooms need modern (negative-pressure) ventilation systems (see below).
- The results of smear examinations for AFB on respiratory specimens should be available within 24 hours (see Chapter 12: ‘Mycobacteriology: Laboratory Methods and Standards’), enabling the removal from isolation of those in whom active disease is not confirmed.
- HIV-infected patients should be nursed in separate wards from TB patients. Nosocomial TB outbreaks have been documented overseas in HIV-infected people.
- Any patient hospitalised with suspected or known infectious pulmonary *multi-drug-resistant* disease must be transferred to a facility with a negative-pressure ventilation system.
- Infectious TB patients should wear masks when they leave the isolation room for investigations in other parts of the hospital.
- Universal precautions will protect against the (unlikely) possibility of cutaneous transmission of TB from body substances containing *M. tuberculosis*.
- TB wound care requires the wearing of particulate respirators and gloves.
9.3 Personal protective equipment

Health care workers must wear NIOSH-approved (N95) particulate respirators when providing care for adult patients with known or suspected infectious pulmonary TB. Suitable respirators available in New Zealand are 3M 1860, Moldex 2200, Gerson G1920 and Tecnol PFR 95.

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 conducted).
- N95 particulate respirators are intended to be disposable and the manufacturers advise that they be discarded on exiting the isolation facility. Some New Zealand facilities re-use these because of the high cost. If this is done, careful labelling is required.
- Reusable particulate respirators should be labelled for a single staff member’s use and maintained according to the manufacturer’s instructions.
- Alternative protection may be needed for some staff, such as those with beards. Advice may be obtained from the manufacturer.
9.4  Hospital engineering controls*

9.4.1  Background

Physical isolation of the patient in a well-ventilated room without negative pressure does not reliably prevent airborne transmission. Opening a window will change the direction of airflow and may contaminate areas outside the isolation room. Isolation areas require adequate ventilation with direct engineering controls.4

Engineering controls can be thought of as different ways of achieving dilution of airborne droplet nuclei, which contain TB bacilli. For facilities designers and maintenance staff to fully implement all the guidelines is expensive, and to date there is little empirical evidence to indicate what provides best results for the investment.22 Some systems, unless very carefully designed and maintained, will not provide the protection expected.23 24 Performance of equipment such as fans deteriorates with age and may be altered by structural alterations to the building or inappropriate maintenance.22 There are reports of facilities where the design intention was good but the function was poor.25 26 Regular checks of performance of the system, by techniques such as smoke testing, are needed.

9.4.2  Negative-pressure rooms

Negative-pressure ventilation extracts air and lowers the pressure in the isolation room. This ensures that contaminated air does not flow from the isolation room to clear areas. However, this does not protect the health care workers who enter the room: they need to wear appropriate face masks. An anteroom outside the isolation room will further reduce the risk of 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 designs a system to change the air more than the recommended number of times per hour. The Centers for Disease Control recommend more than six air changes per hour (ach) for general patient areas such as waiting rooms, and over 12 ach for areas used to nurse TB patients.5

It takes a long time to completely clear a room from the aerosol introduced by a cough. Even at the recommended air change rate (12 ach) the room will not be completely clear (99.9% clean) for 35 minutes.5 The following table illustrates this effect.

<table>
<thead>
<tr>
<th>Percent aerosol removed</th>
<th>90%</th>
<th>99%</th>
<th>99.9%</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 ach</td>
<td>28 mins</td>
<td>55 mins</td>
<td>83 mins</td>
</tr>
<tr>
<td>12 ach</td>
<td>12 mins</td>
<td>23 mins</td>
<td>35 mins</td>
</tr>
</tbody>
</table>

Table 9.1:  Time required to remove the aerosol produced by a cough

*  For a review of this topic, see Blumberg.21
Thus dilution takes time and further demonstrates the need for personal respiratory protection. The information in the above table also assumes perfect mixing – which is rare in practice. To get ideal mixing of all air in the room, with minimal short-circuiting between inlet diffuser and extractor, it is necessary to have sufficient velocity out of the ceiling diffusers to establish turbulence down to the health care worker’s head level. The consequent drafts are unlikely to be tolerated by the patient.

### 9.4.3 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 recirculated air within the room can be viewed as a method of increasing the effective dilution without increasing the number of air changes per hour. Filtration by high-efficiency particulate attenuation (HEPA) filters built into the ceiling space is required if air in a TB isolation room is recirculated.

Self-contained portable HEPA filtration units are available. These claim cost-effective performance, but they are prone to short-circuiting of the air flow and are not recommended.

### 9.4.4 Ultra-violet germicidal irradiation

There is incomplete evidence on the effectiveness of ultra-violet germicidal irradiation (UVGI) on the TB aerosol, either for the intensity needed or the time required to kill the bacilli. It has the following disadvantages.

- All the air must have a minimum residence time within a specified distance from the UVGI lamp.
- UVGI can cause kerato-conjunctivitis and skin erythema.
- As lamps get old and dirty the residence time for air sterilisation increases.
- The system becomes ineffective if the lamps are replaced incorrectly, and if they are not replaced before the intensity of irradiation drops below the acceptable level.

Therefore UVGI is used only as a supplement to other dilution systems. At present the role of UVGI in rooms where TB patients are nursed is unclear, so no recommendation on the use of these lamps can be given. Some authors have suggested that they may have an application in general hospital areas such as corridors and waiting rooms, where air circulation is likely to be lower than the 12 ach required in isolation rooms. In these situations, where unsuspected TB patients may be present, one would expect UVGI to be helpful, but there is little published evidence of this.

### 9.4.5 Monitoring the effectiveness of engineering controls

A programme of regular testing is necessary to ensure that engineering controls of air quality are effective. This should include:

- monthly smoke tests (these ensure that air flow direction is as intended)
- checks that negative-pressure gauges are functioning correctly
- regular review and replacement of HEPA filters.
For more information, refer to the Centers for Disease Control web site:
http://www.cdc.gov/nchstp/tb/notes/TBN_2_00/training.htm.
9.5 Diagnostic procedures with transmission potential

9.5.1 Procedures requiring isolation

Aerosol-generating procedures such as bronchoscopy and sputum induction on patients with TB (and certain other infections) should be carried out in respiratory isolation conditions. When bronchoscopy is performed on TB cases with suspected or proven infectious TB, respiratory isolation conditions are required. Particulate respirators should be worn when TB is a possible diagnosis.

9.5.2 Decontamination of equipment with *M. tuberculosis* and other mycobacteria

Instruments such as bronchoscopes and nebulisers, when used for patients with TB and other mycobacterial diseases, become contaminated. If the cleaning and sterilisation of the equipment is inadequate, there is the possibility of transferring organisms 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 culture (see Chapter 12: ‘Mycobacteriology: Laboratory Methods and Standards’).

There should be a system of surveillance, supervised by an infection control committee. Standards New Zealand has published advice on the cleaning and sterilisation of instruments. Monthly mycobacterial cultures from bronchoscopes are recommended.
9.6 Staff screening

9.6.1 Pre-employment screening

Health care staff who have contact with patients or infectious materials must have pre-employment screening. This 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 (LTBI) so that they can be counselled and offered treatment where appropriate
- obtain baseline data about Mantoux status for comparison with readings obtained during routine surveillance or following exposure to TB.

Students of nursing, medicine, physiotherapy etc. should receive similar screening by their educational institutions. Health care facilities that host students must ensure that this is included in their agreements with universities and polytechnic institutions. When hospitals employ agency (bureau) staff, the contract should specify similar screening for the agency workers. Larger hospitals should have an in-house occupational health unit, as this facilitates co-operation with other services such as infection control and public health.

Pre-employment screening is unnecessary in rest homes. Among 288 cases over 70 years of age who were notified in 1995–99, only 15 (8.9%) 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.

Pre-employment screening consists of a pre-employment questionnaire, Mantoux testing and, if appropriate, a CXR.

**Pre-employment questionnaire**

The questionnaire should cover:

- birth, residence or extended travel in countries of high TB prevalence
- previous TB
- previous tuberculin skin-test results
- known TB exposure from family or work
- previous occupations
- proposed new occupation
- health problems that increase the risk of developing TB (see Table 3.3, Chapter 3: ‘Latent Tuberculosis Infection’).
**Two-step Mantoux testing**

Pre-employment Mantoux testing is essential. Failure to use the two-step test may later lead to an incorrect diagnosis of a Mantoux conversion and to unnecessary treatment or CXR investigation. A full discussion of the two-step Mantoux test is included in Chapter 2: ‘Mantoux Testing’.

**Chest X-ray**

A CXR should be offered to those with a positive Mantoux reaction. Where concerns are raised as a result of the questionnaire, a CXR may also be required. Abnormal CXRs should be discussed with a respiratory physician, who may need to examine the applicant.

**Pre-employment BCG**

The place of BCG for health care workers is controversial.\(^5\)\(^{30}\) It is recommended by British guidelines, although the evidence for its effectiveness is not strong.\(^30\) Universal use of BCG for staff and students cannot be supported in New Zealand at present because of the comparatively low risk of occupationally acquired TB for most workers. It also has low efficacy in adults and makes the further use of the Mantoux as a diagnostic tool more difficult.

However, where the risk is higher than usual, as in those working in units where unsuspected cases of infectious TB occur frequently, the advantages and disadvantages of BCG should be discussed with a prospective worker and vaccination provided if the worker decides to have it. BCG is a live, although attenuated, bacterium and should not be given to those who are immune-compromised. A detailed discussion of BCG is included in Chapter 8: ‘BCG Vaccination’.

**9.6.2 Surveillance during employment**

This is a controversial issue, with practice in the US requiring regular Mantoux testing\(^{19}\) and British hospitals taking *laissez faire* approach and treating workers as contacts where there has been exposure.\(^{30}\)

Surveillance can consist of regular:

- TB symptom questionnaires
- Mantoux tests
- CXRs.

Staff working in TB or general respiratory wards, bronchoscopy or induced sputum rooms, TB laboratories, and post-mortem examination rooms are at high risk of TB exposure. Such staff should have an annual questionnaire about TB symptoms and recent exposure, and a Mantoux test (if they are Mantoux-negative).
Staff working in lower-risk areas require no routine surveillance during employment. Staff working with immunosuppressed patients do not require regular screening for TB. However, part of their responsibility should include awareness of their own health, including knowledge of TB symptoms.

Routine, periodic CXR screening is no longer recommended for health care workers.

Staff with Mantoux test conversion require a CXR. Those with abnormal X-rays should be examined by a respiratory physician. If TB disease is excluded, treatment of LTBI may be considered.

Little is known about the epidemiology of occupationally acquired TB in New Zealand hospitals. Well-designed sample studies of Mantoux conversion rates in hospitals should be conducted. These should be confined to settings where unsuspected TB cases are more likely to occur, such as in wards caring for large numbers of people from Pacific, Asian and African populations. These data should be published. Decisions can then be made about reduction, refocusing or expansion of retesting programmes.

**9.6.3 Staff exposed to patients with infectious TB**

Staff exposed to an infectious TB case are managed as contacts (see Chapter 6: ‘Contact Investigation’).
References


Further reading


Chapter 10: TB Control in Non-Clinical Settings

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Summary

TB in correctional facilities

- Correctional facilities are an important reservoir of TB infection in most parts of the world. In many countries, including New Zealand, disproportionately high rates of diagnosed TB cases in prisons have been reported.

- These guidelines recommend that all inmates be screened on entry into a correctional facility. Figure 10.1 is a flow diagram proposed for the screening of inmates for TB. The following methods for TB screening are recommended:
  - symptom and history inquiry
  - physical examination
  - investigation, if there are symptoms
  - Mantoux test
  - CXR.

- Identification and treatment of cases of latent TB infection (LTBI) should be applied as an important TB strategy in correctional facilities. Additional resources will be required for prison services to effectively administer LTBI.

- Directly observed therapy is essential for the treatment of all TB cases in correctional facilities. Close liaison between prison medical staff and local health authorities is required.

Occupational exposure to TB

- Recommendations for non-health-care workers at risk of TB exposure are made. Based on New Zealand and overseas data, it appears justified to screen and monitor prison staff, mortuary staff (particularly if carrying out post-mortems), funeral directors and abattoir/freezing/meat workers.

- The following procedures are recommended for new employees at risk of TB exposure itemised in the previous paragraph:
  - inquiry into prior TB exposure, BCG vaccination and risk factors for infection progressing to disease (see Table 3.3, Chapter 3: ‘Latent Tuberculosis Infection’) at the time of first employment
  - two-step baseline Mantoux testing for employees with no documented history of a positive skin-test result or no skin test in the preceding 12 months
  - CXR for an employee with a positive skin-test result
  - treatment of LTBI may be considered for employees with positive Mantoux reactions if they are at high risk of developing TB disease (see Table 3.3, Chapter 3: ‘Latent Tuberculosis Infection’)
  - annual Mantoux testing programmes should be undertaken only after consultation with the Ministry of Health, since they are epidemiological exercises requiring careful planning
  - wearing well-fitted face masks (N95 particulate respirator) when working with material and/or people with infectious TB
  - BCG vaccination is not recommended.

- In other occupations, including police, ambulance personnel, teachers, farm workers and possum hunters, the risk of TB exposure is much lower. No particular screening or protective measures are needed.
TB in overseas travellers

There is strong evidence that TB infection occurs during long-haul flight travel and visits to high-prevalence countries. The risk of active disease also appears to be increased, but is difficult to quantify.

The following are recommendations for travellers to countries with high TB incidence.

- BCG vaccination is unnecessary in most travellers.
- BCG vaccination, if not previously administered, may be appropriate in people travelling to undertake health care work in a country with a high TB incidence.
- BCG vaccination should be offered to children under five years old (if not previously administered) if travel to a country with a high TB incidence is likely to exceed three months.
- Two-step Mantoux testing (see Chapter 2: ‘Mantoux Testing’) should be undertaken prior to travel exceeding three months in a high-incidence country (provided there has not been a previous positive reaction). Those travelling to undertake health care work and other high-risk activities should have pre-travel two-step Mantoux testing even if they are travelling for shorter durations. The Mantoux should be repeated (no earlier than eight weeks) after return.
- If Mantoux test conversion has occurred, investigations for TB disease should be undertaken. If the TB search is 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.
Introduction

Health care workers have an increased risk of contracting TB, and limited data suggest that the incidence of TB is also higher in some other occupational groups. An association with TB might be expected in groups such as abattoir and other animal workers resulting from exposure to animals infected with mycobacteria. Correctional facilities are another setting in which a disproportionately high incidence of TB may be found.

This chapter reviews the risk of TB infection and disease in some of these settings, and makes recommendations for monitoring and control.
10.1 TB in correctional facilities

10.1.1 The problem of TB in prisons

Correctional facilities are an important reservoir of TB infection in most parts of the world, particularly in countries that already have a high incidence of TB. Conditions within correctional facilities that may contribute to TB transmission include overcrowding, poor hygiene and inadequate ventilation. Factors common to the inmates of correctional facilities that predispose this population towards TB infection and disease are also important, and include:

- high representation from low socioeconomic backgrounds
- increased incidence of HIV infection
- high rates of substance abuse
- underlying poor health and/or nutrition
- Māori and Pacific peoples (groups with high rates of TB) are over-represented in New Zealand prisons.

In many countries disproportionately high rates of diagnosed TB cases in prisons (up to 50 times the national rate) have been reported. In New Zealand there were 18 TB cases notified from 1997 to 2001 involving prison inmates or people recently held in prisons. Given that the average prison population in New Zealand at the time was 5574, this represents an average annual incidence of 66.1 per 100,000 compared with an average national rate of TB of 10.3 per 100,000 for the same period. This may be an underestimate of the size of the problem in New Zealand, however, as failure to be able to identify TB cases from prisons may result from incomplete data on TB notification case report forms.

Prison incarceration was linked to an outbreak of TB in the North Island in 1999. Although the exact extent of transmission within prison was not made clear, the outbreak highlights the public health consequences of TB in this setting. Cases of multi-drug-resistant TB from correctional facilities have not been reported in this country but contribute a high proportion of cases in other countries.

10.1.2 Screening of inmates in correctional facilities

The purpose of screening is to identify people who have active TB disease or latent TB infection (LTBI). International guidelines recommend that all inmates be screened on entry into the correctional facility. Figure 10.1 is a flow diagram proposed for the screening of inmates for TB. The procedures undertaken will be determined by the length of stay in the facility and previous screening results. It may be impractical to undertake Mantoux testing and/or CXRs in persons who are on remand or serving short sentences, and in these circumstances screening for TB disease by symptom questionnaire only is recommended.
The following methods for TB screening are recommended.

**Symptom and history inquiry**

Symptoms of pulmonary TB should be sought. However, chronic cough is common in this population due to the high level of smoking and smoking-related lung disease. Symptoms and their relationship with CXR appearances are discussed in Chapter 13: ‘Awareness, Clinical Features and Early Identification of Tuberculosis’ (Clinical Features; CXR).

The history of active TB disease, LTBI or previous treatment for TB should be documented. The family history of TB and other contact history should be elicited.

**Physical examination**

A thorough medical examination should be undertaken if positive responses suggesting possible TB disease are returned.

**Investigate if there are symptoms**

Sputum specimens should be examined for acid-fast bacilli, and a CXR undertaken if there is a suspicion of TB disease.
Mantoux test
Details of Mantoux testing are covered in Chapter 2. Mantoux testing should be mandatory in all inmates entering long-term correctional facilities who do not have a documented history of a positive or recent skin-test result.

Mantoux test results should be recorded in the inmate’s medical records and be accessible on any transfer. Mantoux-positive results should be highlighted in the medical records so that a high index of suspicion is always maintained for the development of active disease.

Mantoux testing may not be feasible in short-term inmates.

Chest X-ray
A PA CXR should be requested if the symptom inquiry is suspicious for possible TB disease. There is evidence from the US that miniature CXR screening for TB in jails is a cost-effective process. On-site miniature CXR may be difficult to justify in New Zealand, however, particularly in smaller correctional facilities and in areas where the incidence of TB is low.

CXRs suggesting the possibility of TB should be discussed with an appropriate hospital specialist without awaiting results of sputum culture for TB.

10.1.3 Communicating TB screening information
A nationally standardised form should be developed for TB information on all new inmates, which will be kept in the individual’s health file and passed to any new prison to which the inmate is transferred. Medical records should be marked (see Chapter 13: ‘Awareness, Clinical Features and Early Identification of Tuberculosis’, Table 13.5) to readily identify those individuals with:
- increased risk of contact with TB (especially family history)
- clinical factors increasing risk of TB infection progressing to disease.

10.1.4 Treatment of latent TB infection (LTBI) in correctional facilities
Identification, adherence problems and treatment
The treatment of LTBI is discussed in Chapter 3: ‘Latent Tuberculosis Infection’. Identification and treatment of cases of LTBI is an important TB control strategy. The adherence rates to courses of isoniazid however are found to be very low in prisoners with LTBI. In particular, only a minority continue with treatment after discharge from prison, and adherence within a month of discharge has been found to be as low as 3%.10

Regular education and the offer of incentives can improve follow-up rates when cases leave prison on isoniazid, although only the former improved the rate of completion of therapy. Therefore, with appropriate resources and modest interventions, this captive population, with high rates of LTBI, offers a good opportunity for effective identification and treatment.
Treatment of LTBI may be considered for inmates with positive Mantoux reactions if they are at high risk of developing TB disease (see Chapter 3: ‘Latent Tuberculosis Infection’, Table 3.3). It is recommended that directly observed therapy (DOT) (see Chapter 5) be used for treating LTBI in prisons. The use of short-course rifampicin plus pyrazinamide may improve completion rates. Additional resources will be necessary for prison services to effectively administer LTBI treatment.

Three groups in particular should be targeted for treatment of LTBI in prisons:

- contacts of prisoners with sputum smear-positive pulmonary TB
- HIV-infected prisoners
- in women’s prisons, infants of mothers with pulmonary TB.

10.1.5 Role of BCG vaccination in prisons

The role of BCG is discussed in detail in Chapter 8: ‘BCG Vaccination’. The efficacy of BCG vaccination in adults in New Zealand is unclear, but overseas trials suggest it is significantly lower than the efficacy of most other vaccines (eg, hepatitis A and B). Routine BCG vaccination of prisoners is not recommended, although this may be reviewed on the basis of local epidemiology, incidence within institutions and in consultation with the medical officer of health.

10.1.6 Treatment of TB cases in correctional facilities

The treatment of TB is covered in detail in Chapter 16: ‘Treatment of Tuberculosis’. Although it might be expected that TB in inmates of correctional facilities should be easier to manage, paradoxically there is a high rate of treatment failure.\(^\text{12}\) Short duration of incarceration and a high turnover rate in institutions are major factors contributing to this. Successful treatment in correctional facilities requires:

- DOT for all cases of TB
- close liaison between prison medical staff and the local health authorities
- ensuring completion of treatment, and, when prisoners are released back into the community, appropriate transfer of responsibility 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 and/or social worker may assist follow-up and completion of treatment.

10.1.7 Infection control in prisons

An infectious case (a sputum smear-positive case who has received fewer than two weeks’ appropriate anti-TB treatment) should be immediately transferred to a correctional facility or hospital with a negative-pressure room until at least two weeks’ appropriate anti-TB treatment has been completed by DOT. However, the threshold of two weeks should not be considered a fixed or absolute term (see Chapter 9: ‘Infection Control’ for more detail).
A more difficult situation arises in the rare instance where an infectious patient who is not subject to a criminal conviction warranting imprisonment cannot be cared for in a public hospital because of violent behaviour. Responsibility for the detention of this person is unclear, and resolution between District Health Boards and the Department of Corrections has not yet been achieved.

All staff in correctional facilities should be familiar with the infection control policy for that institution. This should include how to access N95 particulate respirators in the event of the possibility of infectious TB in an inmate.

When an infectious TB case is discovered or managed in prison:

- it is essential that the clinician involved promptly communicates details of the case (especially the infectious potential and treatment details) to both the corrections and public health medical and nursing teams
- close liaison and timely written communication between these three must 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.

### 10.1.8 Contact investigation in correctional facilities

It is important that if a TB case is newly diagnosed in prison, the prison medical service seeks early guidance from the local public health office concerning contact investigations. This is because contact investigation is a specialised task (see Chapter 6), and because contacts within the correctional facility will often be released before their investigation and definitive management is complete.

### 10.1.9 TB protocols

It is recommended that protocols for the screening and management of TB be drafted within all correctional facilities. These may be adapted for local variations as appropriate. Education of prison medical officers and other staff about TB should be central to all protocols.
10.2 Occupational exposure to TB

The occupational risk of TB in New Zealand is unclear because comprehensive occupational data are not reliably collected with case notifications. Overseas data suggest there are settings in which there is increased occupational risk relating to the higher prevalence of *Mycobacterium tuberculosis* or *M. bovis*. The risk to the worker in these settings and recommendations for screening and protection are discussed below.

10.2.1 Occupations with risk of exposure to TB

*Health care workers*

The increased risk for occupational exposure to TB in health care workers is well established. This is discussed fully in Chapter: 9 ‘Infection Control’.

*Silica workers*

Silica workers are well documented as having a high incidence of TB, particularly when silicosis has developed. This is not an important problem in New Zealand, however.

*Prison workers*

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. An increased occupational risk of TB has been confirmed in studies of North American prison workers based on the prevalence of positive tuberculin skin-test reactions. In the US an outbreak of multi-drug-resistant TB resulted in transmission to prison employees. TB transmission from inmates to guards has also been reported in a short-term jail, verified by DNA fingerprint analyses. In New Zealand a female prison guard was reported to develop TB following intermittent exposure to an inmate with unsuspected active disease.

*Abattoir workers*

*M. bovis* is recognised as an occupational hazard to abattoir workers in Australia. In New Zealand, bovine TB is an important disease of livestock, having been documented in cattle, deer, sheep, pigs and goats. A high incidence of TB has been noted in New Zealand abattoir, freezing and meat workers, with 21 cases notified between 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 exposure to livestock and domestic animals, veterinarians are at risk of infection by zoonotic pathogens. As well as livestock mentioned above, other domestic animals, including cats and dogs, may also be infected by *M. bovis*. Surprisingly there has been no report of TB transmitted from a diseased animal to a veterinarian.
**Farm and animal workers**

Farm and animal workers have the potential for extensive contact with zoonotic pathogens. In a survey of occupation and active TB cases in 29 states of the US from 1984 to 1985, higher rates were identified in farm workers, as well as in funeral directors (see above).\(^{20}\) The high rate in farm workers in the US may be attributed to the high level of migrant workers in this area. There are no data to indicate that farm workers in New Zealand are at increased risk of TB.

There are a small number of case reports of TB occurring in animal workers. *M. bovis* infection was transmitted from an infected rhinoceros to seven zookeepers,\(^{21}\) and a seal trainer developed pulmonary TB from *M. bovis* transmitted from seals in a marine park.\(^{22}\)

**Possum hunters**

In New Zealand, possums are reservoir hosts for *M. bovis*, responsible for the spread of infection in domestic and wildlife stock.\(^ {23}\) The respiratory route is probably the most important mechanism of transmission among possums since a high proportion of tuberculous adult possums have lung lesions whereas mesenteric lymph nodes appear to be involved only in late stages of disease. It is estimated that around 15–20% of possums in an endemic area become infected at some stage of life. 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.\(^ {23}\) Current research is assessing the potential role of vaccination of wild possums as a bovine TB control strategy.\(^ {24}\)

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 are early reports of small outbreaks of TB aboard ships of the US navy.\(^ {25,26,27}\) These have been attributed to TB occurring in a ‘closed environment’. Epidemiological data of the Greek armed forces also found a high incidence of TB cases compared with the civilian population.\(^ {28}\) The incidence of TB declined following the introduction of BCG vaccination in Greek military recruits in 1980, but still remained relatively high.

There is no recent evidence of increased risk of TB in New Zealand armed forces personnel. Recommendations for armed forces personnel working in high-incidence countries are the same as for other travellers (see 10.3.3, ‘Recommendations for overseas travellers’ below).
**Miscellaneous occupations**

Analysis of data from the US National Occupational Mortality Surveillance database identified disproportionately high numbers of deaths from TB in funeral directors, food service and preparation workers, machine operators, as well as health care workers and occupations with silica exposure.\(^{29}\) Whereas TB in food service and preparation workers and machine operators may be ascribed to confounding risk factors associated with their low socioeconomic status, there may be a true risk of exposure to funeral directors from cadavers, as suggested by other surveys.\(^{20,30}\) This would also be consistent with the findings of higher rates in pathologists and mortuary workers.

A review of TB cases in New Zealand from 1995 to 1999 found that 10% of cases aged over 70 years had recent or current residence in a rest home.\(^2\) The number of rest home staff that were infected or developed disease was not able to be documented, however. The screening and control of TB in rest home workers is discussed in Chapter 9: ‘Infection Control’.

There is no evidence of increased risk of TB in New Zealand for teachers, despite the fact that approximately 167 children of school age were identified with TB between 1996 and 2000. Moreover, there have been at least three schoolchildren with multi-drug-resistant TB in the Auckland region since 1995 but no evidence of spread of disease to their teachers (AC Harrison, personal communication).

There is no evidence, either, of increased risk of TB in New Zealand for early childhood workers, police, conservation or ambulance workers.

**10.2.2 Recommendations for non-health-care workers at risk of TB exposure**

Prison staff, mortuary staff (particularly if carrying out post-mortems), funeral directors and abattoir/freezing/meat workers are classified as having higher risk of TB exposure than the general population. The following procedures are recommended for new employees in these groups.

- Inquiry into prior TB exposure, BCG vaccination and risk factors for infection progressing to disease (see Chapter 3: ‘Latent Tuberculosis Infection’, Table 3.3) should be undertaken at the time of first employment.

- Two-step baseline Mantoux testing is required for employees with no documented history of a positive skin-test result or no skin test in the preceding 12 months.

- CXRs should be undertaken for employees with a positive skin-test result.

- Treatment of LTBI may be considered for employees with positive Mantoux reactions if they are at high risk of developing TB disease (see Chapter 3: ‘Latent Tuberculosis Infection’, Table 3.3).

- An annual Mantoux testing programme should be undertaken only after consultation with the Ministry of Health, since they are epidemiological exercises requiring careful planning.
Well-fitted face masks (N95 particulate respirator) should be worn when working with material and/or people with infectious TB.

BCG vaccination is not recommended.

In all other occupations – including police, ambulance personnel, teachers, farm workers and possum hunters – the risk of TB exposure is much lower. No particular screening or protective measures are needed.
10.3 TB in overseas travellers

TB remains highly endemic in large parts of the world, so an assessment of the risk of acquiring TB during visits to an endemic country needs to be made. Exposure may occur during long-haul air travel, and prolonged visits to an endemic country, particularly for workers in health care settings.

10.3.1 Transmission of TB associated with air travel

With the vast numbers of people travelling internationally on commercial aircraft it is not surprising that cases of passengers with active pulmonary TB are regularly reported. There is concern that fellow passengers sitting within the confines of an aircraft cabin, particularly during long-haul flights, are at risk of also becoming infected and developing disease.

While a number of studies have documented infection in passengers and flight crew following exposure to a passenger with highly infectious pulmonary TB, the risk of infection appears to be very low. No case of active TB has been reported in the literature as a result of exposure while on a commercial aircraft.

There is no evidence that air recirculation during flights facilitates transmission of \textit{M. tuberculosis}. In modern commercial jets, air is recirculated within the passenger cabin at an approximate rate of 20 air-changes/hour through high-efficiency particulate air filters. Furthermore, airflow is laminar, with air flowing downward in a circular pattern to outflow grills in the sidewalls near the cabin floor. Hence any airborne transmission of infectious diseases in aircraft is limited to person-to-person spread within close proximity.

Accordingly, evaluation is recommended for contacts seated within two rows of an infectious TB case during flights lasting more than eight hours. More extensive contact screening is not routinely justified. If the index case is notified in New Zealand, the contact follow-up (including international contact tracing) should be co-ordinated by the local medical officer of health. This is discussed in more detail in Chapter 6: ‘Contact Investigation’.

10.3.2 Travel to areas of high TB endemicity

TB notification data do not include information about disease that might have been acquired abroad, because such an assessment is difficult to make with confidence, even for foreign-born cases. The risk for travellers to high-incidence countries has not often been quantified, but will be related to the length of stay and the background prevalence of TB within the visited country.

One longitudinal study suggests that Asian people travelling from the UK to the Indian subcontinent can develop TB. A Dutch study of 1072 BCG-naive travellers measured tuberculin skin reactions before and after travel to countries in which TB is highly endemic. After a median duration of 23 weeks’ travel the risk of \textit{M. tuberculosis} infection was found to have increased to the same level as that estimated for the host countries. This risk was increased further if the traveller was involved in health care work.
In a case-control study of Californian children under the age of six years, positive tuberculin skin-test reactions were strongly related to travel to a country with a high prevalence of TB within the previous 12 months. The duration of travel was unable to be assessed but the results indicate that young children appear to be particularly susceptible to TB infection when visiting other countries.

10.3.3 Recommendations for overseas travellers

Overall, there is strong evidence that TB infection occurs during long-haul flight travel and visits to high-prevalence countries. The risk of active disease also appears to be increased, but is difficult to quantify. Currently there is no international consensus policy on what interventions should be introduced for the international traveller.

- BCG vaccination is unnecessary in most travellers.
- BCG vaccination, if not previously administered, may be appropriate in people travelling to undertake health care work in a country with a high TB incidence.
- BCG vaccination should be offered to children under five years old (if not previously administered) if travel to the endemic country is likely to exceed three months.
- Two-step Mantoux testing (see Chapter 2) should be undertaken prior to travel exceeding three months in a high-prevalence country (provided there has not been a previous positive reaction). Those travelling to undertake health care work and other high-risk activities should have pre-travel two-step Mantoux testing even if they are travelling for shorter durations. The Mantoux should be repeated (no earlier than eight weeks) after return.
- If Mantoux test conversion has occurred, investigations for TB disease should be undertaken. If the TB search is 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.

* All countries except Australia, Austria, Belgium, Canada, Czech Republic, Denmark, Finland, France, Germany, Greece, Holland, Iceland, Ireland, Israel, Italy, Luxembourg, Malta, Monaco, New Zealand, Norway, Slovakia, Sweden, Switzerland, United Kingdom and the United States of America.
10.4 Future directions
The following recommendations are made for improving TB control in non-clinical settings.

- Improvements are required in the quality of TB surveillance in New Zealand. Completeness of data is lacking in many areas, including occupational data.
- Epidemiological studies are required to assess the risk of TB in occupational groups in New Zealand.
- Adequate resources will need to be applied to ensure the establishment of TB screening programmes in correctional facilities and workplaces.
- The implementation and efficacy of TB screening programmes established in correctional facilities need to be assessed. This should include a study to determine the impact of the recommendations made in this chapter.


Chapter 11: Health Promotion and Health Education

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Summary

Health promotion

TB is a disease with powerful personal, cultural and socioeconomic aspects. The Whare Tapa Whi framework developed by Mason Durie provides a wide perspective which can be used to inform the development of effective health promotion programmes. Health promotion programmes relating to TB could focus on socioeconomic factors such as housing and poverty, the training of culturally appropriate health staff, or ways to assess and reduce the stigma of TB.

There are many other possibilities – few have been explored to date in New Zealand. Affected community groups need to be fully involved in order to develop effective TB health promotion programmes with sustainable results.

Health education

A concerted effort to provide health education, using interesting resources targeted carefully to the audience, is also a valuable way to improve knowledge and decrease the fear and misunderstanding that surrounds TB.

Messages can be delivered in a variety of formats, including leaflets, comic books, videos, radio and television, newspapers, speakers and theatre groups.

This chapter lists New Zealand and international health education resources. There is a growing number of reputable web sites with health information resources, including resources in other languages (with English translations).
Introduction

The successful control of TB cannot be achieved by medical interventions alone. TB has political, socioeconomic, cultural, social, psychological as well as physical aspects. In New Zealand many patients with TB have poor access to mainstream services because of socioeconomic deprivation or English as a second language. Additionally, the diagnosis of TB carries enormous stigma in many cultures, and the information given by health care providers may conflict with the patient’s knowledge.

A person with TB has emotional and social needs as well as the need for effective treatment. A health promotion framework enables TB control programmes to address these factors in a systematic way.
11.1 Health promotion

11.1.1 What is health promotion?
Health promotion is concerned with promoting health by seeking to influence lifestyle, health services and, above all, environment. Environment encompasses not only the physical environment but also the cultural and socioeconomic circumstances that substantially determine health status.

A number of definitions of health promotion have been developed. Most emphasise the need for a broad definition of health, participation from the community, and empowerment of individuals. The most well known, the Ottawa Charter for Health Promotion (1986) sets out a framework for action that includes healthy public policy, intersectoral collaboration and community participation.

Health education has an important part to play as part of a broader health promotion strategy. One writer has distilled the relationship between health education and health promotion into the formula:

\[
\text{Health promotion} = \text{health education} + \text{healthy public policy}.^1
\]

11.1.2 Whare Tapa Whä: a framework for health promotion
The Whare Tapa Whä model is a holistic construct of health, which accords with Mäori thinking on health. This model compares the essential elements of health to the four walls of a house, all of which are necessary for strength and symmetry.² These elements are:

¶ taha wairua – the spiritual domain, including cultural and environmental relationships
¶ taha hinengaro – emotional, behavioural and psychological health
¶ taha tinana – physical health
¶ taha whänau – the social, historical and economic domains of health.

Whare Tapa Whä reflects the Mäori world view, but is universal in its application.³ Other cultures also have concepts of health that differ sharply from the biomedical Western model. In Auckland a refugee community health liaison worker has recommended that TB services look at a more holistic approach to health, which includes physical, social, traumatic, psychiatric and cultural perspectives.⁴

As well as describing a unified model of health, Whare Tapa Whä can be used to design a response to a complex disease.³ Health promotion programmes related to TB must recognise the holistic concept of health, and the wider social, political and environmental domains represented by this model.
11.1.3 Socioeconomic factors

TB is clearly linked to socioeconomic deprivation. In New Zealand this association was supported by a study in the Wellington region between 1992 and 1999, which found that the most deprived areas of the Wellington region had the highest notification rates, after controlling for age and ethnicity. There were significant associations with disease rates for all four socioeconomic measures examined: index of deprivation, household crowding, unemployment, and median household income. Deprivation was more strongly associated with TB for Māori and Pacific peoples than for European and ‘Other’ groups. This indicates that different approaches may be needed for different ethnic groups for the prevention and control of TB.

11.1.4 Cultural factors

The perspective of patients may differ considerably from that of the health provider with respect to the meaning of their illness and the effect of the treatment on their lives. This perspective is determined by the beliefs about TB held by their family, their community and their culture. The cultural context of TB is beyond the scope of these guidelines, but as a practical guide providers need to be aware of the following.

- Explanations of disease causation may be different in different cultures.
- Social constructs of disease affect the way people experience and describe their symptoms.
- Traditional therapeutic practices may be at variance with prescribed treatment regimens.
- The stigma of TB is very strong in some cultures. Social rejection and social stigma are powerful forces. One study concluded that ‘the predominant cognitive/affective reactions towards TB were personal threat, social rejection and social stigma’.
- Religious and cultural activities may take precedence over taking medications and attending a clinic. A particular problem in this regard is that Muslim patients sometimes believe that they are prohibited from taking medication during Ramadan. This is a misconception and the assistance of a religious leader from the appropriate community should be sought.
- People from developing countries may be surprised at the recommendation for taking medication for latent TB infection when they are not unwell, as only sick people are treated for TB in their country of origin.

It is important to avoid simplistic or stereotyped views of culture. Health providers cannot realistically hope to gain an accurate understanding of the cultural constructs of TB for all their patients, but need to recognise that differing perspectives exist and that these may result in miscommunication. It should be noted that cultural misunderstandings, although important, are often overemphasised as a cause of non-adherence and unsuccessful TB programmes, when pragmatic and logistic factors may be to blame for lack of success in a TB control programme.
11.1.5 Workforce factors

There is currently a marked cultural mismatch between providers and patients in TB control in New Zealand. Relatively few doctors and public health nurses are Māori, Pacific, Asian or African – the groups disproportionately affected by TB. A number of TB programmes have found that using culturally appropriate outreach workers enhances compliance and improves case finding. 12 Ethnic directly observed therapy (DOT) and social workers have been used successfully in the Auckland public health unit.

Apart from facilitating cross-cultural understanding, there are other potential benefits from cross-cultural programmes using outreach workers. These include improving access for the community to mainstream facilities, keeping the emphasis on a holistic perspective to health, and empowering individuals and communities to develop their own resources and solutions to problems.

11.1.6 How can health promotion improve TB control in New Zealand?

Well-planned health promotion strategies can minimise the burden of TB. The target group needs to be defined and may include family or whānau, small community groups, ethnic or cultural groups, certain age groups, schools, church groups, or wider groups in the population. Similarly, the objectives and intended outcomes of a health promotion programme should be clearly defined and evaluation built in from the beginning.

In the broadest definition of health promotion, intersectoral public policy to improve housing or reduce socioeconomic disadvantage in New Zealand may lead to a decline in TB rates. This approach is complex, but may provide the greatest results over the long term in reducing TB burden.

Community-based programmes that consider the cultural constructs around TB (eg, stigma, interpretation of symptoms and mistrust of the mainstream system) may lead to a change in perception and a greater knowledge of TB. This in turn may lead to a reduction in stigma, which will improve the quality of life for people with TB and decrease diagnostic delay.

Participation and partnership are essential to community-based health promotion programmes. The goals of the programme should be identified by the target group and may include the need for information, as well as broader concerns such as access to health services or housing. The programme needs to occur in a setting that is familiar to the community group.

The choice of the messenger is critical. Enlist the support of respected community members. For Pacific peoples, church leaders should be involved in planning and delivery of health promotion programmes. There may also be a need for peer educators using a ‘train-the-trainer’ model.

Developing outreach teams with cross-cultural workers will improve communication and understanding between health providers and communities. Empowering individuals and communities affected by TB to develop their own resources is more likely to promote sustained change in knowledge and behaviour, thereby improving adherence.
11.2 Health education

11.2.1 Scope of health education

A concerted effort to provide health education, using interesting resources targeted carefully at the audience, is also a valuable way to improve knowledge and decrease the fear and misunderstanding that surrounds this disease.

The intended audience should be defined. This may include individuals affected by TB, their family and whānau, community groups and professional groups (including health professionals). Health education messages then need to be delivered in a way that is understood by and credible to the people being addressed. Messages can be delivered in a variety of formats, including leaflets, comic books, videos, radio and television, newspapers, speakers and theatre groups.

If English is not the person’s first language, translated materials and interpreters may be required (see Chapter 4: ‘Adherence to Treatment’ regarding the use of interpreters).

Messages about TB depend on the audience, but in general it is important to emphasise:
- TB is usually entirely curable
- TB can infect anyone
- the method of transmission
- the difference between latent TB infection and TB disease
- symptoms
- if not treated properly drug resistance can occur
- TB treatment is free.

11.2.2 Delivering TB health education to patients and their families

Usually two groups are involved in caring for people with TB:
- the hospital team / specialist who makes the diagnosis and prescribes treatment
- public health staff.

Ideally, both will be involved in providing TB education.

Education should begin when TB is first suspected. There may be a number of people providing information in the hospital setting and it is essential that the messages are simple and consistent. Efforts must be made to ensure that the patient has the ‘right’ information by asking them what they know about the various aspects of TB. Besides checking the understanding of the patient and their family, this will also help to identify whether team members have communicated clearly and accurately.

It is important that health staff who are inexperienced with TB recognise the limits of their knowledge. Having to correct misinformation puts the credibility of the team at risk. Where team members are in doubt as to how to answer particular questions, they should be honest and say they will find out.
The public health nurse who is the primary case worker has a key role in health education. This person will become the most familiar caregiver and needs to be seen as a trusted and accurate source of information. The public health nurse needs to spend a considerable amount of time with the patient soon after the diagnosis, providing information, answering questions and exploring the patient’s issues. (For more information on how to communicate TB information to patients, see Chapter 4: ‘Adherence to Treatment’).

TB health education should be given by people who are trained and experienced with TB, or who have acquired a very good understanding of this complex disease. TB clinicians and medical officers of health can help put those not trained in touch with people who are experienced in teaching about TB.

### 11.2.3 Resources

A wide range of health education resources on TB are available, both internationally and within New Zealand (see Table 11.1). Other than two Auckland resources, there is little translated material available locally. A careful internet search, particularly of recognised US web sites, may uncover the right resource for your client. Overall there is little translated material for Pacific peoples.

#### New Zealand resources

Table 11.1 summarises the health education resources available in New Zealand.

<table>
<thead>
<tr>
<th>Title and topic</th>
<th>Format</th>
<th>Comments</th>
<th>Contact</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis (TB)</td>
<td>Colour pamphlet</td>
<td>Basic information on TB disease; English only</td>
<td>Ministry of Health</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>12-page A5 booklet with pictures</td>
<td>Useful resource available in Arabic, Amharic, Cook Island Māori, English, Fanti, J an-ti, Khmer, Persian, Samoan, Somali, Tongan, Vietnamese</td>
<td>Auckland Healthcare</td>
</tr>
<tr>
<td>Do You Have Any of the Following? Side effects of medication for LTBI**</td>
<td>A4-sized checklist with cartoon pictures</td>
<td>Useful resource available in Arabic, Amharic, Chinese, Cook Island Māori, English, Oromo, Persian, Samoan, Somali, Tongan, Vietnamese</td>
<td>Auckland Healthcare</td>
</tr>
<tr>
<td>Tuberculosis: A germ is spread by ... Explaining TB infection</td>
<td>11-pages of illustrated charts</td>
<td>Could cause confusion between LTBI and disease; found to be useful in Auckland; has been translated into Somali</td>
<td>Auckland Healthcare</td>
</tr>
<tr>
<td>Tuberculosis: Causes, signs, symptoms, testing, treatment</td>
<td>11-page flipchart</td>
<td>English and Māori; can also be used on Powerpoint</td>
<td>Northland Health</td>
</tr>
<tr>
<td>BCG: Assessing the risk of TB for babies Guide for LMCs</td>
<td>A4-sized checklist</td>
<td></td>
<td>Auckland Healthcare</td>
</tr>
</tbody>
</table>
### Vaccination against TB

#### Instruction for parents on care of the BCG site

- Card with diagram on how to cover a weeping BCG site

#### TB infection

- Pamphlet

#### LTBI

- Information sheets on LTBI
  - From Protocol for Treatment of LTBI
    - Appendix contains information sheets on TB infection, isoniazid, rifampicin, rifinah, pyrazinamide, cartoon of side-effects (in translation, see above), letter for client on completion of treatment

### Remember to Take Your Medications

- Fridge magnet with picture

### Ministry of Health

- Basic information on what to expect at BCG site
- Explains the difference between TB disease and LTBI, the need for treatment, and possible side effects

### Wellington Regional Public Health

- Card with diagram on how to cover a weeping BCG site
- Pamphlet
- Information sheets on LTBI

### Auckland Healthcare

- Information sheets on LTBI

### International resources

#### Booklets

**Fighting TB.** A 28-page comic book with a garish graphic style containing basic information on TB disease. Useful for some teenagers, less so for adults. To obtain copies write to TB Program, World Health Organization, 20 Avenue Appia, CH-1211 Geneva 27, Switzerland; or request a colour photocopy from Auckland Healthcare or Wellington Regional Public Health.

#### Videos

**You can beat TB.** 12-minute video. Useful for people with TB disease and LTBI. It looks at the experiences of several Hispanic and black people and covers LTBI and TB disease, DOT, drug resistance and side-effects.

**TB and HIV: The connection.** 12-minute video. This is useful for people with HIV. It uses case studies to inform about HIV and LTBI, HIV and TB disease, DOT and drug resistance. It covers isoniazid for treatment of LTBI, but does not cover shorter courses of treatment for LTBI.

Both videos are produced by the Bureau of TB Control, New York City Department of Health.

**Think TB: A program for physicians.** This is an expert panel discussion on aspects of TB management. USDHSS Public Health Service and Centers for Disease Control.

* Contacts for obtaining resources:
  - Auckland Healthcare: 09 262 1855 (Jill Miller)
  - Northland Health: 09 430 4100 (Co-ordinator, Resource Development Unit, Community Health, Northland Health Ltd)
  - Wellington Regional Public Health: 04 570 9002 (Health Information Assistant)
  - Ministry of Health: 04 496 2000 (Advisor, Print Co-ordinator, Communications).

**LTBI:** Latent TB Infection.
TB and me. 15-minute video by Queen’s University, Kingston, Ontario. Acted vignettes cover transmission, treatment and DOT. This is targeted at young adults but is suitable for older adults. http://www.its.queensu.ca/qtv/graphictb.html

Resources on the Internet

General

http://www.cpmc.columbia.edu/tcpp
New York Department of Health resource. Four leaflets with excellent illustrations and clear language: What You Need to Know about Tuberculosis, Treatment to Prevent Tuberculosis, The Tuberculin Skin Test and TB: Getting Cured.

http://www.cdc.gov/nchstp/tb/
Centers for Disease Prevention and Control. This site links to Questions and Answers about TB. a 16-page booklet about TB transmission, skin test and treatment, including DOT and the side-effects of medications. Also under frequently asked questions is a one-page leaflet, TB: Get the facts (available in other languages via EthnoMed website).

http://www.umdnj.edu/ntbcweb/index.html
A TB “Frequently Asked Questions” pamphlet.

The web site of the Global TB Network. This contains a long list of TB organisations in the US and internationally.

http://www.tb.int.gtb
WHO web site, which includes factsheets on TB for the public as well as a large amount on WHO global TB programmes and strategies.

Web sites with TB resources in other languages

http://ethnomed.org/
This Seattle-based site has information on cultural beliefs, medical issues and other issues pertinent to health care of recent immigrants to Seattle. The TB resource page contains the following TB patient resources:

- Pills to Prevent TB for You and Your Family: a leaflet available in Cambodian, Chinese, Korean, Tagalog, Vietnamese, Oromiffe, Somali and Spanish. Translations include English alongside the target language.
- Tuberculosis: Get the facts: a Centers for Disease Control pamphlet in English, Somali, Spanish and Vietnamese.
- Medication for the Treatment of TB: in Amharic, Cambodian, Somali, Tigrinya and Vietnamese.
- The TB Skin Test: in Somali, Spanish and Vietnamese.

http://www.aapcho.org/
The Association of Asian Pacific Health Organisations web site. Basic TB information is provided in Vietnamese, Chinese, Korean and Tagalog.
This bilingual web site was developed by the Hong Kong Government (Department of Health and Hospital Authority). It contains useful information, which Chinese-speaking clients (with the appropriate Chinese software) can easily access.

http://www.nationaltbcenter.edu/
The web site of Francis J. Curry National TB Center in California. It includes a resource inventory sorted by language, with US fax addresses for ordering resources.

A two-page leaflet with basic information on TB infection and TB disease; available in Arabic, English, Chinese, Farsi, Filipino, Indonesian, Korean, Spanish, Timorese, Vietnamese. The final paragraph is specific to NSW health services.

New Zealand web sites

http://www.ethnicaffairs.govt.nz/oeawebsite.nsf/Files/ethnicLet'sTalk
A 40-page online booklet with guidelines on why trained interpreters should be used, how to get an interpreter, the importance of interview briefing and debriefing with the interpreter, how to contract and pay the interpreter, etc. This is essential reading for health professionals using interpreters.

http://moh.govt.nz/
TB-related information available via this site:

- **Refugee Health: A handbook for health professionals:** an excellent guide with information for health workers on communicating with refugee clients, and advice on health care issues, including TB. Copies can be ordered via the Ministry of Health (Folio Communications, ph: 04 499 5989).

- **NZ Public Health Reports:** includes New Zealand surveillance information on TB and some articles on national TB issues.
11.3 Future developments

There is great scope for effective health promotion programmes related to TB prevention and control in New Zealand. Nationally standardised translations of health education resources into common Pacific, Asian and African languages are needed.

There is also a need for local anthropological research on the social construction of TB and perceptions of the TB health care service among non-European ethnic groups affected by TB in New Zealand.

Workforce development in TB control needs to aim for more ethnic diversity in health care providers, to more closely reflect the ethnic and cultural groups affected by the disease in New Zealand. Medical officers of health in the main centres of TB care in New Zealand should monitor:

- whether the ethnic/cultural mix of TB health care providers (hospital and public health) becomes more diverse with time
- which ethnic/cultural groups are and are not well served by ethnically appropriate healthcare workers, the sizes of the groups and the number of TB cases they provide.

Measures of quality and effectiveness of TB health promotion and education are currently lacking in New Zealand. Simple, practical tools are needed that will enable data collection and analysis, and these then need to be incorporated effectively into the routine health care of TB patients and their families.
References


Chapter 12: Mycobacteriology: Laboratory Methods and Standards

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This chapter is endorsed by the Thoracic Society of Australia and New Zealand

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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', hence the term 'acid-fast bacilli' (AFB).
- The M. tuberculosis complex contains M. tuberculosis, M. bovis, M. microti, M. canettii, and M. africanum.

Diagnostic testing for TB

Specimen collection and transport

- All relevant clinical details need to be written on the form. Request forms need to clearly indicate all the tests required on the specimen (eg, routine culture, cytology).
- Specimens should be collected aseptically, minimising contamination with commensal flora.
- Swabs are not recommended for the isolation of mycobacteria.
- Collect sufficient material for all the tests required (eg, routine microbiology, cytology, histopathology).
- Transport to the laboratory in as short a time as practical to avoid overgrowth by contaminating commensal flora.
- Refrigerate specimens wherever possible if transport is to be delayed.

Sputum specimens

- An early morning specimen from deep productive cough is preferred. Samples produced later in the day are acceptable.
- Send one sample on each of three consecutive days.

Processing sputum specimens

- During processing there are many potential opportunities for generating splashes and aerosols that can lead to cross-contamination of specimens. All handling should be done in a way that reduces the risk of cross-contamination.

Processing other specimens

- 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 and easiest procedure to provide preliminary laboratory confirmation of the diagnosis of mycobacterial infection.
- There are three commonly used staining methods to detect AFB: the two carbolfuchsin-based stains, Ziehl-Neelsen and Kinyoun, and fluorochrome stains.
Both carbolfuchsin methods stain the mycobacterial cells red against the methylene blue counter stain. Both are examined under oil immersion at 1000 x magnification, and at least 300 fields should be examined before calling a slide negative.

A fluorochrome stain, auramine O or auramine-rhodamine, is the screening method recommended for laboratories with a fluorescent (ultraviolet) microscope.

The specificity of a positive smear as a predictor of TB, as opposed to infection with non-tuberculous micobacteria (NTM) will depend on host factors such as age, immune competence and underlying disease.

**Reporting smear results**

- For uniform reporting of smear results it is recommended that the Centers for Disease Control reporting system be used (see Table 12.1, page 14).

**TB culture methods**

- At least one solid medium must be used for each mycobacterial culture.
- Liquid media reduce the time to detect the growth of mycobacteria by about seven days, and all mycobacterial cultures should include a liquid culture medium.
- The Centers for Disease Control reporting system is recommended for uniform reporting of culture results (see Table 12.2, page 15).

**Susceptibility testing**

- All initial isolates from patients with culture-proven TB should have susceptibility testing performed.
- The BACTEC and the BD960 system are acceptable for breakpoint testing of *M. tuberculosis* isolates against the four first-line drugs, and streptomycin.

**Mycobacterial identification with DNA probes**

- Nucleic-acid identification systems allow same-day identification of referred cultures of *M. tuberculosis* complex. Each probe is specific for an individual mycobacterial species. Specific mycobacterial DNA or RNA fragments are detected by nucleic acid hybridisation.

**Nucleic acid amplification tests (NAAT) for TB**

- These tests use various molecular methods to amplify target nucleic acid sequences in specimens or cultures. When used on sputum specimens the performance of NAAT depends on the number of organisms present. Most (~95%) smear-positive specimens have positive NAAT results, but only ~50% of smear-negative specimens are NAAT-positive.
- Because of their cost, as well as sensitivity and specificity issues, NAAT should be reserved for situations where the result will have a significant bearing on management decisions.
Immunological tests for TB

- Immunological methods attempt to measure specific humoral (antibody) or cellular responses to infer the presence of past or present mycobacterial infection. They are performed on blood samples, not on a specimen from the site of infection.

Lymphocyte stimulation (interferon-release) tests

- In these assays peripheral blood lymphocytes from blood samples from patients with known or suspected infection are stimulated with mycobacterial antigens. If the lymphocytes recognise the antigens, they produce interferon-\(\gamma\) and this is measured by enzyme immunoassay.
- More epidemiological and costing information is needed, but reports so far do not support using interferon-release assays as a replacement for the Mantoux test.

Serological tests

- The current performance characteristics of serological tests for TB do not allow their recommendation for routine use in the diagnosis of infection in New Zealand.

Molecular typing (fingerprinting) of \(M.\) tuberculosis

- The routine typing of \(M.\) tuberculosis isolates in New Zealand has been recently introduced to:
  - support epidemiological information on the likely source and spread of \(M.\) tuberculosis
  - identify strains of high infectivity
  - identify false-positive cultures due to cross-contamination of specimens during collection, processing or culture.
- Restriction fragment length polymorphism (RFLP) has become the standard international method for fingerprinting isolates of \(M.\) tuberculosis.
- Most strains of \(M.\) tuberculosis contain from 6 to 20 copies of a particular insertion sequence called \(\text{IS}_{6110}\). The location and number of copies of \(\text{IS}_{6110}\) varies between strains.
- After cutting up the genome with restriction enzymes and separating different-sized fragments by gel electrophoresis, the fragments are probed with a labelled \(\text{IS}_{6110}\) probe. The position and number of bands, called the strain’s ‘fingerprint’, characterise the strain. Strains with identical fingerprints are considered clonal and indicative of recent transmission, while isolates with unique patterns are considered unrelated.

Laboratory issues

Levels of service: recommendations

Level I service – microscopy only:
- a routine five-day working week service for acid-fast microscopy
- out-of hours acid-fast microscopy, particularly for hospital-based laboratories
- smear results reported within 24 hours of specimen collection
- a more rapid AFB smear service available for urgent situations.

Level II service – microscopy and culture:
- a broth medium included in all mycobacterial cultures
if a broth culture system is not available for all specimens, immediately forward critical samples to a laboratory where liquid-cultures are performed.

Level III service – microscopy, culture, identification to species level, and susceptibility testing:

- culture and (DNA probe) 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.

Timely reporting of results:

- 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.

**Laboratory safety**

- Tubercle bacilli are a hazard to laboratory workers. Stringent safety precautions are required at all stages in the processing of samples and handling of culture. All sputum specimens should be handled as if they contain tubercle bacilli.
- Safety precautions include the following:
  - a separate room for mycobacteriology
  - a properly certified and maintained class I or class II biological safety cabinet (BSC) in which all specimen handling is performed; class I cabinets vented to the outside are the preferred option
  - suitable face masks and particulate respirators such as 3M No. 1814.
- A policy for monitoring the health of staff should be in place (see Chapter 9: 'Infection Control').

**Cross-contamination and false-positive cultures**

- False-positive cultures are not uncommon, and many may not be recognised as such by laboratory and clinical personnel.
- False-positive cultures can adversely affect patients, their contacts, hospitals, and the public health system.
- If false-positive cultures and/or contamination are suspected, laboratory staff should notify the patient's doctor and have DNA fingerprinting performed on isolates from the putative source and the potentially contaminated specimen.
- Clinicians should have a high index of suspicion of contamination as an explanation for unexpected culture results. They should contact the laboratory.

**Quality control**

- Quality standards for the laboratory diagnosis of TB should cover all aspects of the service, from transportation of samples to the laboratory to issuing reports and the collation of data.
Internal quality control

- Contamination rate: laboratories should monitor to ensure that essentially all smear-positive specimens grow a mycobacterium, and that the bacterial and fungal contamination rate is acceptable (<5%).
- Cross-infection: all smear-negative, single-isolate positive cases should have their DNA fingerprints compared with other concurrent isolates the laboratory has recovered to ensure the result is not due to cross-contamination.
- Air flow and biological safety cabinet performance: the airflow into the mycobacteria processing area and the performance of the BSC used for specimens and culture processing need regular maintenance and checking to ensure maximal safety for laboratory staff.
- Meeting reporting guidelines: laboratories should review their turnaround times for reporting smear, culture or identification results to ensure they are meeting the 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 control programme covering these procedures (e.g., The Royal College of Pathologists of Australasia (RCPA) programme).
- Level III laboratories should participate in the College of American Pathologists (CAP) programme, which covers identification and susceptibility testing.

Current status of TB testing in New Zealand

- The last survey undertaken in 2001 showed a high overall standard of laboratory practice in mycobacteriology, with the opportunity for improvement in some areas:
  - all laboratories performing mycobacteriology participated in a quality control programme
  - all used a BSC for mycobacterial work
  - most level II/III laboratories (93%) used a liquid culture medium, with most (87%) using a solid medium as well
  - a minority (33%) of laboratories did not have an active staff-screening programme for those working in mycobacteriology.

Future developments

- Regular review of the growing literature on lymphocyte stimulation assays should be undertaken to determine when there is enough evidence for their being a worthwhile replacement for the Mantoux test.
- Fingerprinting of all new isolates of *M. tuberculosis* recovered in New Zealand began in July 2002. A standardised national procedure must be developed for linking fingerprinting data to notification data and to the findings of conventional epidemiological investigations if the potential gains in disease control from fingerprinting are to be realised.
- Further improvements to laboratory practice should include the following.
  - Laboratories culturing fewer than 15 specimens a week should consider sending mycobacterial cultures to a laboratory processing more specimens.
  - All laboratories performing mycobacterial cultures should have an active staff-screening programme for staff who do this work.
- Standard ways of reporting smears and cultures are needed throughout New Zealand (see 12.2.1).
- Consideration could be given to a standard method of providing cumulative reports for patients being cultured while on treatment.
Introduction

Clinical mycobacteriology laboratories play an important role in TB control through the timely detection, isolation, identification, and drug-susceptibility testing of *Mycobacterium tuberculosis*. In addition to testing and reporting, it is important for laboratories to have a working relationship with clinicians and with services responsible for TB control, such as medical officers of health and ESR.

This chapter deals with the laboratory diagnosis of TB, and updates the quality, performance and safety issues in laboratories performing mycobacterial testing. There are, however, many other mycobacteria that are accepted as true human pathogens. These organisms are discussed in Chapter 19: ‘Non-tuberculosis Mycobacteria’.
12.1 Classification of mycobacteria

12.1.1 What are mycobacteria?
Mycobacteria are aerobic, slightly curved or straight bacilli (ie, rod shaped), 0.2–0.6 x 1.0–10 μm in size. They have cell walls with a high lipid content that includes waxes. These waxes have characteristic mycolic acids with long, branched chains.

The lipid content of the cell wall excludes the usual aniline dyes used to stain bacteria. Mycobacteria are not therefore readily stained using the Gram stain method. They are, however, considered gram-positive. Special staining methods are 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 to very slow (eg, M. tuberculosis takes 16–18 hours to undergo one cycle of replication).

12.1.2 Classification
The genus is divided into the M. tuberculosis complex and the rest. The M. tuberculosis complex contains M. tuberculosis, M. bovis, M. microti, M. canettii and M. africanum.1 M. bovis is the name given to the bovine tubercle bacillus in 1896. It has a limited number of biochemical and genetic differences from M. tuberculosis. The bacillus Calmette-Guérin (BCG), used as a vaccine against TB, has the properties of M. bovis from which it was derived, except that it has attenuated pathogenicity. M. africanum and M. microti occupy positions along the phenotypic continuum between M. tuberculosis and M. bovis. They are not discussed further.

The rest of the genus have been referred to by a variety of terms, 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. These mycobacteria are not really atypical at all, however, and are in fact characteristic of their own species. Therefore the term NTM is now preferred7 and will be used when referring to these species as a group. An overview of NTM is provided in Chapter 19: ‘Non-Tuberculous Mycobacteria’.
12.2 Diagnostic testing for TB 1-6

12.2.1 Smear and culture testing

Specimen collection and transport

All relevant clinical details need to be written on the request form, which should clearly indicate all the tests required on the specimen (eg, routine culture, cytology). Use sterile, leak-proof disposable plastic containers labelled with the patient’s name and specimen type, and the date and time of collection.

Collect specimens aseptically, minimising contamination with commensal flora. Swabs are not recommended for the isolation of mycobacteria. Collect sufficient material for all the tests required (eg, routine microbiology, cytology, histopathology). Do not use fixatives or preservatives for culture specimens.

Transport to the laboratory in as short a time as practical to avoid overgrowth by contaminating indigenous flora. Refrigerate specimens wherever possible 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.

Sputum specimens

An early morning specimen from deep productive cough is preferred, although samples produced later in the day are acceptable. Send one specimen on three consecutive days. For additional comments, see Chapter 14: ‘Clinical Investigation and Assessment of Tuberculosis’, section 14.1.4, ‘Spontaneous sputum mycobacterial smear and culture’).

Do not pool specimens. Pooling specimens over several days delays the time for the smear result to be known 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 that the efficacy of treatment can be followed. It is recommended that patients on treatment, who are still producing smear-positive sputum should have specimens sent for quantitative smear reporting and culture approximately every two weeks.

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 14: ‘Clinical Investigation and Assessment of Tuberculosis’.
**Early morning urines (EMUs)**

The complete first morning urine should be collected into clean containers. The minimum volume required is 40–50 ml. Send one on three consecutive days.

Unacceptable specimens include pooled urine from catheters, and a volume less than 40 ml. Indications for EMU tests are discussed in Chapter 14.

**Tissues, curettings, bone and aspirates**

Collect into sterile containers and note clearly on the request form that mycobacterial culture is required. If histopathology is also required, the specimens should be processed first for microbiology and then sent on for histopathology.

**Blood and bone marrow**

Specimens must be inoculated immediately into the mycobacterial blood culture system used by the receiving laboratory. This must be done at the bedside.

**Wound swabs**

Swabs are acceptable only if a biopsy or aspirate cannot be obtained. If used, they must be placed in transport medium.

**Gastric aspirate (lavage)**

If possible, these 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 14: ‘Clinical Investigation and Assessment of Tuberculosis’.

**Processing sputum specimens**

Sputum specimens contain contaminating oropharyngeal flora, which, because of their far faster growth rate, will overgrow TB cultures unless they are eliminated. Mycobacteria are recovered optimally from clinical specimens by using procedures that reduce or eliminate contaminating bacteria while releasing mycobacteria trapped in organic material (mucus, cells, serum and other proteinaceous material).\(^1\)

Sputum requires liquefaction. Sodium hydroxide is the most commonly used decontaminant. It also serves as a mucolytic agent. The stronger the decontamination agent used, the higher its temperature while acting on the specimen; and the longer it is in contact with the specimen, the greater the killing action will be on contaminants and mycobacteria.
After neutralising the decontamination agent the specimen must be centrifuged to concentrate the mycobacteria. Centrifugation must be carried out at $3000 \text{ g}$ for 15 minutes.

All decontaminating methods are toxic to mycobacteria to some extent. The best yield from cultures will be with the mildest decontamination procedure that sufficiently controls contaminants. However, even under optimal conditions decontamination kills all but 10–20% of mycobacteria in a specimen. Insufficient decontamination is generally defined as a contamination rate of 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 in a way that reduces the risk of cross-contamination (see section 12.4.4 for more information on cross-contamination.

### Processing other specimens

Other specimens that contain contaminating bacterial flora also require decontamination. Tissues or aseptically collected body fluids do not usually require the digestion and decontamination procedures used for contaminated specimens. Tissues can be ground and inoculated directly to both solid and liquid media. Infected body fluids commonly contain only few mycobacteria and should be concentrated by centrifugation to maximise the yield of culture.

### Smear microscopy and staining

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. All specimens, except urine, should have a stained smear read to detect the presence of AFB. Smears of urine are usually negative and are usually not cost-effective.

Smears should be fixed by placing the prepared slides on a heated surface. Heat-fixing smears does not kill mycobacteria and all slides must be handled as if infectious.

There are three commonly used staining methods to detect AFB: the two carbol fuchsin-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 carbol fuchsin methods stain the mycobacterial cells red against the methylene blue counter stain. Both are examined under oil immersion at 1000 x magnification, and at least 300 fields should be examined before calling a slide negative.
A fluorochrome stain, auramine O or auramine-rhodamine, is the screening method recommended for laboratories with a fluorescent (ultraviolet) microscope. These stains fluoresce under ultraviolet illumination and mycobacteria appear bright yellow against a dark background. Because of this, smears can be scanned at lower magnification and more of the smear can be read in less time compared with Ziehl-Neelsen or Kinyoun stained smears. Positive fluorochrome stains can be overstained with a carbolfuchsin method to confirm the presence of AFB.

If there are too few AFB present to call a smear ‘positive’ (see Table 12.1), another smear should be made from the same specimen (if possible), and a repeat specimen requested. For smears to be positive, approximately $10^5$ AFB/ml of sputum are needed. Cultures can be expected to be positive with 10–100 AFB/ml of sputum.

Acid-fast smears have high specificity but some other organisms may also stain acid-fast, including *Nocardia*, *Rhodococcus* and *Legionella micdadei*.

The proportion of cases of culture-proven pulmonary TB varies in different populations. In New Zealand about 40% of culture-positive cases are AFB smear-positive.

Examination of smears for AFB remains the most rapid and economical means of detecting infectious cases of pulmonary TB. The specificity of a positive smear as a predictor of 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 uniform reporting of smear results it is recommended that the Centers for Disease Control reporting system be used.\(^8\) The report wording and the corresponding number of AFB present in the smear are summarised in Table 12.1. It is also recommended that laboratories report, alongside the 1+ to 4+ result, the numerical result in brackets; eg, 2+ AFB seen (1–9 AFB/10 fields).

Laboratories using carbolfuchsin-stained smears simply report as indicated in Table 12.1. Laboratories using a fluorochrome stain will need to convert the number of AFB seen to the corresponding number seen on a carbolfuchsin-stained smear.
Table 12.1: Acid-fast smear evaluation and reporting

<table>
<thead>
<tr>
<th>Report</th>
<th>AFB seen by staining method and magnification</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fuchsin stain x 1000</td>
</tr>
<tr>
<td>No AFB seen</td>
<td>0</td>
</tr>
<tr>
<td>Doubtful; repeat</td>
<td>1–2/300 F (^b) (3 sweeps) (^c)</td>
</tr>
<tr>
<td>1+</td>
<td>1–9/100 F (1 sweep)</td>
</tr>
<tr>
<td>2+</td>
<td>1–9/10 F</td>
</tr>
<tr>
<td>3+</td>
<td>1–9/F</td>
</tr>
<tr>
<td>4+</td>
<td>&gt; 9/F</td>
</tr>
</tbody>
</table>

\(^a\) Adapted from Kent and Kubican.\(^8\)
\(^b\) F = microscope fields.
\(^c\) In all cases, one full sweep refers to scanning the full length (2 cm) of a smear 1 cm wide by 2 cm long.

**TB culture methods**

A variety of media are available to use for the recovery of mycobacteria, including solid and liquid media.\(^1\)\(^3\) Media may be made selective by the addition of one or more antibiotics to prevent overgrowth of contaminating bacteria or fungi.

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.\(^1\) Agar-based media have the advantage of being transparent, allowing earlier detection of mycobacterial colonies. They are more expensive than LJ, however, have a shorter shelf life,\(^1\) 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. At least one solid medium must be used for each mycobacterial culture.\(^1\)\(^3\)

Several liquid media are available for recovering mycobacteria. Although they cost more than solid media, they 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. All mycobacterial cultures should include a liquid-culture medium.\(^1\)\(^3\)

All New Zealand laboratories should use a standardised, semi-quantitative method for reporting mycobacterial culture results. The method from the Centers for Disease Control in America is recommended, and is shown in Table 12.2.
### Table 12.2: Reporting scale of mycobacterial cultures on solid media

<table>
<thead>
<tr>
<th>Colony count observed</th>
<th>Reporting method</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 50 colonies</td>
<td>Record actual count</td>
</tr>
<tr>
<td>50–100 colonies</td>
<td>1+</td>
</tr>
<tr>
<td>100–200 colonies</td>
<td>2+</td>
</tr>
<tr>
<td>Semi-confluent growth</td>
<td>3+</td>
</tr>
<tr>
<td>Confluent growth</td>
<td>4+</td>
</tr>
</tbody>
</table>

Source: American Thoracic Society.1

### Susceptibility testing

All initial isolates from patients with culture-proven TB should have susceptibility testing performed.2,9,10 Routine susceptibility testing on isolates recovered from patients on treatment is not required.9,10 Whether the susceptibility tests on isolates recovered from patients during treatment should be repeated depends on the patient’s clinical progress, the isolate’s initial susceptibility results and the continuity of treatment.

If there has been a period of more than about three weeks in which only a partial regimen has been taken (eg, during drug challenge testing to identify which drug is causing side-effects), repeat susceptibility testing should be requested by the clinician because of the risk of drug resistance developing (see also Chapter 15: ‘M. tuberculosis, TB Medicines and Monitoring’, section 15.8, ‘Management of drug reactions’).

Current susceptibility methods for *M. tuberculosis* define resistance as growth of greater than 1% of an inoculum in the presence of a ‘critical’ concentration of the anti-tuberculous drug. Critical concentrations were adopted by international convention. They represent the lowest concentration of drugs that inhibit 95% of ‘wild strains’ of *M. tuberculosis* (ie, strains that have never been exposed to the drugs), while at the same time not inhibiting the growth of strains isolated from patients not responding to treatment, and that are considered resistant. When greater than 1% of the tested *M. tuberculosis* inoculum is resistant to the critical concentration of a drug, that drug is not, or soon will not be, useful for anti-tuberculous chemotherapy.

For susceptibility testing, the BACTEC radiometric method and the BD960 system are acceptable for breakpoint testing of *M. tuberculosis* complex isolates against the four first-line drugs: isoniazid, rifampicin, ethambutol and pyrazinamide. Both methods are also reliable in determining streptomycin susceptibility.

Isoniazid testing may be performed using two concentrations: critical and higher concentration. Isolates resistant to the critical concentration but susceptible to the higher concentration should have the following comment appended to the report:

*These test results indicate low-level resistance to isoniazid. Some evidence indicates that patients infected with strains exhibiting this level of resistance may benefit from continuing isoniazid treatment. A specialist in the treatment of TB should be consulted concerning the appropriate treatment regimen.*
Supplemental susceptibility testing is available for isolates with resistance to any first-line agent at LabPlus, Auckland Hospital. Testing is available for amikacin, capreomycin, ciprofloxacin, clarithromycin, cycloserine, ethionamide, rifabutin, and streptomycin. Capital and Coast Health also performs second-line drug susceptibility testing.

*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 performed to fully speciate the isolate.

### 12.2.2 Nucleic acid amplification tests (NAAT) for TB

Nucleic acid amplification tests (NAAT) use various molecular methods to amplify target nucleic acid sequences in specimens or cultures. Most of these methods have the ability to provide confirmation of the presence of the target organism within a single working day. Despite this advantage, the role of NAAT in the diagnosis of TB is not settled.\(^5\)\(^6\)

When used on sputum specimens, the performance of NAAT depends on the number of organisms present. Around 95% of smear-positive specimens have positive NAAT results but only ~50% of smear-negative specimens are NAAT positive.\(^6\) There should not be over-reliance on NAAT testing in this latter situation: a TB expert should advise if the probability of TB is sufficient to warrant starting TB treatment regardless of the NAAT result.

Because of their cost, as well as sensitivity and specificity issues, NAAT should be reserved for situations where the result will have a significant bearing on management decisions. (See also: ‘Recommendations for NAAT testing’, below.)

#### Sensitivity and specificity

Sensitivity of such assays can be as low as 10 mycobacteria, as judged by serial dilutions of a suspension of known colony count. The assays target the insertion sequence IS\(^{6110}\). Therefore both *M. tuberculosis* and *M. bovis* are indistinguishably detected. Rare strains of *M. tuberculosis* lacking IS\(^{6110}\) have been reported from China and Vietnam. Strains such as these will be missed in this assay, but none have yet been encountered in New Zealand.

Specificity is 100% where amplicons are sequenced to confirm identity. As with all PCR assays, DNA contamination is a possible source of false-positive results. Specimens that are inhibitory to *Taq* polymerase cannot be assayed by PCR.

#### Applicability

A positive diagnosis of TB is best made by culture, where possible. PCR is relevant as an alternative way to make the diagnosis:

- as an adjunct to culture, where speed of diagnosis is a premium (eg, TB meningitis)
- where fresh tissue is not available (eg, retrospective analysis of fixed tissues that are histologically suggestive of TB). Formalin fixation does however affect the molecular arrangement of DNA and may lead to a decrease in the efficacy of
amplification. The larger the tissue has been fixed, the greater likelihood for decreased sensitivity.

Occasionally other samples may be relevant (eg, pleural biopsy, pleural or pericardial effusion, or ascitic fluid). In every case, an adequate sample must also be sent for culture. Fine-needle biopsy may be suitable, but not if the specimen only comprises the rinsings from a biopsy needle (after histology and other culture aliquots have been taken). Sputum samples should be sent for culture. They are not accepted for PCR by all laboratories (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 the laboratory. 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.

**Nucleic-acid amplification tests available for use on respiratory specimens**

Available assays for TB include:
- Gen-Probe Amplified *M. tuberculosis* Direct Test (MTD)
- Abbott LCX method
- Becton Dickinson Protech system
- Roche Amplicor test.

**Recommendations for NAAT testing**

The routine use of NAAT for respiratory specimens is not justified. These tests should only be used where diagnostic, therapeutic or infection control issues require a rapid result. NAAT should be considered for:
- 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 with 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, tissue sent in formalin).

Requests for NAAT testing for TB should be discussed with the laboratory microbiologist.
NAAT should not be considered for:

- smear-negative specimens with low probability of TB
- smear-positive patients with high probability of TB and of no public health concern
- paucibacillary non-respiratory specimens (e.g., pleural fluid; pleural biopsy is the preferred specimen)
- checking the response to therapy, because it will be positive
- testing for cure, because it may be falsely positive (some mycobacterial DNA may persist for a time after all organisms have been killed by treatment).

12.2.3 Immunological tests for TB

Culture and NAAT methods detect the presence of *M. tuberculosis* in the specimen. For a variety of reasons, including time to a positive report and cost, several immunological methods to diagnose active TB have been evaluated. Because of the problems associated with the Mantoux test, immunological tests have also been evaluated for the diagnosis of latent TB infection (LTBI).

Immunological methods attempt to measure specific humoral (antibody or cellular) responses to infer the presence of past or present mycobacterial infection. They have the benefit of not requiring a specimen from the site of infection – only an appropriate blood sample.

**Lymphocyte stimulation (interferon-release) tests**

In these assays peripheral blood lymphocytes from blood samples from patients with known or suspected infection are stimulated with mycobacterial antigens. If the lymphocytes recognise the antigens, they produce interferon-γ and this is measured by enzyme immunoassay. These assays have been called interferon-γ release assays (IGRA). Unlike Mantoux testing, these tests do not require a return visit by the patient for reading the skin reaction. They do, however, require technically complex testing.

Several studies suggest that the test may be an accurate method for detecting LTBI. There is a relationship between the amount of interferon produced by a person’s lymphocytes and the degree of induration on Mantoux testing. In the large American Centers for Disease Control study there was moderate to good correlation between Mantoux results and interferon release. This study also found that interferon release-negative, Mantoux-positive people were seven times more likely to have received BCG vaccination, suggesting the assay may discriminate between *M. tuberculosis* infection and BCG vaccination.

Another study showed significant differences between the results of IGRA testing and the tuberculin skin test (TST). That study compared the results of both tests in a population with a high prevalence of TB (> 200/100,000) in Ethiopia, and in a low-prevalence population (15/100,000) in Baltimore, Maryland. The TST results had a bimodal distribution, allowing a cut-off for positive results to be made. This did not occur with the IGRA results and a cut-off for positivity could not be determined. Moreover, the TST was more sensitive, specific and reproducible than the IGRA test. The authors concluded that in its present form the IGRA performed poorly in comparison to the TST.
accompanying editorial also concluded that current IGRA tests cannot replace the TST for the detection of active or latent infection with \textit{M. tuberculosis}.\textsuperscript{15}

Increased specificity with IGRA tests may be possible by refining the antigens used to stimulate patients’ lymphocytes (eg, by using early secreted antigen-6 (ESAT-6), an antigen present in \textit{M. tuberculosis} and very few other mycobacteria but not in BCG).\textsuperscript{11} Several studies have reported promising results. A recent UK study compared the response of interferon-$\gamma$-releasing T cells to ESAT-6 in patients with active TB, patients with non-tuberculous illnesses, healthy household contacts of patients with TB, and unexposed BCG-vaccinated people.\textsuperscript{16} Almost all (96%) of the 47 patients with TB had circulating interferon-$\gamma$-secreting T cells responding to ESAT-6, whereas only 8% of the 47 controls responded to ESAT-6. Of the patients with TB who had a TST, 69% were positive versus 96% positive to ESAT-6 in the stimulation assay. In addition, most (86%) of the TST-positive exposed household contacts had ESAT-6-specific T cells compared with none of 26 unexposed BCG-vaccinated subjects.\textsuperscript{16} This study did not evaluate the ability of the test to predict which TB contacts were likely to develop TB at a later time.

One small study based in Ethiopia has, however, investigated this issue.\textsuperscript{17} Samples were taken from 24 healthy household contacts of cases of active TB, and again approximately two years later. At the time of exposure those contacts whose T-cells recognised ESAT-6 in their T-cell stimulation tests were more likely to develop clinical TB than those who remained healthy or had non-tubercular disease. This is the first study to demonstrate a strong association between \textit{in vitro} responsiveness to ESAT-6 and the later progression to TB.\textsuperscript{17} Larger prospective studies that include children are required to evaluate the ability of such tests to identify those at risk of TB, so they can be offered preventive chemotherapy.

More epidemiological and costing information is needed, but reports thus far do not support using interferon-release assays as a replacement for the Mantoux test.

\textbf{Serological tests}

Numerous serological tests have been evaluated. These have involved a variety of tuberculous antigens including the heat-shock proteins, lipopolysaccharides, and peptides of \textit{M. tuberculosis}. Only rarely has more than one test been evaluated with sera from the same group of individuals. A recent large comparative study of seven serological tests found only moderate sensitivity for active TB, ranging from 16 to 57%.\textsuperscript{18} Although the tests had good specificity in Mantoux controls, they had poor specificity for anonymous serum controls.\textsuperscript{18}

The current performance characteristics of serological tests for TB do not allow their recommendation for routine use in the diagnosis of infection in New Zealand.
12.3 Molecular typing (DNA-fingerprinting) of *M. tuberculosis*

The routine typing of *M. tuberculosis* isolates in New Zealand has been recently introduced in order to:

- support epidemiological information on the likely source and spread of *M. tuberculosis* in New Zealand
- identify strains of high infectivity
- identify false-positive cultures due to cross-contamination of specimens during collection, processing or culture.

All isolates of *M. tuberculosis* look the same on culture plates. Previous 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 very limited value because the majority of isolates in New Zealand (83% in 2000) are fully susceptible.

The only adequate way to show the uniqueness, or otherwise, of an isolate of *M. tuberculosis* is by using molecular typing methods. Restriction fragment length polymorphism (RFLP) has become the standard international method for fingerprinting isolates of *M. tuberculosis*. Most strains of *M. tuberculosis* contain between 6 and 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 probed with a labelled IS6110 probe. The position and number of bands, called the strain’s ‘fingerprint’, characterise the strain. Strains with identical fingerprints are considered clonal and indicative of recent transmission, while isolates with unique patterns are considered unrelated.

Strains with no or low copies of IS6110 require alternative typing methods to test their relatedness. Options include spacer oligonucleotide typing (spoligotyping) and variable-number tandem repeat typing (VNTR). Spoligotyping is a PCR-based technique which detects the presence or absence of spacers in the direct-repeat locus of *M. tuberculosis*. In VNTR, also a PCR method, each isolate is typed by the number of copies of repeated units at 12 independent loci scattered throughout the genome. The high resolution, fast turnaround time and ability to easily compare the digital results between laboratories make VNTR an attractive method for typing isolates.

A recent large comparison of IS6110, spoligotyping and VNTR for typing isolates with low copy numbers of IS6110 showed that VNTR had resolution surpassing both other methods. VNTR is in common use in Australia and will become the secondary typing method in New Zealand.
DNA fingerprinting has already been useful in New Zealand. In an Auckland school and community outbreak, typing information confirmed transmission of a single strain of *M. tuberculosis*, as it did in a large chain of transmission in an Auckland church group.\textsuperscript{23, 24} Typing has also been of pivotal importance in determining the duration and extent of a prolonged outbreak in the North Island.\textsuperscript{25} Without typing, the link between patients in geographically diverse places would not have been possible. (See also Chapter 6: ‘Contact Investigation’.)
12.4 Laboratory issues

12.4.1 Levels of service

**Level I service: microscopy only**

Laboratories that send specimens to a larger centre for processing may find referral on a daily basis impractical because of the cost involved in packaging and transportation. Such laboratories should undertake examination of direct smears, at least on respiratory specimens. A ‘spot’ smear on unconcentrated sputum will detect highly infectious cases.

All level I laboratories should:
- have the ability to perform and interpret acid-fast stains
- use a routine five-day working week service for acid-fast microscopy
- provide for out-of-hours acid-fast microscopy, particularly for hospital-based laboratories
- report smear results within 24 hours of specimen collection
- have available a more rapid AFB smear service for urgent situations, such as serious illness or important infection control issues.

**Level II service: microscopy and culture**

A broth medium should be included in all mycobacterial cultures. Any laboratory not using a broth culture system for all specimens must immediately forward critical samples to a laboratory where liquid cultures are performed. Critical samples include those from smear-positive patients, or patients in whom active TB is indicated as clinically likely on the request form.

**Level III service: microscopy, culture, identification to species level, and susceptibility testing**

The three laboratories offering services for identification and susceptibility testing (Auckland, Waikato and Wellington Hospital laboratories) use liquid media methods for breakpoint susceptibility testing of *M. tuberculosis* complex. A reference service for identification and susceptibility testing should be backed up by specialised clinical advice.

Nucleic-acid identification systems allow same-day identification of referred cultures of *M. tuberculosis* complex. The Accuprobe system is the commercial nucleic acid probe available at present. Accuprobes are also available for *M. kansasii*, *M. gordonae*, *M. avium*, *M. intracellularare* and *M. avium* complex (MAC).

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.
12.4.2 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 e-mail. If e-mail is used there must be a system in place so that the messages are cleared daily.

12.4.3 Laboratory safety

Tubercle bacilli are 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 tubercle bacilli. The following standards are recommended:1,2

- a separate room for mycobacteriology
- a properly certified and maintained class I or class II biological safety cabinet (BSC) in which all specimen handling is performed; class I cabinets vented to the outside are the preferred option
- a sealed bucket centrifuge
- suitable face masks and particulate respirators such as 3M No. 1814 (see also Chapter 9: ‘Infection Control’)
- gowns or aprons and gloves must be worn during work and discarded or disinfected after use
- for identification and susceptibility work, the area should have controlled access and be under negative pressure relative to adjoining areas; a separate extraction system with all air leaving the area through HEPA filters is desirable
- doors to the area should be kept closed and access restricted to personnel working there
- sharps should be avoided whenever possible
- all materials, including slides, in contact with potentially tuberculous material must be decontaminated after use
- a policy for monitoring the health of staff should be in place (see Chapter 9: ‘Infection Control’).

12.4.4 Cross-contamination and false-positive cultures

A positive culture of *M. tuberculosis* has been considered definitive evidence for disease. False-positive cultures are, however, not rare.26–32 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.27
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 error for many reasons, including:

- the ability of some culture systems to identify mycobacteria when few organisms are present
- the multiple steps involved in processing mycobacterial cultures
- the viability of *M. tuberculosis* for long periods in laboratory environments
- the large number of mycobacteria present in some specimens.

The potential for error underscores the need for prompt recognition of false positives.

Potential mechanisms resulting in contamination and laboratory error include:

- mislabelling or switching 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, during sampling of sequential vials by the BACTEC 460 system, and by airborne contamination by aerosols in the BSC.)

Primary prevention of laboratory error requires use of standardised laboratory procedures that minimise the potential for errors.

Indicators of potential false-positive *M. tuberculosis* cultures are:

- all specimens from a patient are AFB smear-negative, and only one 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 the suspected culture 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 mislabelling specimens where they are collected.
Practice points

Timely recognition and investigation of false-positive cultures of *M. tuberculosis* requires the co-operation of 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 DNA fingerprinting 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. These include:

- reducing the number of smear-positive specimens processed from a patient
- separate handling of high-risk specimens (e.g., proficiency test samples)
- only having one tube uncapped at a time in the BSC
- 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.

12.4.5 Quality control

Quality standards for the laboratory diagnosis of TB should cover all aspects of the service, from transportation of samples to the laboratory to issuing reports and the collation of data. 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**

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 bacteria. Laboratories should monitor to ensure that essentially all smear-positive specimens grow a mycobacterium and that the bacterial and fungal contamination rate is acceptable (< 5%). Checking the reagents and the time of exposure used in decontamination is required if problems are encountered.

**Cross-infection**

All smear-negative single isolate positive cases should have their DNA fingerprintings compared with other concurrent isolates the laboratory has recovered to ensure the result is not due to cross-contamination.
Air-flow and biological safety cabinet performance

The air flow into the mycobacteria processing area and the performance of the BSC used for specimens and culture processing need regular maintenance and checking to ensure maximal safety for laboratory staff. An adequately performing BSC is 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 to ensure they are meeting the 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 control programme covering these procedures (eg, The Royal College of Pathologists of Australasia (RCPA) programme). Level III laboratories should participate in a programme that covers identification and susceptibility testing (eg, the College of American Pathologists (CAP) programme).

The Australian Society for Microbiology Special Interest Group for Mycobacteria provides an annual survey, which also gives excellent coverage of identification and susceptibility testing. Recent surveys have included PCR and fingerprinting assessments. This is voluntary for participating laboratories.
12.5 Current status of TB testing in New Zealand

Surveys of laboratory practice have been undertaken in 1994, 1998 and 2001. In 1994 55% of laboratories in New Zealand cultured for mycobacteria, with most (72%) culturing fewer than 10 specimens a week and only a minority (16%) using a liquid culture medium. The last survey undertaken in 2001 showed a high overall standard of laboratory practice in mycobacteriology, with the opportunity for improvement in some areas (V Talbot, personal communication, 2002). The following is a brief summary of the results of the 2001 survey.

- Forty-two of 57 (74%) laboratories replied to the survey.
- No laboratory offered level I service alone.
- Twelve laboratories offered level II service.
- Three laboratories offered level III service.
- All laboratories performing mycobacteriology participated in a quality control programme:
  - all used a BSC for mycobacterial work
  - eight (53%) laboratories used a carbolfuchsin stain
  - seven (47%) laboratories used a fluorochrome stain.
- Four laboratories using a fluorochrome stain overstained with a carbolfuchsin stain to confirm positive smears.
- Most (80%) level II/III laboratories offered an urgent out-of-hours service for AFB microscopy.
- Most level II/III laboratories (93%) used a liquid culture medium, with most (87%) also using a solid medium.
- A minority (40%) of those culturing for mycobacteria processed fewer than 15 specimens a week.
- A minority (33%) of laboratories did not have an active staff-screening programme for those working in mycobacteriology.
12.6 Future developments

12.6.1 Immunological tests for TB
Current work into the genomics of mycobacteria may allow for the recognition of antigens specific for *M. tuberculosis*. The use of several specific TB antigens should allow for better diagnostic reagents, especially for diagnosing LTBI. Regular review of the growing literature on lymphocyte stimulation assays should be undertaken to determine when there is enough evidence for their being a worthwhile replacement for the Mantoux test.

12.6.2 DNA fingerprinting
Fingerprinting of all new isolates of *M. tuberculosis* recovered in New Zealand began in November 2002. The level III laboratories outside Auckland send isolates for fingerprinting (typing) at LabPlus at Auckland Hospital. Typing requires a certain amount of DNA and therefore a heavy growth of the isolate is required. Typing results should be available within four weeks of receipt at the typing laboratory.

The typing result will be sent to the laboratory that forwarded the isolate and this information should be reported to the local public health service.

Typing results will also be included in the national TB database and will be reviewed regularly at ESR. A yearly report on the molecular epidemiology of TB in New Zealand will be produced.

Surveillance data should be reviewed for clusters of positive cultures from a laboratory and for case-patients associated with predictors for false-positive cultures (see section 12.4.4, ‘Cross-contamination’).

12.6.3 Detection of antibiotic resistance
If multi-drug resistance becomes more prevalent, the use of molecular methods to detect resistance may be required (see also Chapter 15: ‘*M. tuberculosis*, TB Medicines and Monitoring’). At present the low incidence of resistance does not warrant the establishment of molecular resistance tests.

12.6.4 Determining when a patient becomes ‘non-infectious’
This topic is discussed in Chapter 9: ‘Infection Control’, where the point is made that it is not certain when a smear-positive patient becomes ‘non-infectious’ to others during treatment.
12.6.5 Further improvements to laboratory practice

While there has been a steady and reassuring improvement in laboratory practice in mycobacteriology over the past eight years, there are several areas that could be improved.

- Laboratories culturing fewer than 15 specimens a week should consider sending mycobacterial cultures to a laboratory processing more specimens.
- All laboratories performing mycobacterial cultures should have an active staff-screening programme for staff who do this work (see Chapter 9: ‘Infection Control’).
- All laboratories performing mycobacterial cultures should use a broth and at least one solid medium for each specimen.
- Standard ways of reporting smears and cultures are needed throughout New Zealand (see section 12.2.1, ‘Smear and culture testing’).
- Consideration could be given to a standard method of providing cumulative reports for patients being cultured while on treatment. Such reports could contain:
  - date of starting treatment
  - dates when all sputum specimens were received at the laboratory
  - quantitative smear result of each specimen (see Table 12.1)
  - time to growth detection in liquid medium
  - semi-quantitative culture results (see Table 12.2).

Where more than one laboratory is involved, there would need to be good liaison between them, and agreement as to which laboratory would provide the cumulative report.
References


Chapter 13: Awareness, Clinical Features and Early Diagnosis of Tuberculosis

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This chapter is endorsed by the Thoracic Society of Australia and New Zealand

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Summary

Clinical awareness of tuberculosis

A high level of clinical awareness of TB is essential

- This is because:
  - in New Zealand the highest proportion of TB cases present to clinicians
  - delay in the diagnosis of TB continues to be an important issue.
Thus, improved clinical awareness of TB is a key factor in the control of TB in New Zealand.

Delayed diagnosis of TB

- Intervals between onset of symptoms and start of treatment in New Zealand, 1995-1999 were as follows:
  - 50% of cases were notified within one month of onset of the illness
  - 65% were notified within two months of onset
  - in 28% of cases this interval was three months or longer
  - in 10% of cases the interval was six months or longer.
- During the same period there was an average of 17 deaths from TB each year, with a case fatality rate of 4.5%. Thus, delay in making the diagnosis of TB is an important problem in New Zealand.

Types and sites of delay in the control of TB

- The types of delay include:
  - patient delay
  - delay in referral from the community
  - hospital / clinician delay: delays by hospital doctors or private specialists; delayed diagnosis (through delay in performing tests, or incorrect interpretation of X-rays etc); delayed notification of cases to public health
  - mycobacteriology laboratory delays: delay in receiving specimens; delay in performing or reporting tests; laboratory accidents and specimen contamination
  - delays from ancillary services: requests, reports or X-rays mislaid or lost
  - system delays
  - public health delay: delay in the follow-up of contacts of infectious cases.
- Delay in communication is a common factor that can occur at every stage.
- In an Auckland study the median values for delays were: patient delay = one week; doctor delay = 7 weeks; and total delay = 12 weeks.

Factors contributing to clinical delays in diagnosis

- The symptoms, signs and results of many investigations are non-specific.
- TB is a silent condition, with either no or few symptoms or signs until the condition is advanced.
- TB is relatively uncommon in New Zealand, and, because most doctors come across cases rarely, their awareness of TB may wane.
For all these reasons, a high index of suspicion is needed if TB is to be diagnosed early.
This is particularly true for doctors whose practice populations contain people from Pacific, Asian and African countries. Among these groups the disease is not rare in New Zealand.

Hospital / clinician delays

Failure to consider the diagnosis of TB is an important factor with hospital doctors and specialists in private practice. The other type of doctor-related delay in hospitals or with private specialists, is treatment delay.

Typical causes of delayed diagnosis of TB in hospitals

These include:
- unrecognised TB cases in wards
- surgeons not sending resection specimens for TB testing (sadly, a common omission, particularly when lymph nodes are excised)
- TB not considered when needle aspirates and other tissue specimens are taken
- people waiting for a clinic appointment
- doctors waiting for culture results in complex cases.

Consequences of delays: delayed presentation, referral, diagnosis and treatment

Delays in identification and treatment of more than two months have been shown to result in:
- spread of infection and disease in household contacts
- worsened severity of disease
- worsened long-term health following cure as a result of tissue destruction and scarring
- increased case fatality rate
- lost opportunities for preventing TB in child contacts.

The more advanced the disease, the more critical are further delays. By the time symptoms are present, it is urgent to consider the possibility of TB, to institute appropriate tests immediately, and to refer the patient without waiting for all results: symptomatic TB is far more likely to be advanced in its pathology and infectious to others.

Can delays be reduced in New Zealand?

Reducing delayed presentation

Delayed presentation (patient-related delay) might be minimised by:
- raising TB awareness among ethnic groups, associations, and those caring for people with conditions which put them at risk for becoming infected with, or developing, TB
- making opportunities to improve public knowledge about TB, thereby reducing fear and stigma about it
- making health care facilities more accessible to high-risk groups.

Key messages to promote early presentation with TB include:
- TB can be cured – and the earlier it is found, the easier it is to cure.
- People catch TB like they catch a ‘cold’: there should be no personal judgements associated with having TB.
- If you think you could have TB, tell your doctor and ask for tests.
- Tests and treatment for TB are free for everyone, even non-residents in New Zealand.
- Tell your doctor if someone in your family, or someone you know well, has had TB in the last few years. Then that doctor will know to be on the lookout for TB when you have health problems.
- There are many causes of cough, and TB is one possible cause. The chance of TB causing cough is increased if you have been in close contact with someone with infectious TB.
- Not all TB is infectious.
- If you get a cough, don't keep going from one family doctor to another, trying to get it fixed. Your best chance of finding the cause and getting better is to go back to the same doctor, several times if necessary.
- Ask the doctor to check for TB if you have had the cough for three weeks.

**Solving system-related problems**

1. As system-related delays are identified, those involved should endeavour to correct them promptly. Where the problem is not easily resolvable, or it applies to other regions, the local medical officer of health and the Ministry of Health Tuberculosis Working Group should be advised.

**Reducing doctor-related delays**

1. Key messages need to be given in medical school and be reinforced during postgraduate training in all sectors of medicine. They are summarised in the box in section 13.1.4.

**What duration of health-care-system delays are acceptable?**

1. There are no national or internationally accepted standards. Suggested standards are discussed in the text.

**Early identification of TB**

**Factors that lead to early detection**

1. The early identification of TB following presentation depends on:
   - heightened clinical awareness of TB in all areas of medicine: all doctors should have a low threshold for considering TB as a cause of a wide variety of symptoms and signs
   - knowledge of factors that increase the risk of an individual having TB (see below)
   - knowledge of the protean clinical features of TB
   - prompt initiation of appropriate investigations – including pursuing the diagnosis with invasive tests if necessary
   - referral to a TB clinician in a timely manner
   - investigation of contacts: for asymptomatic contacts this will usually be carried out by the public health service (see Chapter 6: ‘Contact Investigation’).
**Risk factors**

- Three types are associated with TB:
  - For developing TB infection, see Chapter 3: ‘Latent Tuberculosis Infection’, Table 3.2.
  - For developing TB disease, see Chapter 3: ‘Latent Tuberculosis Infection’, Table 3.3.
  - For reactivation of TB, see this chapter, Table 13.5.

**Clinical features of TB**

**General symptoms**

- It is rare for primary TB to cause symptoms. When they do occur, they are usually related to local complications.
- TB is usually asymptomatic until the condition is advanced.
- When they do occur, symptoms of TB are non-specific.
- Symptoms are often localised to the site(s) of disease.
- Systemic symptoms include malaise, fever, anorexia, weight loss and night sweats.

**Pulmonary TB**

- This is the most common form of TB.
- Pulmonary TB symptoms:
  - Inactive pulmonary TB is asymptomatic
  - Active TB may be asymptomatic initially, but as the extent and severity of disease progress, symptoms such as cough, sputum, breathlessness and (much less frequently) haemoptysis may occur.
- Atypical chest X-ray appearances are seen with immuno-suppression (eg, HIV/AIDS or diabetes mellitus).
- A characteristic of pulmonary TB is that there are few symptoms or signs despite extensive parenchymal disease. Abnormal chest signs are usually the result of lung fibrosis, cavities or pleural disease.

**Endobronchial TB**

- This may be misdiagnosed as asthma or lung cancer.

**Lymph node TB**

- This is the most common form of extra-pulmonary TB.

**Pleural effusion and tuberculosis**

- Tuberculous pleuritis is the second most common form of extra-pulmonary TB.
Future developments

1. Quality control programmes (see 13.1) that are computerised and relatively easy to complete and to monitor, offer the hope that clinical, laboratory and ‘system’ delays will diminish in the future. To be effective, these programmes must:
   - have performance indicators that clearly define specific causes of delay
   - be accompanied by the ability to undertake appropriate corrective measures.
Introduction

The themes of this chapter are awareness about TB (and problems relating to delays in its recognition), and the clinical features of TB disease. These topics lead on to the next chapter, which is about the investigation and assessment of TB. Together, these two chapters cover the factors relevant to the early identification of TB. The present chapter does not focus on latent tuberculosis infection (LTBI), which is covered in Chapter 3.
13.1 Clinical awareness of TB

There are two important facts that make clinical awareness of TB of great relevance to all clinicians:

1. by far the highest proportion of notified cases of TB in New Zealand are the result of people presenting to clinicians (see Table 13.1)
2. delay in the diagnosis of TB continues to be an important issue, as it has been for decades.1

The consequence of these two facts is that improving clinical awareness of TB is a key factor in improving TB control in New Zealand.

Table 13.1: How TB cases were discovered in New Zealand, 1995–2001

<table>
<thead>
<tr>
<th>Method of discovery</th>
<th>No. cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attended practitioner with symptoms</td>
<td>1547</td>
<td>59.3</td>
</tr>
<tr>
<td>Follow-up of a contact</td>
<td>278</td>
<td>10.7</td>
</tr>
<tr>
<td>Other method (not specified)</td>
<td>246</td>
<td>9.4</td>
</tr>
<tr>
<td>Immigrant/refugee screening</td>
<td>240</td>
<td>9.2</td>
</tr>
<tr>
<td>Reported as ‘Unknown’</td>
<td>200</td>
<td>7.7</td>
</tr>
<tr>
<td>Information missing on notification form</td>
<td>97</td>
<td>3.7</td>
</tr>
<tr>
<td>Total</td>
<td>2608</td>
<td>100</td>
</tr>
</tbody>
</table>

Note: Cumulative data from TB notification forms completed by practitioners: from ESR, Wellington.

13.1.1 Delay – a key factor affecting the control of TB

Delay is a major problem in the control of TB throughout the world. This occurs at a number of levels:

1. patient delay
2. delay in referral from the community
3. hospital/clinician delay, including delays by hospital doctors or private specialists, delayed diagnosis (through delay in performing tests, or incorrect interpretation of X-rays, etc.), and delayed notification of cases to public health
4. laboratory (and other ancillary service) delay, including delay in receiving specimens; delay in performing or reporting tests; laboratory accidents; and requests, reports or X-rays being mislaid or lost*
5. system delays
6. public health delay: delay in the follow-up of contacts of infectious cases.*

Delay in communication is a common factor that can occur at every level.

* Laboratory and public health delays will not be considered further in this chapter.
In New Zealand, the following intervals between onset of symptoms and start of chemotherapy were reported for TB cases notified between 1995 and 1999:\(^2\)

- 50% of cases were notified within one month of onset of the illness
- 65% were notified within two months of onset
- in 28% of cases this interval was three months or longer
- in 10% of cases the interval was six months or longer.

During the same period there was an average of 17 deaths from TB each year, with a case fatality rate of 4.5%. This shows that delay in making the diagnosis of TB is an important problem in New Zealand.

### 13.1.2 Types and causes of delay

**Patient delay: delay in presentation**

This is an important cause of delayed diagnosis and treatment of TB. The incidence of delays from this cause varies in different reports. Although there is extensive literature on this subject, only three recent studies will be cited – further references can be found in these papers.

In Auckland,\(^3\) 100 of 134 consecutive consenting adults with TB were studied. The median values for delays were:

- patient delay = one week
- doctor delay = seven weeks
- total delay = 12 weeks.

There were no significant differences in these delays for smear-positive and -negative cases. Only a minority experienced socioeconomic or knowledge barriers to seeking care. Longer patient delay was found in:

- smokers (adjusted odds ratio [OR] 2.11; 95% CI 0.74–6.05)
- patients who reported cough (OR 4.28; 95% CI 1.30–14.11)
- patients who hoped their symptoms would go away on their own (OR 1.95; 95% CI 0.73–5.21)
- patients reporting fear of what would be found on diagnosis (OR 9.15; 95% CI 0.94–89.47).

Queensland has a low incidence of TB, with only 2.69 cases per 100,000 population in 1998. The median patient delay for 782 symptomatic cases that were confirmed bacteriologically or histologically between 1985 and 1998 was 29 and 30 days for the total group and the pulmonary smear-positive (PSP) group respectively.\(^4\) Patient delay was longer than other delays, which is different from the Auckland experience.
In Los Angeles county Asch et al\textsuperscript{5} examined self-reported delay of more than 60 days from symptom onset. From a cohort of TB cases in which 72\% were immigrants, 50 (20\%) of the 248 symptomatic respondents (response rate of 60\%) delayed seeking care for more than 60 days (mean = 74 days, SD = 216 days). Significantly different reasons between delaying (n = 50) and non-delaying symptomatic cases (n = 198) were:

- patient factor – being unemployed
- perceived access barriers – no regular doctor; unsure where to go for care; anticipated high cost; long wait in office or long wait for appointment; fear of immigration authorities
- lack of perceived need – thought they could self-treat.

There were a number of other socio-ethnic factors in all three categories that did not influence delay. Improving the availability of services for high-risk groups was identified as having the potential to substantially reduce delay in seeking care for TB.

**Delay in referral from the community (GP delay)**

There are several factors that contribute to delay in recognising TB as a clinical possibility. These apply to clinicians at all levels of health care.

- The symptoms, signs and results of many investigations are non-specific.
- TB is a silent condition, with either no or few symptoms or signs until the condition is advanced.
- TB is relatively uncommon in New Zealand, and because most doctors come across cases rarely their awareness of TB may wane.

For all these reasons, a *high index of suspicion* is needed if TB is to be diagnosed early. This is particularly true for doctors whose practice populations contain people from Pacific, Asian and African countries. Among these groups the disease is *not* rare in New Zealand.

In the Auckland study,\textsuperscript{3} ‘doctor delay’ was the most important contributor to delay in diagnosis and commencement of treatment. The 100 patients saw 216 doctors (median = 2, range 2–6). The median number of times the patient was seen before receiving treatment was 4 (range 1–25). Of the doctors first consulted, 12\% requested a Mantoux test, 23\% a sputum test, 46\% a chest X-ray, and 35\% enquired about past exposure to TB. Sputum tests and chest X-ray are the most useful in diagnosing TB, but relatively few ordered them.

Longer doctor delay was associated with patients who:

- had pre-existing lung disease, particularly asthma (OR 7.37; 1.47–36.87)
- consulted multiple doctors (OR 3.75; 0.95–14.83).

Shorter doctor delay was found if the doctor:

- inquired into a history of TB in the family or household (OR 0.16; 95\% CI 0.04–0.69)
- requested a chest X-ray (OR 0.32; 95\% CI 0.08–1.27).
Cough (median delay 10 weeks), weight loss (10 weeks) and shortness of breath (11 weeks) were associated with longer delays than haemoptysis (four weeks), fever (six weeks) sweats (six weeks) or chest pain (five weeks).

In the Queensland study, diagnostic delays of more than 90 days occurred in 28 (7.5%) of symptomatic pulmonary smear-positive (PSP) cases. The most common causes of prolonged diagnostic delays were:

- failure to investigate a cough, which was treated symptomatically (12/27 cases)
- misdiagnosis of a chest X-ray (5/27 cases).

There were longer delays with increasing length of residency of migrants in Australia. The authors noted that doctors may need to be reminded that people from high-incidence countries have a life-long higher risk of TB.

<table>
<thead>
<tr>
<th>Practice points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lessons for New Zealand (and Queensland) practitioners from this study include:</td>
</tr>
<tr>
<td>- consider TB even in those immigrants who have been in the country a long time</td>
</tr>
<tr>
<td>- beware of TB in patients with other forms of respiratory disease</td>
</tr>
<tr>
<td>- GPs need access to chest X-rays</td>
</tr>
<tr>
<td>- feedback to radiologists is appropriate (as it is to all doctors) when important errors are made.</td>
</tr>
</tbody>
</table>

**Hospital and clinician delays**

As with doctors in the community, diagnostic delay (as a result of not considering the diagnosis) is an important factor for hospital doctors and specialists in private practice. The other type of doctor-related delay in hospitals or with private specialists is treatment delay, and we look at these in turn below.

**Delayed diagnosis**

Delayed recognition of TB in hospitals is a long-standing, well-described problem. This is evident from the following reports.

- In 1971 Stack reported undue delay in 17 of 71 (24%) TB cases at Edinburgh’s Western General Hospital. In eight this was due to failure to include TB in the differential diagnosis. Three patients died as a result of the delay.
- In 1980, at a 1200-bed general hospital in the US, Greenbaum et al found that TB was not suspected initially in 16 of 32 patients with pulmonary TB, and had not been diagnosed by the time of discharge in 10.
In a 1985 review in Tel-Aviv, 82 cases of active TB between 1960 and 1980 were found to have been diagnosed only at autopsy, and the major cause of death in many cases was related to TB. Pulmonary disease was present in 90%, 20% had received prolonged steroid treatment, 20% had epithelial malignancies, 8.5% had diabetes mellitus, and 5% had chronic renal failure.

**Practice points**

Three important lessons can be learned from the Tel-Aviv study.

- **TB can often accompany other conditions**: a critical time to consider TB is when other conditions don't respond to appropriate treatment.
- **Failure to think of TB** was evident in this study, and it is still a cause of delayed investigation, and thus of delayed diagnosis and treatment.
- **Vigilance is required with immunosuppression**, both that caused by treatment and from immunosuppressive conditions. These are recognised risk factors for progression from latent TB infection to active TB disease (see Chapter 3: ‘Latent Tuberculosis Infection’, Table 3.3).

Typical causes of delayed diagnosis of TB in hospitals include:

- unrecognised TB cases in wards*
- surgeons not sending resection specimens for TB testing* (sadly, a common omission, particularly when lymph nodes are excised)
- TB is not considered* when needle aspirates and other tissue specimens are taken
- waiting for a clinic appointment
- waiting for culture results in complex cases.

Finally, it has been reported that fluoroquinolone treatment of pneumonia may also lead to the delayed diagnosis of TB, as a result of the marked activity of these agents against *Mycobacterium tuberculosis*. Among patients treated empirically with fluoroquinolones for pneumonia, the median time between presentation to the hospital and initiation of antituberculosis treatment was 21 days (interquartile range 5–32 days); among those who were not treated it was five days (interquartile range 1–16 days; \( p = .04 \)).

**Treatment delays**

Treatment delay is defined as the time difference between making the diagnosis (unconfirmed or confirmed) and the start of treatment. In this type of delay, clinical judgement (which should be that of a clinician experienced in the treatment of TB) often dictates when treatment should be started.

---

* Failure to think of TB is an important contributor to doctor delays.
Treatment delays may be appropriate or inappropriate.

- **Inappropriate treatment delay** occurs when the patient is ill, and delay in treatment compromises the patient’s health, protracts suffering, or in general is not in the best interests of the patient.

- **Appropriate treatment delay** is when treatment is delayed to obtain culture or susceptibility results without compromising the patient’s wellbeing or best interests, such as in the case of a person recently arrived from a high-incidence country, who has relatively minor symptoms from cervical adenopathy, a strongly positive Mantoux, and a clear chest X-ray. Here, one should wait and at least obtain the FNA smear results. Then, if the smears are positive, also await the susceptibility pattern. The alternative is to start four-drug treatment once a positive FNA smear has been obtained. Even social reasons can be acceptable causes of treatment delay if no additional risks are created. However, a policy of starting treatment as soon as possible after making the diagnosis is optimal, and is generally appropriate.

**Mycobacteriology laboratory delays**

- Delays may occur before the laboratory is involved; for instance, because of slow transportation of specimens to the laboratory.

- Delays within TB laboratories are dealt with in Chapter 12: ‘Mycobacteriology: Laboratory Methods and Standards’. These include errors in performing tests, delays resulting from contamination of specimens, and delays in providing results.

**Delays from ancillary services**

Errors in the interpretation of results, and failure to report the degree of likelihood of active TB on chest X-rays, contribute to delayed identification of TB. Delays in getting reports to clinicians after tests or X-rays have been completed can be a problem, as can the situation when results or X-ray films are lost or misplaced.

**System-related delays**

It is arguable whether this category should be listed or not. From the discussion below it will be apparent that responsibility for system-related delays and their resolution can be assigned to one or more groups.

- In New Zealand, system-related delays include situations that cause uncertainty in the minds of GPs, such as one service (the hospital) caring for active TB and another service (public health) caring for Mantoux-positive individuals. GPs could also be uncertain whether potential TB cases should be referred to the local secondary service or to the regional tertiary TB service – a situation that exists in Auckland. Such uncertainties are known to cause delay in referral, and delay in referrals receiving action if they are sent to the wrong service. Rarely, this can have lethal results. Always there is increased risk to the health of the individual and their family, and the risk of greater costs to the health provider.
Implementing the system that operates in some Australian states, whereby hospital and public health medical and nursing staff work together in a joint TB facility, would overcome these problems, as there would be a TB control unit to which all TB problems could be referred.

Delay is not uncommon when a GP asks for a CXR to be performed by a public hospital. A mechanism may be needed in some areas, whereby CXRs ordered because of suspicion of active TB are performed without delay. This is a problem that could be overcome by liaison by the Ministry of Health with District Health Boards and GPs. However, for such a priority X-ray system to be successful, it would be essential for it to remain free of abuse. An individual GP would only need to access the system occasionally.

System-related factors may differ from country to country. They include failure to require notification of TB by private practitioners in some countries, lack of cooperation between different health care sectors, or delayed investigation of contacts, perhaps through inadequate staffing of public health services.

13.1.3 Consequences of delays

Delays in identification and treatment of more than two months have been shown to result in:

- spread of infection and disease in household contacts: an average of eight contacts were exposed per TB case in the report by Asch et al
- worsened severity of disease
- worsened long-term health following cure, due to tissue destruction and scarring
- increased case fatality rate
- lost opportunities for preventing TB in child contacts

The more advanced the disease, the more critical are further delays. By the time symptoms are present it is urgent to consider the possibility of TB, to institute appropriate tests immediately, and to refer the patient without waiting for all results: symptomatic TB is far more likely to be advanced in its pathology and infectious to others.

13.1.4 Can delays be reduced in New Zealand?

Reducing delayed presentation

The data presented thus far in this chapter underline the importance of making every effort to reduce patient-related delays. The study of diagnostic delay in Auckland by Calder et al showed there is definite potential to reduce both kinds of delay, and pointed to key practices that may reduce them. However, there is no research demonstrating that any of the delays discussed above have been shortened by planned interventions. The efficacy of interventions in these areas is unknown.
Delayed presentation (patient-related delay) might be minimised by:

- raising TB awareness among ethnic groups, associations, and those caring for people with conditions that put them at risk of becoming infected with, or developing, TB
- making opportunities to improve public knowledge about TB, thereby reducing the fear and stigma surrounding it
- making health care facilities more accessible to high-risk groups.

Education about TB is discussed elsewhere in these Guidelines. Important messages to be understood by communities are shown in Table 13.2.

**Table 13.2: Key messages to promote early presentation with TB**

<table>
<thead>
<tr>
<th>Message</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>TB can be cured - and the earlier it is found, the easier it is to cure.</td>
<td></td>
</tr>
<tr>
<td>People catch TB like they catch a ‘cold’: there should be no personal judgements associated with having TB.</td>
<td></td>
</tr>
<tr>
<td>If you think you could have TB, tell your doctor and ask for tests.</td>
<td></td>
</tr>
<tr>
<td>Tell your doctor if someone in your family, or someone you know well, has had TB in the last few years. Then that doctor will know to be on the lookout for TB when you have health problems.</td>
<td></td>
</tr>
<tr>
<td>There are many causes of cough - TB is just one possible cause. The chance of TB causing cough is increased if you have been in close contact with someone with infectious TB.</td>
<td></td>
</tr>
<tr>
<td>Not all TB is infectious</td>
<td></td>
</tr>
<tr>
<td>If you get a cough, don’t keep going from one family doctor to another, trying to get it fixed. Your best chance of finding the cause and getting better is to:</td>
<td></td>
</tr>
<tr>
<td>go back to the same doctor, several times if necessary</td>
<td></td>
</tr>
<tr>
<td>ask the doctor to check for TB if you have had the cough for three weeks.</td>
<td></td>
</tr>
</tbody>
</table>

**Reducing doctor-related delays**

Achieving greater awareness of the possibility of TB among doctors in all clinical disciplines continues to be a priority issue. Education is required. Key messages need to be given in medical school and reinforced during postgraduate training in all sectors of medicine. These messages are summarised in Table 13.3.
Table 13.3: Reducing doctor-related delays in TB diagnosis

**Knowledge**
Be aware of the clinical features and appropriate investigations for diagnosing TB.

**Practice system**
Mark patient records to identify those:
1. known to be Mantoux-positive
2. who have been treated in the past for TB or LTBI*
3. with increased risk of LTBI (especially those with a known contact, a family history** of TB, or history of living in a high-prevalence country)*
4. with clinical factors that increase the risk of TB infection progressing to disease.

**Good clinical habits**
Perform:
- CXR, if cough persists for three weeks (a general clinical rule)
- sputum TB tests, without delay if active TB is suspected
- Mantoux test, judiciously, because of its low diagnostic specificity, but:
  - avoid using the Mantoux as a screening test for LTBI
  - avoid using the Mantoux test as a first-line diagnostic test: if TB is suspected, sputum testing and CXR are needed. Mantoux testing for diagnostic purposes is reserved for difficult diagnostic situations (see Chapter 14: ‘Clinical Investigation and Assessment of Tuberculosis’).

* Mantoux screening by GPs to detect people who may be in categories 2 and 3 above is not justified, because the Mantoux test is not sufficiently specific to make such screening cost-effective. (It is, of course, unnecessary for people in category 1.)

** See Vidal et al. 12

**Solving system-related problems**
As system-related delays are identified, those involved should endeavour to correct them promptly. Where the problem is not easily resolvable, or may apply to other regions, the local medical officer of health and the Ministry of Health Tuberculosis Working Group should be advised.

**13.1.5 What constitutes acceptable delay?**
There are no national or internationally accepted standards. ‘Acceptable delay’ is a subjective decision, based on the presence or absence of symptoms, co-morbidities and the availability of health care, although the following criteria for acceptable delay have been used:
- delay between first consultation and start of treatment: one month or less 13
- delay between onset of symptoms and commencement of treatment: one to two months 14 15 16
At Green Lane Hospital TB unit in Auckland a number of performance indicators are used. They may well change with time. They are ‘reasonable,’ and are not evidence-based. Other hospitals may decide they could reduce some time intervals. We do not believe they should be extended. They are shown in Table 13.4. Collection of this data would be a useful part of a clinical TB quality assurance programme.

**Table 13.4:** Monitoring clinical delays in hospitals

<table>
<thead>
<tr>
<th>Type of case</th>
<th>Performance indicators</th>
<th>Performance aims: % of cases to meet the performance indicators*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical assessment within:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infectious</td>
<td>2 days of referral</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>Probably infectious</td>
<td>1 week of referral</td>
<td>&gt; 95%</td>
</tr>
<tr>
<td>Probably active, non-infectious</td>
<td>2 weeks of referral</td>
<td>&gt; 80%</td>
</tr>
<tr>
<td>Acutely ill from TB / extensive disease**</td>
<td>6 hours of diagnosis</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>Active TB, not acutely ill, not extensive disease</td>
<td>24 hours of diagnosis</td>
<td>&gt; 80%</td>
</tr>
</tbody>
</table>

* The performance aims represent proposed minimal levels of acceptability in New Zealand.
** Extensive disease may be pulmonary disease alone, or multi-system disease.
13.2 Early identification of TB

13.2.1 Factors that lead to early detection

The early identification of TB following presentation depends on:

- heightened clinical awareness of TB in all areas of medicine: all doctors should have a low threshold for considering TB as a cause of a wide variety of symptoms and signs
- knowledge of factors that increase the risk of an individual having TB (see below)
- knowledge of the protean clinical features of TB
- prompt initiation of appropriate investigations – including pursuing the diagnosis with invasive tests, if necessary
- referral to a TB clinician in a timely manner
- investigation of contacts – for asymptomatic contacts this will usually be carried out by the public health service (see Chapter 6: ‘Contact Investigation’).

13.2.2 Risk factors

Developing TB infection

Awareness of these risk factors enables the clinician to know which people are more likely to have been exposed to, and infected with, *M. tuberculosis*. These factors are discussed in Chapter 3: ‘Latent Tuberculosis Infection’, see Table 3.2.

Developing TB disease following infection

Knowledge of these factors is important to enable health care workers to target infected people for treatment of LTBI. These factors are discussed in Chapter 3: ‘Latent Tuberculosis Infection’, see Table 3.3.

Risk factors for reactivation of TB

The factors listed in Table 13.5 are similar to those given in the previous sub-heading. But here the risk factors apply to the development of active TB in those with past TB disease rather than past infection.
Table 13.5: Risk factors for reactivation of TB

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No previous treatment</td>
<td></td>
</tr>
<tr>
<td>Inadequate therapy</td>
<td>This could be due to non-adherence or an inadequate regimen.</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>In the US reactivation is more common in blacks than in whites; and in Canada, in Canadian Indians than in non-Indians. There are no published New Zealand data. Foreign-born people from non-Western countries are at higher risk. Ethnicity may not be a risk factor in its own right.</td>
</tr>
<tr>
<td>Socioeconomic status</td>
<td>There is some evidence for an association with lower socioeconomic status, related to nutrition and immune suppression from stress. Long-term homeless people are at high risk.</td>
</tr>
<tr>
<td>Extent of original disease</td>
<td>Relapse is more likely if the initial disease was extensive or included the presence of cavities, or residual X-ray abnormalities resulted after a previous episode of TB.</td>
</tr>
<tr>
<td>Development of:</td>
<td></td>
</tr>
<tr>
<td>¶ HIV infection</td>
<td>There are no extra risks from these factors if adequate treatment has previously been given.</td>
</tr>
<tr>
<td>¶ immunosuppressive treatment*</td>
<td></td>
</tr>
<tr>
<td>¶ medical conditions*</td>
<td></td>
</tr>
</tbody>
</table>

* See Chapter 3: ‘Latent Tuberculosis Infection’, Table 3.3.

Section 13.3 and section 14.1 of Chapter 14: ‘Clinical Investigation and Assessment of Tuberculosis’ have been included to assist with the recognition and appropriate investigation of TB. For more comprehensive reviews of these subjects, refer to the references cited.
13.3 Clinical features of TB

There are several principal references for this section, which are also appropriate for further reading.\textsuperscript{17} \textsuperscript{18} \textsuperscript{19}

13.3.1 General symptoms

It is rare for primary TB to cause symptoms. When symptoms do occur, they are usually related to local complications. (For a detailed discussion of the clinical aspects of primary pulmonary TB, see Friedman and Selwyn.\textsuperscript{18})

TB is usually asymptomatic until the condition is advanced. When they do occur, symptoms of TB are non-specific. Symptoms are often localised to the site(s) of disease. Systemic symptoms include malaise, fever, anorexia, weight loss and night sweats. Chest symptoms are discussed in the next section.

13.3.2 Pulmonary TB

This is the most common form of TB.

Symptoms of pulmonary TB

\begin{itemize}
  \item Inactive pulmonary TB is asymptomatic, and it may have a variety of radiographic appearances. (These are discussed in Chapter 14: ‘Clinical Investigation and Assessment of Tuberculosis’.)
  \item Active TB may be asymptomatic initially, but as the extent and severity of disease progress, symptoms such as cough, sputum, breathlessness and (much less frequently) haemoptysis may occur.
  \item Haemoptysis may occur with active or inactive (past) pulmonary TB. Blood-streaked sputum is not uncommon with both. Massive haemoptysis fortunately occurs less commonly. In a retrospective review of embolization for haemoptysis by Goh \textit{et al} there were 97 TB patients.\textsuperscript{32} Five (5.2\%) had no angiographic abnormality found, seven (7.2\%) had normal bronchial arteries but abnormal non-bronchial systemic (collateral) arteries, and 30 (30.9\%) had abnormal bronchial and non-bronchial arteries. The majority – 55 cases (56.7\%) – had abnormal bronchial arteries. There were 17 failures among 92 TB cases embolized (18.5\%); 10 required surgery and seven died from massive haemoptysis. All cases requiring repeat embolization (15.5\%) were due to TB, and were due mainly to collateral non-bronchial systemic arteries rather than recanalization of previously occluded vessels. With massive haemoptysis, these authors recommend a concerted search for abnormal, non-bronchial systemic arteries, and embolization of these if hypervascularity is demonstrated. Commencement of TB treatment is also likely to assist with control of haemoptysis in those cases with active pulmonary TB. See also TB cavities, below.
\end{itemize}
Typical appearances of active pulmonary TB

Often ‘shadowing’ is seen apico-posteriorly in the upper and, to a lesser extent, the lower lobes. As the disease progresses, so too does the extent of consolidation, and cavities are likely to develop. Extensive consolidation and/or cavities invariably mean the condition is infectious.

A ‘miliary pattern’ is the term used to describe the chest X-ray appearance that corresponds with this pattern of haematogenously disseminated TB: tiny nodules (of similar size to millet seeds) are usually evenly scattered throughout the lung parenchyma. With radiological ‘miliary TB’ it may be difficult to obtain a definitive diagnosis, even with bronchial washings; transbronchial lung biopsies may be needed. (Miliary TB is discussed in more detail later in this section.)

Atypical chest X-ray appearances in pulmonary TB

Atypical chest X-ray appearances are seen in a variety of conditions associated with varying degrees of immunosuppression. HIV/AIDS is an important example of this, and the chest X-ray appearances in this condition are discussed in Chapter 18: ‘Tuberculosis and HIV’. Diabetes mellitus is another condition which may cause the appearances to be atypical.

TB cavities

Cavity formation is uncommon in primary TB. It is not uncommonly seen in ‘reactivation’ TB, where a heightened immune host response is far 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.

Other aspects of pulmonary TB

- Commonly, asymptomatic pulmonary TB is detected by chance on a CXR.
- A characteristic of pulmonary TB is that there are few symptoms or signs despite extensive parenchymal disease.
- Abnormal chest signs are usually the result of lung fibrosis, cavities or pleural disease.
- In people with pulmonary TB, a tuberculous pleural effusion or mediastinal lymph node enlargement may also be evident on the CXR: both of these latter sites are classified as extra-pulmonary TB.

Endobronchial TB

This is uncommon now, but is important because it may result in tracheal or bronchial stenosis, and may be misdiagnosed as asthma or lung cancer. The exact incidence of involvement of the bronchial tree in pulmonary TB is unknown.
Seven sub-types of involvement have been described. The probable outcome with antituberculous treatment – stenosis or full resolution – varies with the appearance. New lesions may develop during treatment.24

13.3.3 Lymph node TB

TB is the most common mycobacterial cause of adenopathy involving the neck and supraclavicular regions in adults.

In countries with low TB prevalence, non-tuberculous mycobacteria (NTM) are a more common cause of mycobacterial adenopathy in children.25

Women are more predisposed to develop TB adenitis than men (ratio = 2:1). Also, it occurs more commonly in non-Caucasians.

Tuberculous lymphadenopathy is a prominent feature in people who have HIV/AIDS and TB. It occurs in up to a third of these cases.

TB adenitis can involve any lymph node group. Mediastinal TB adenitis is commonly present with extensive or severe local pulmonary TB. TB adenitis is often painless, but acute inflammation and pain can also occur. Abdominal TB adenitis may be a cause of abdominal pain.

The behaviour of tuberculous adenitis can be unpredictable with treatment. Sometimes involved nodes regress and disappear. Sometimes they expand, develop into a lymph node abscess and spontaneously perforate, discharging 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 and decrease in size alternately during, and even after, the course of TB treatment.26

13.3.4 Pleural effusion and TB

Tuberculous pleuritis is the second most common form of extra-pulmonary TB after lymph node TB.

The onset is acute in two-thirds and chronic in one-third of subjects.

Tuberculous pleural effusion can occur in primary and reactivation TB.

It occurs more commonly in adults than in children with TB.

A lymphocytic, exudative effusion is characteristic, but initially neutrophils may predominate. Work with previously immunised animals has shown that they develop a large pleural effusion a few days after tuberculoprotein is injected into their pleural space. Consequently, it is thought that tuberculous pleural effusions in humans result initially from the rupture of a small sub-pleural pulmonary focus, in most cases, although it may also develop through lympho-haematogenous spread, or by spread from an adjacent site, such as a tuberculous lymph node or spinal TB. The mycobacterial antigens in the pleural space cause a delayed hypersensitivity reaction, which, along with the inflammatory response to the pleural infection, causes pleural fluid accumulation. TB requires exclusion in any lymphocyte-predominant exudative pleural effusion.

A tuberculous empyema, evidenced by the presence of frank pus on pleural aspiration, may develop later in the course of pleural TB. This is not a common
clinical finding now, and a tuberculous *empyema necessitatis* (rupturing through the chest wall or into the lung) is decidedly rare in Western countries.

### 13.3.5 Skeletal TB

Skeletal TB occurs in the elderly in developed countries, but is more common at a younger age in other countries. Any bone or joint may be affected, but vertebral TB (Pott’s disease) is the most common site. Collapse of bone may produce pain, 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.

The onset of infection is often insidious, and is usually a late complication of unrecognised primary pulmonary disease as a result of lympho-haematogenous spread. Delay in the diagnosis is common because of the often mild, chronic, non-specific nature of the symptoms. Radiographic features may give a clue to the diagnosis.

Although rare, Ponçet’s disease deserves mention. Sometimes known as ‘tuberculous rheumatism’, it is a sterile polyarthritis originally described in association with abdominal TB. It is probably a hypersensitivity reaction associated with active TB, as cultures and PCR tests on synovial fluid and biopsy specimens are negative. Treatment of TB is needed for the condition to settle. Other diagnoses should be considered.19

### 13.3.6 Abdominal TB

- **Peritoneal TB** is more common than all other forms of intra-abdominal TB. ‘Isolated’ peritoneal TB usually occurs as a result of rupture of a small caseous peritoneal focus, which has developed as a result of haematogenous spread during a primary infection. It may also develop as a result of rupture of a larger focus within the abdomen, such as a viscus or lymph node. Symptoms are often insidious, with abdominal pain and systemic symptoms of TB. Occasionally it presents as an acute abdomen, preceded by more long-standing symptoms. Some ascites is usually present, as well as omental thickening. Pleural effusion and co-existing pulmonary TB are commonly present. Tuberculous peritonitis is now well described as an occasional complication of peritoneal dialysis.27

- **Enteric TB** may involve any part of the gastro-intestinal tract, but the ileo-caecal and ano-rectal regions are the most common sites of disease. The clinical features may be variable, depending on the sites and extent of disease, and are beyond the scope of this chapter.

- **Hepatic TB** is common when disseminated TB is present. Hepatic dysfunction is commonly present at the time of diagnosis in people with extensive pulmonary and pulmonary TB, and often settles within two weeks after starting anti-tuberculous treatment. Whether this represents tuberculous involvement of the liver, or non-specific hepatotoxicity associated with major infection, is often not worth pursuing diagnostically unless there is hepatomegaly, upper abdominal pain or tenderness, or the hepatic dysfunction is very marked or gets worse. Symptoms and signs, and the histology of hepatic TB, can be very variable depending on the type and degree of involvement.
The biliary tract is rarely involved by TB, but may be indirectly compromised by lymph node enlargement at the porta hepatis.

13.3.7 Genito-urinary TB

There is usually a period of years between haematogenous dissemination and the onset of genito-urinary TB. Any part of this system may be involved.

Renal TB has several possible appearances on IV urogram, which is more sensitive than ultrasound examination. Renal dysfunction may result from direct involvement by the disease, or indirectly as a result of ureteric stenoses. Symptoms may be absent or insidious. TB cystitis is not common, nor is TB prostatitis. Treatment considerations with the latter site are discussed in Chapter 16: ‘Treatment of Tuberculosis’, section 16.8.

A ‘cold abscess’ is a traditional presentation of testicular TB, but epididymitis with local thickening is more common. In females the distal salpinges, the ovary and the endometrium are the main sites of involvement, in descending order of frequency. Fallopian tube involvement is a recognised cause of sterility, particularly in developing countries.

13.3.8 Neurological TB

Any part of the nervous system can be involved.

TB meningitis classically occurs in children between the ages of six months and five years. Adults with TB meningitis are usually elderly, or partially immunosuppressed.

The onset is usually insidious, and the following stages of progression are often seen:

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

TB meningitis should be sought in people who are seriously ill with disseminated TB: there should be a low threshold for performing a lumbar puncture in these people. The brain and spinal cord may be affected, the latter usually being indirectly involved as a result of epidural disease compressing the spinal cord. Intra-cerebral tuberculomas are not common. They may be asymptomatic or produce focal signs. Tuberculomas may progress to form a brain abscess.

The eye and ear may be involved with TB, though otologic involvement is now rare. Ocular TB may involve any part of the eye, but the cornea and choroidae are most commonly affected.
Practice point

Fundoscopic examination may be hazardous to the examiner if the patient is infectious, or possibly infectious, pulmonary TB is present. If there are concerns about ocular symptoms or signs, an ophthalmologist should be consulted. Routine ocular examination by junior medical staff for conditions such as hypertension or diabetes should be deferred until the person has been rendered non-infectious. Consultants need to bring this recommendation to the attention of their medical staff.

The management of TB of the central nervous system is discussed in Chapter 16: ‘Treatment of Tuberculosis’, section 16.9.

13.3.9 Cardiovascular TB

Cardiovascular TB is rare, with pericarditis being the most common manifestation. Tuberculous pericardial effusion usually occurs in the context of disseminated disease. It needs consideration whenever a substantial tuberculous pleural effusion is present, and when cardiomegaly is present in active TB. The role of oral steroid treatment is discussed in Chapter 16: ‘Treatment of Tuberculosis’, section 16.10. Constrictive pericarditis can be a late complication of TB pericarditis. Tuberculous carditis and aortitis are rare.

13.3.10 TB laryngitis

TB laryngitis usually accompanies pulmonary TB, and the pulmonary disease is then often cavitatory. However, isolated TB laryngitis may occur very occasionally, and can be a form of infectious TB with a normal chest radiograph. Cough, voice change and (later) throat pain are the main symptoms.

13.3.11 Skin manifestations of TB

- Erythema nodosum is occasionally observed during the course of primary or post-primary TB; it is not pathognomonic for this particular condition.
- Isolated involvement of the skin is an uncommon manifestation of TB. More often it is the result of extension of TB osteomyelitis, or the end of a sinus tract from another more deeply seated focus.
- Acute miliary TB of the skin is rare, and is seen mainly in severely immunocompromised AIDS patients with CD4 T cell counts < 100/mm³. It is a manifestation of acute haematogenous dissemination of TB.28

13.3.12 Endocrine involvement by TB

Adrenal TB usually occurs during or after haematogenous dissemination of TB. Adrenal insufficiency from TB is uncommon, as the majority of the adrenal glands must be destroyed to cause insufficiency. A strongly positive Mantoux and adrenal insufficiency are indications to search for active TB, and often for giving preventive treatment, particularly if adrenal calcification is evident radiologically. The finding of enlarged adrenal glands on abdominal CT scan in a Mantoux-positive individual with hypothalamic adrenal should raise suspicion that active adrenal TB is present. Note that the
addition of rifampicin may unmask borderline adrenal insufficiency (see Chapter 16: ‘Treatment of Tuberculosis’, section 16.10.3).

*Pituitary tuberculoma* is apparently 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 very rare.

### 13.3.13 Disseminated TB

The term ‘disseminated TB’ refers to TB that involves multiple body systems. It is the result of acute haematogenous spread of TB. Disseminated TB only occurs in about 3% of non-HIV TB cases in Western countries, but may carry an overall mortality rate as high as 38%. The absence of miliary changes on the chest radiograph, in the presence of pulmonary and multi-system TB, indicates a much higher mortality rate (around 85%).

Malnutrition, if present, may need particular attention in people with severe or extensive TB.

‘Miliary TB’ refers to the presence of multiple, small and uniformly-sized (usually < 2 mm in diameter) nodules of active TB throughout the body. All miliary TB is disseminated, by definition, but not all disseminated TB is miliary.
13.4 Future developments

Quality performance programmes (see section 13.1) that are computerised, and are relatively easy to complete and monitor, offer the hope that clinical, laboratory and ‘system’ delays will diminish in the future. To be effective, these programmes must:

- have performance indicators that routinely identify specific causes of delay
- be accompanied by the ability to undertake appropriate corrective measures.

Nurses and doctors at a variety of levels (primary, secondary and tertiary; clinical and public health) would need to take ownership of and responsibility for these programmes. The Ministry of Health has a potential leadership role in their development and implementation.
References


Chapter 14: Clinical Investigation and Assessment of Tuberculosis

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References
Summary

Clinical investigation

- A comprehensive history and examination are required.
- Important initial tests include a CXR and sputum mycobacterial tests. (The role of the Mantoux test is discussed below.)

Chest X-ray

- A CXR is an essential test whenever TB is considered.
- CXR appearances of active and inactive TB are summarised in Table 14.1
- Practice points about CXR with cough, other symptoms, or old fibrotic TB scarring: see box in 14.1.2.

Radiological criteria for detailed mycobacteriological testing

- Recommendations in Table 14.2 show the usual decision-making process, but the action taken for an individual case may vary depending on the patient's age, the presence of absence of risk factors for reactivation of disease, and the patient's wishes.
- In general, the aims are to:
  - prove inactivity (if the decision is not to treat unless active disease is identified)
  - obtain culture results so that drug-resistant cases are identified, and appropriate treatment is then given to cases of active TB.

Chest X-ray in extra-thoracic TB

See full text for a review of this topic.

Mantoux test

- This is only required for diagnostic purposes if the diagnosis of TB has not been made, but seems possible, and sputum or induced sputum smears are negative.
- A Mantoux test is not required if:
  - the diagnosis of active TB has been made, or is likely to be easily secured (e.g., the CXR is strongly suggestive of infectious TB and the person has cough and sputum)
  - a Mantoux result from within the last month is available
  - the person is known to have had a strongly positive Mantoux test in the past.
- For a list of practice points, see the box in 14.1.3.

Spontaneous sputum mycobacterial smear and culture

- Sputum should be sent for TB tests if TB is suspected from the clinical features or CXR.
- The clinician should request three early morning spontaneous sputum specimens for TB testing.
Not all of these need to be processed by the laboratory if sputum is found to be smear-positive: if one sputum specimen is smear-positive, it has an 88% chance of being culture-positive. In this situation, the laboratory should examine only two specimens.

There has been no change to the recommendation to process three specimens of sputum for culture when acid-fast bacilli (AFB) smears are negative.

Sputum smear-negativity in a person who is producing a substantial amount of sputum, strongly indicates that active pulmonary TB is unlikely. It should be obvious that this comment does not apply to those with only scanty sputum.

**Urine microscopy: do not perform urine AFB tests unless sterile pyuria is present**

- 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 only indication to proceed to early morning urine (EMU) TB tests. TB urine cultures are expensive and should not be performed on the basis of a single abnormal midstream urine (MSU).
- An MSU containing more than 20 white or red cells warrants a repeat MSU. If the abnormality persists, then other causes should be excluded (eg, do schistosoma serology in people who have resided in endemic areas), and then urine TB cultures should be performed.
- If the MSU is abnormal from an obvious cause (eg, menstruation or a bacterial urinary tract infection), repeat the MSU when the condition has had time to resolve.
- Persistent sterile pyuria is also an indication for an intravenous urogram (IVU), looking particularly for urinary tract stenoses, and other features of urinary tract TB. An IVU is often superior to ultrasound in this situation.

**Induced sputum**

- Induced sputum testing has been shown to be more accurate than bronchoscopy in the diagnosis of pulmonary TB in subjects who are sputum smear-negative.
- Induced sputum testing for TB is an attractive proposition for the reasons explained above, with the following riders.
  - 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 a high-efficiency particulate attenuation (HEPA) filtration system.
  - Staff must wear suitable face masks.
  - The principal patient safety concern is with air-flow obstruction. Nebulised bronchodilator should precede the hypertonic saline in people with asthma and COPD.
  - 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.
- Bronchoscopy is more readily available, and there is greater experience with this procedure, in many parts of New Zealand at present. Nevertheless, there should now be a move away from bronchoscopy as the procedure of choice for the investigation of possible TB.
**Bronchoscopy**

- TB that is obvious from the CXR will usually be diagnosed from sputum without the need for either of the detailed microbiological tests (induced sputum or bronchoscopy). When pulmonary TB is included in the differential diagnosis, less invasive tests should be done first, unless there is real urgency.
- Broncho-alveolar lavage (BAL) is probably more effective than simple bronchial washings. BAL should replace bronchial washings when investigating the possibility of pulmonary TB.
- Bronchoscopy probably carries a greater risk of nosocomial infection from *M. tuberculosis* than does induced sputum testing, provided the latter is performed in respiratory isolation conditions.
- When bronchoscopy is performed and TB is a possible diagnosis, the procedure should be performed in a room that meets TB isolation ventilation requirements. Where this is not available, a portable HEPA filter can be used.
- The bronchoscopist and assistants must wear special masks designed to limit the inhalation of droplets containing TB when TB is a possible diagnosis.
- Careful cleaning of bronchoscopes is required to prevent the cross-contamination of specimens and cross-infection of patients with *M. tuberculosis*.
- Bronchoscopy may still be indicated for other diagnoses, preferably when the diagnosis of TB has been made and the infectious potential reduced or removed by treatment. These indications (including miliary TB) are detailed in the full text.

**Gastric juice examination**

- The role of this procedure is discussed in the full text.

**Blood culture for mycobacteria**

- This is an important test, but only in HIV-infected subjects.
- Disseminated *M. avium* complex disease (DMAC) occurs late in the course of HIV infection. Mycobacterial blood cultures have a good chance of being diagnostic.

**Testing for HIV**

- Routine HIV testing is strongly advocated when TB is diagnosed because:
  - HIV/AIDS commonly presents with active TB
  - questioning for risk factors often fails to detect people at risk for HIV/AIDS
  - the development of pulmonary TB in a person with HIV/AIDS enhances HIV-1 replication in areas of lung affected by TB by a factor of about 10. The combination of diseases puts these patients at risk of accelerated HIV-1 replication and mutation.
- The WHO recommends counselling and voluntary HIV testing of TB patients.

**Pleural investigations**

- Laboratory features of tuberculous pleural effusions are discussed in the full text.
- The sensitivity of the pleural fluid TB culture (10–35%) is less than that of pleural biopsy culture (39–65%). Histology and culture of pleural biopsies can yield a diagnosis in up to 86%. Pleural biopsies are essential.
Thoracoscopic pleural biopsy specimens may be needed. Consider it particularly with people from countries with a high incidence of TB and TB drug resistance, where knowledge of the susceptibility pattern of the organism is essential.

**Lymph node TB**

- A CXR is always needed, as pulmonary TB co-exists in about 70% of cases of supraclavicular and cervical lymph node TB.
- Fine-needle aspiration (FNA) of the enlarged nodes is the first step towards the diagnosis when there is no sign of pulmonary disease. However, FNA is not reliable in providing a diagnosis. Cytology results may be suggestive.
- In a person without risk factors for drug resistance, and a clinical situation in which TB adenitis seems virtually certain, the clinician may elect not to obtain further specimens, or to do another FNA and then start TB treatment.
- If there are risk factors for drug resistance, it is essential to obtain the organism and its drug susceptibility pattern. Further diagnostic steps are discussed in the full text.
- Do not start treatment until a positive culture has been obtained, or until an abnormal node has been excised and is being cultured for mycobacteria.
- The principles discussed apply to both peripheral and mediastinal (or intra-abdominal) lymphadenopathy.

**Routine laboratory tests**

- Common abnormalities found in TB disease are discussed in the full text.

**Techniques to enhance the prediction of active TB**

- Attempts have been made to create methods for predicting:
  - which subjects do not need isolation
  - which subjects do require isolation
  - which subjects with smear-negative TB do actually have active pulmonary TB, and should be started on treatment before TB cultures are complete.
- These topics are considered in the full text.

**Assessment of TB activity, extent and severity**

**Active and inactive TB**

Active TB is TB disease in which:

- an *M. tuberculosis*-complex organism has been cultured, or identified in a culture by DNA probe. A positive PCR test on a tissue specimen (as distinct from secretions or other bodily fluids) does not distinguish between active and inactive TB.

- clinical parameters are suggestive of activity, including:
  - a changing radiological infiltrate (worsening or improving) which is compatible with TB, or an infiltrate compatible with active TB
  - other disease features suggestive of TB (eg, supraclavicular or cervical lymphadenopathy)
  - tissue histology compatible with TB
- the Mantoux reaction is positive or has converted
- the person has had contact with an infectious TB case
- the person has risk factors for TB infection progressing to disease.

Inactive TB is TB disease in which full investigation has been performed, other diagnostic possibilities considered, and:

- adequate specimens are smear- and culture-negative for TB
- radiological features are suggestive of inactivity (see Chapter 13: ‘Awareness, Clinical Features and Early Identification of Tuberculosis’)
- clinical indices and tests do not suggest disease activity. For example:
  - fever and other systemic features of active TB are absent
  - the ESR is within normal limits or another clear-cut cause for a raised ESR is identifiable
  - the MSU does not show sterile pyuria.

Additionally, if the person receives treatment, lack of radiological change after three months’ treatment also argues against disease activity.

**Severity of TB**

- Bacillary load, extent of disease and anatomical site are considerations in determining the severity of TB. This is true whether judging the severity of current or past TB.
- Severe active disease is judged to be present if there is:
  - acute threat to life (eg pericardial TB), or
  - risk of subsequent severe handicap: this is most likely to occur with the following types of TB disease:
    - pulmonary TB with bilateral very extensive disease (eg, three or more lobes heavily involved) or widespread cavitatory disease (more than 2 lobes involved);
    - extra-pulmonary TB: spinal TB, TB meningitis, miliary TB, TB pericarditis, TB peritonitis, bilateral or extensive pulmonary effusion, intestinal, or genito-urinary TB
    - or both.

**Extent of TB**

Radiological extent of pulmonary disease:

- There is no widely accepted system for classifying extent of disease. The Harrison-Wells method (Auckland) has been validated and has been modified here by adding one additional grade of extensive disease. The radiological grades of disease extent are:
  - Grade 0: no disease
  - Grade 1: trivial disease, where the total possible volume of old and/or active TB is equivalent to, or less than one broncho-pulmonary segment
  - Grade 2: intermediate disease, where the total possible TB volume is greater than one broncho-pulmonary segment but less than or equal to one lobe
  - Grade 3: extensive disease, with the total TB volume greater than one lobe, and up to one lung field
  - Grade 4: very extensive disease, exceeding one lung field.

- Parenchymal disease should be categorised as unilateral or bilateral. The presence of lymphadenopathy, pleural disease or miliary abnormalities should also be noted.
Disseminated TB

- This term refers to TB that involves multiple body systems. It is, by definition, extensive.
- Disseminated TB only occurs in about 3% of non-HIV TB cases in Western countries, but may carry an overall mortality rate as high as 38%. The absence of miliary changes on the chest radiograph, in the presence of pulmonary and multi-system TB, indicates a much higher mortality rate (around 85%).
- Malnutrition, if present, may need particular attention in people with severe or extensive TB.

Investigation of TB in people from countries with a high incidence of TB

Clinical investigation of suspected TB

- The process of investigation does not differ from other groups, although there is a need to be aware of language and cultural considerations, and possible HIV/AIDS.
- Because some immigrants will be arriving from countries with a high prevalence of HIV infection, it is important to:
  - maintain a high index of suspicion for HIV
  - ask about personal risk factors
  - have a low threshold for seeking permission to perform an HIV test
  - do an HIV test if it is thought that treatment of latent TB disease (LTBI) or preventive treatment are appropriate, or if active TB is suspected or discovered.
- Only with X-ray abnormalities from trivial, healed TB should an HIV test be omitted.
- A low threshold for obtaining bronchial specimens is appropriate, as positive exclusion of active TB is required. Table 14.2 gives details of radiological criteria for detailed mycobacteriological testing.

‘Immigration clearance’ for TB

- Currently the costs of all investigations and treatment for TB for non-residents are borne by the New Zealand taxpayer, if the medical officer of health considers the health care services to be compulsory.
- Besides excluding TB, the clinician must consider:
  - if other diagnoses are possible (particularly lung cancer in current or past smokers, COPD or bronchiectasis)
  - whether detailed mycobacteriological tests for TB are appropriate (see below)
  - whether other investigations (eg, CT scan of the chest), or even no investigations, are required
  - if either treatment of LTBI or full (preventive) treatment of inactive TB is required.

Items in the immigration medical

- History: use an interpreter if the applicant cannot speak sufficient English. Key information includes previous TB, details of treatment, contact with TB (including possible occupational exposure) and TB symptoms. Also take a general medical history.
- Physical examination : ensure lymph node groups are examined.
A recent chest radiograph: if the person is asymptomatic, films taken three to four weeks earlier are satisfactory; otherwise a repeat X-ray is needed. If chest or systemic symptoms of TB are present, the chest radiograph should not be more than two weeks old. Always ask if previous films can be obtained for comparison if none are offered.

General tests: a full blood picture, ESR and MSU test should be done.

A Mantoux is needed if the CXR appearance is suggestive of a condition other than TB. A negative Mantoux will make it even less likely that TB is the cause of the X-ray abnormality. If the appearance is typical of current or old TB, a Mantoux test is not likely to add extra information, as clinical suspicion is already high. Sometimes a strongly positive Mantoux reaction will persuade the clinician or the client that some form of TB treatment is appropriate.

Sputum tests (three specimens) – this is only appropriate if the person has lower (not upper) respiratory tract secretions. If the person has very little or no sputum, other tests are necessary, as follows.

Indications for detailed mycobacteriological testing: the key indication is an abnormal CXR in which old or active TB is included in the differential diagnosis. The importance of full testing increases if there is suspicion of TB from a positive Mantoux or symptoms (see Table 14.2).

- Induced sputum tests (three specimens): this is the procedure of choice in people who have little or no spontaneous sputum.
- Bronchoscopy with broncho-alveolar lavage: if induced sputum facilities are not available, or are not available in the required time frame, bronchoscopy is the next best choice.

Future developments

Desired diagnostic developments include:
- earlier identification of active TB and isolation of infectious cases
- replacement of the Mantoux test with a serological test that is a reliable and reproducible pointer to active TB

Computer methodology providing accurate prediction would be useful in the following areas:
- prediction of who is infected with live M. tuberculosis organisms
- prediction of active TB
- prediction of infectivity: which patients actually need isolation
- ability to make these predictions in general practice as well as in hospital.
Introduction

This chapter focuses mainly on the clinical investigation of TB, including requirements in the ‘immigration medical’. In addition, techniques to assist with the early diagnosis of TB, and whether or not the condition is infectious, are considered. Documentation of the extent and severity of TB should always be part of the clinical assessment, and this too is discussed.
14.1 Clinical investigation

This section deals with common investigations. It does not attempt to show how to investigate complex situations.

14.1.1 Introduction

A comprehensive history and examination are required. Important initial tests include a CXR, a Mantoux test, and sputum mycobacterial tests. Delay in performing these is an important contributor to delay in the diagnosis of TB, as explained in Chapter 13: ‘Awareness, Clinical Features and Early Identification of Tuberculosis’, section 13.1.

14.1.2 Chest X-ray

This is an essential test whenever TB is considered. The possibility of TB is often discovered as a result of a CXR done for other reasons. This is possible because, although pulmonary TB may have a non-specific appearance on X-ray, typical appearances are also common.

CXR appearances of active and inactive TB is a large topic, beyond the scope of this chapter. An outline of common, typical CXR features is shown in Table 14.1.

<table>
<thead>
<tr>
<th>Anatomical site</th>
<th>Active TB</th>
<th>Inactive TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td><strong>Consolidation</strong> variable size:</td>
<td>Linear scarring</td>
</tr>
<tr>
<td></td>
<td>† unifocal, commonly</td>
<td>Dense scarring</td>
</tr>
<tr>
<td></td>
<td>† ‘soft’, ‘fluffy’ areas with poorly defined margins</td>
<td>Volume loss</td>
</tr>
<tr>
<td></td>
<td><strong>Cavities</strong></td>
<td>Destroyed lobe or lung</td>
</tr>
<tr>
<td></td>
<td><strong>Nodules</strong>: either:</td>
<td>Calcification</td>
</tr>
<tr>
<td></td>
<td>† focal, non-calcified; or</td>
<td>Nodules, calcified (tuberculomas):</td>
</tr>
<tr>
<td></td>
<td>† miliary pattern</td>
<td>† Ghon focus (scar from primary infection)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>† secondary (Simon) foci</td>
</tr>
<tr>
<td>Mediastinum and hila</td>
<td><strong>Lymphadenopathy</strong> – hilar and/or paratracheal</td>
<td>Calcified lymph nodes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pericardial calcification</td>
</tr>
<tr>
<td>Pleura</td>
<td><strong>Pleural effusion/empyema</strong></td>
<td>Pleural thickening:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>† basal</td>
</tr>
<tr>
<td></td>
<td></td>
<td>† apical (irregular, &gt; 1cm thickness)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pleural calcification</td>
</tr>
</tbody>
</table>

* Lymphadenopathy is very common in paediatric TB

Notes:
- Most of these CXR features are not specific to TB.
- TB also produces atypical radiological features, particularly in TB associated with HIV, diabetes, and other causes of immunosuppression (see Chapter 18: ‘Tuberculosis and HIV’).
- High-resolution chest CT is more sensitive at detecting cavities, lymphadenopathy, the factors contributing to ‘apical fibrosis’, and post-TB complications such as bronchostenosis and bronchiectasis.
The radiological features in active TB are discussed in more detail in Chapter 13: ‘Awareness, Clinical Features, and Early Identification of Tuberculosis’, section 13.3.2. The significance of the radiological features of inactive pulmonary TB (with respect to the need for preventive treatment) is discussed briefly in Chapter 16: ‘Treatment of Tuberculosis’, section 16.1.2.

Practice points

1. Troublesome cough
Sometimes patients are referred for possible TB on the basis of a troublesome cough, a positive Mantoux test and, often, non-European ethnicity. A CXR will clarify the situation: a normal CXR, or one without typical features of active TB, virtually excludes active TB as the cause of the cough. If the X-ray shows no evidence of TB:
1) sputum AFB testing should be lower in the priority of investigations than it would be if the CXR suggests past TB
2) be prepared to go over relevant parts of the history and examination again – these may help identify the cause of the cough
3) a repeat CXR may be done two to three weeks after the initial film to increase certainty that TB is unlikely.
The primary reason for referral to a chest physician should be ‘troublesome cough’, not ‘suspected pulmonary TB.’ This will help with more accurate triage of such patients. Certainly, a new, persistent cough should always be investigated until a cause is found.

2. Other symptoms, but CXR shows no features of active pulmonary TB
There is considerable evidence that a normal CXR makes active pulmonary TB highly unlikely. Where there are concerns because of symptoms and a positive Mantoux test, sputum mycobacteriological testing and a repeat CXR two to three weeks later are appropriate. A normal CXR does not exclude extra-pulmonary TB, and if there are extra-pulmonary, system-specific symptoms, these may need to be investigated.
Techniques that may help with accurate prediction of activity and infectivity of pulmonary TB are discussed in 14.2.

3. ‘Old, fibrotic, inactive TB’ abnormalities on CXR
When abnormalities fitting this description are seen on a CXR, they should never be classified as or assumed to be due to inactive TB, unless either:
1) previous films show the abnormalities have been stable for at least three to six months (the longer period is appropriate when the abnormalities are more than trivial), or
2) detailed mycobacteriological testing has been done.
See also Chapter 16: ‘Treatment of Tuberculosis’, section 16.1.2.

Radiological criteria for detailed mycobacteriological testing
Methods for performing detailed mycobacteriology tests are discussed below in the sections on induced sputum testing and bronchoscopy. At this point we will consider the radiological indications for these tests.
Recommendations in Table 14.2 show the usual decision-making process, but the action taken for an individual case may vary, depending on the patient’s age, the presence or absence of risk factors for reactivation of disease, and the patient’s wishes. In general, the aims are to:

- prove inactivity (if the decision is not to treat unless active disease is identified)
- obtain culture results so that drug-resistant cases are identified, and appropriate treatment is then given to cases of active TB.

**Table 14.2:** Radiological criteria for detailed mycobacteriological tests*

<table>
<thead>
<tr>
<th>Chest X-ray shows</th>
<th>Do induced sputum x 3 (or bronchoscopy + bronchoalveolar lavage)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>No abnormality</td>
<td>No</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>&lt;10 mm single granuloma</td>
<td>No</td>
</tr>
<tr>
<td>Minor lobar scarring or several tiny (&lt;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. Consider transbronchial lung biopsies too.</td>
</tr>
<tr>
<td>Definite infiltration or consolidation or caviation</td>
<td>Yes. Consider transbronchial lung biopsies too.</td>
</tr>
</tbody>
</table>

* Induced sputum is the preferred procedure; see text below.
** Tests shown are for subjects at risk of TB disease who have no sputum, or have scanty sputum, which is smear- or culture-negative.

**The chest X-ray in extra-thoracic TB**

There is little in recent medical textbooks on chest radiograph findings in patients with extrapulmonary TB. A literature review reveals a wide range of findings in forms of TB not involving the thorax.

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 Spain, 76% were considered primary, and the lung fields were thus normal.5 In Malaysia, 61% of 54 cases of TB pleural effusion had no CXR evidence of parenchymal disease.6

The chest radiograph is abnormal, suggesting current or past intra-thoracic TB in:

- 44–69% of cases with meningitis7 8 9
- 16–44% of cases with superficial lymph node disease9 10 11
- 26–50% of those with bone or joint disease9 12
- 8–75% of those with genitourinary disease9 13 14
- 32–78% of those with peritoneal or abdominal TB.9 15-21

Dr N Karalus, Chest Physician, Waikato Hospital, Hamilton wrote this section.
14.1.3 Mantoux test

This is only required for diagnostic purposes if the diagnosis of TB has not been made, but seems possible, and sputum or induced sputum smears are negative.

A Mantoux test is not required if:

- the diagnosis of active TB has been made, or is likely to be easily secured (e.g., the CXR is strongly suggestive of infectious TB and the person has cough and sputum)
- a Mantoux result from within the last month is available
- the person is known to have had a strongly positive Mantoux test in the past (see Chapter 2: ‘Mantoux Testing’, section 2.4.

Practice point

The Mantoux test does not have a major role in the diagnosis of active TB because:

- a positive result is not diagnostic, and may be from:
  - past BCG vaccination, or
  - infection with non-tuberculous mycobacteria (NTM), or
  - M. tuberculosis, either from past inactive TB disease, or
  - M. tuberculosis, active disease
- highly variable proportions of people with active TB in reported series have a negative Mantoux test; up to 30% of patients with tuberculous pleurisy have a negative Mantoux test
- false-positive, as well as false-negative, reactions can occur (for a list of the causes of false Mantoux reactions, see Chapter 2: ‘Mantoux testing’).

The Mantoux test is thus not an important initial test when investigating possible TB disease. The diagnostic emphasis should be on obtaining adequate specimens for mycobacterial smear, culture, and (when appropriate) histological testing (with TB culture on biopsy or specimens).

Although not diagnostic by itself, a positive Mantoux result increases the possibility that the condition under investigation may be due to TB. However, Al Zahrani et al have shown that the magnitude of the positive reaction does not further affect the likelihood of current TB.

14.1.4 Spontaneous sputum mycobacterial smear and culture

Sputum should be sent for TB tests if TB is suspected from the clinical features or CXR. The clinician should request three early morning spontaneous sputum specimens for TB testing. However, not all of these need to be processed by the laboratory in the following situations.
If sputum is found to be smear-positive

Traditionally, the recommendation has been that all three sputum specimens be processed for culture. However, a Denver study showed that if one sputum specimen is smear-positive, it has an 88% chance of being culture-positive, and in this situation examination of only two specimens is now recommended.24 This practice should be adopted in New Zealand laboratories that routinely obtain all specimens at the same time, or on consecutive days. This may not be easy to introduce in laboratories that only occasionally receive sputum for mycobacterial testing.

If sputum is smear-negative

There has been no change to the recommendation to process three specimens of sputum for culture in this situation. However, this may change in the future. Studies performed in Africa, where smear status is the usual criterion for TB diagnosis (cultures are not performed), show there is a substantial incremental cost with the third sputum test, but only a small extra diagnostic yield of 8%.

In developed countries the extra diagnostic yield may be lower as a result of initial screening using fluorescent staining or the Kinyoun stain, and the routine use of mycobacterial culture.25 Another study, in which three sputum specimens were collected, auramine staining was carried out, and one sputum culture was performed per subject, showed only marginal reduction in diagnostic sensitivity (to 97%) using two sputum specimens instead of three.26

Practice point

Sputum smear negativity in a person who is producing a substantial amount of sputum strongly indicates that active pulmonary TB is unlikely.27 It should be obvious that this comment does not apply to those with only scanty sputum.

14.1.5 Urine microscopy – do not perform urine AFB tests unless sterile pyuria is present

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 only indication to proceed to early morning urine (EMU) TB tests. TB urine cultures are expensive and should not be performed on the basis of a single abnormal midstream urine (MSU).

An MSU containing more than 20 white or red cells warrants a repeat MSU. If the abnormality persists, then:

- other causes should be excluded (eg, do schistosoma serology in people who have resided in endemic areas), and then
- perform urine TB cultures.

If the MSU is abnormal from an obvious cause (eg, menstruation or a bacterial urinary tract infection), repeat the MSU when the condition has had time to resolve.
Sterile pyuria is not only an indication to perform early morning urine mycobacterial tests, but also an indication for an intravenous urogram (IVU), looking particularly for urinary tract stenoses and other features of urinary tract TB. An IVU is often superior to ultrasound in this situation.

### 14.1.6 Induced sputum

With induced sputum tests, patients inhale a mist of 3–4% hypertonic saline (via a mouthpiece or face mask) generated by an ultrasonic nebuliser. Although specimens often appear more watery than sputum, these are acceptable for testing.\(^{28}\) The procedure has a very high level of patient safety and acceptability.

Because of the danger of nosocomial transmission of TB, induced sputum testing must only be performed in an area equipped for respiratory isolation conditions. Staff must wear suitable face masks (see Chapter 9: ‘Infection Control’).

Induced sputum testing has been shown to be more accurate than bronchoscopy in the diagnosis of pulmonary TB in subjects who are sputum smear-negative.\(^ {4}\) In a prospective study of 129 subjects who completed three induced sputum tests and bronchoscopy:

- 27 (21%) had smear-negative and culture-positive specimens – 14 (52%) on bronchoscopy and 26 (96%) on induced sputum (p < 0.005). One person was culture-positive on bronchoscopy alone, compared to 13 on induced sputum alone; 13 were culture-positive on both tests. Bronchoscopy was avoided in another 11 active TB cases in whom induced sputum specimens were smear-positive.

- Induced sputum positivity was strikingly more prevalent when chest radiographic appearances showed any features of active TB (20/63, 32%) than when appearances suggested inactivity (1/44, 2%) (p < 0.005).

- Cost analysis showed that, in possible pulmonary TB cases with smear-negative sputum, the most cost-effective strategy is to perform three induced sputum tests, without bronchoscopy.

The McWilliams study\(^ {4}\) confirmed the results of Al Zahrani et al, which showed that multiple tests improve the diagnostic yield of induced sputum testing.\(^ {29}\) In this latter study, the cumulative yield for acid-fast bacilli (AFB) smear and culture was 64% and 70% respectively for one, 81% and 91% for two, 91% and 99% for three, and 98% and 100% for four induced samples from 44 culture-confirmed pulmonary TB cases.

*In conclusion*, induced sputum testing for TB is an attractive proposition for the reasons explained above, 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 9: ‘Infection Control’).

- The principal patient safety concern is with air-flow obstruction. Nebulised bronchodilator should precede the hypertonic saline in people with asthma and COPD.
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.

Bronchoscopy is more readily available and there is greater experience with this procedure in many parts of New Zealand at present. Nevertheless, there should now be a move away from bronchoscopy as the procedure of choice for the investigation of possible TB.

14.1.7 Bronchoscopy

There is little doubt now that induced sputum is a better test than bronchoscopy for the diagnosis of pulmonary TB, particularly where the symptoms and X-ray appearance favour inactive disease.

TB that is obvious from the CXR will usually be diagnosed from sputum, without the need for either of the ‘detailed microbiological’ tests (induced sputum or bronchoscopy). When pulmonary TB is included in the differential diagnosis, less invasive tests should be done first, unless there is real urgency.

**Broncho-alveolar lavage**

Although there is no proof that broncho-alveolar lavage (BAL) produces a better yield than ‘bronchial washings’ (the latter employing 20–40 ml of lavage fluid), there is a suspicion that BAL is more effective, and this should probably now replace bronchial washings when investigating the possibility of pulmonary TB.

**Preventing bronchoscopic transmission of TB**

Bronchoscopy probably carries a greater risk of nosocomial infection from *M. tuberculosis* than does induced sputum testing, provided the latter is performed in respiratory isolation conditions. The latest Thoracic Society of Australia and New Zealand (TSANZ) position paper on bronchoscopy makes no reference to performing bronchoscopy in respiratory isolation conditions for staff protection. Nevertheless, when bronchoscopy is performed for the diagnosis of pulmonary disease where TB is a possible diagnosis, the procedure should be performed in a room that meets TB isolation ventilation requirements (ie equipped with HEPA filtration air conditioning and, ideally with negative-pressure also). Where this is not available, a portable HEPA filter can be used: see also Chapter 9: ‘Infection Control’, where the efficacy of portable HEPA filters is questioned.

The bronchoscopist and assistants must wear special masks designed to limit the inhalation of droplets containing TB when TB is a possible diagnosis (see Chapter 9: ‘Infection Control’). Careful cleaning of bronchoscopes is required to prevent the cross-contamination of specimens and cross-infection of patients with *M. tuberculosis*.

**Indications for bronchoscopy**

Bronchoscopy may still be required, preferably when the diagnosis of TB has been made and infectious potential reduced or removed by treatment, if:

- intra-thoracic cancer needs exclusion
14.1.8 Gastric juice examination

This procedure is carried out on three consecutive mornings following an overnight fast.

In children, gastric juice examination (with gastric lavage, if necessary) is still recommended and performed throughout the world when TB is suspected (or needs exclusion) and spontaneous sputum cannot be produced. However, the choice between performing gastric aspirates and bronchoscopy in infants and children with abnormal CXRs is debated, though ‘it should be noted that gastric aspirates give equal, or even better, microbiological results than bronchial aspirates and BAL’.

In adults, gastric juice examination has been abandoned in most countries, being replaced with bronchoscopy and induced sputum testing. In a study from Pakistan, the yield of gastric lavage was compared with fibre-optic bronchoscopy in adults with possible TB who were unable to produce sputum. AFB stain and culture (solid medium) were performed, and a positive result on either was accepted as being diagnostic of TB. With this limitation, and the small number of subjects (20), the principal findings were that:

- two gastric lavage specimens are adequate: the yield of smear-positivity (80% of 20 cases) or culture-positivity (40% of 20 cases) was not increased by doing a third test
- bronchoscopic wash was superior to gastric lavage in culture, but not on AFB smear results.

Further studies with larger numbers of subjects are needed.

14.1.9 Blood culture for mycobacteria

*M. tuberculosis* bacteraemia is virtually unknown in non-HIV cases of TB. This is an important test only in HIV-infected subjects, where 24–64% of patients with TB have positive blood cultures. In 6.6–18%, blood was the only site from which the organism was recovered.

Disseminated *M. avium* complex disease (DMAC) occurs late in the course of HIV infection. Mycobacteraemia with this organism can be intermittent or sustained, and mycobacterial blood cultures have a good chance of providing the diagnosis.
14.1.10 Testing for HIV and other co-morbidities

Is routine HIV testing necessary when TB is diagnosed?

This question has not been definitively answered in New Zealand. However, the answer is 'yes', with the person’s consent, for three reasons:

- HIV/AIDS commonly presents with active TB
- questioning for risk factors often fails to detect people at risk for HIV/AIDS
- the development of pulmonary TB in a person with HIV/AIDS enhances HIV-1 replication in areas of lung affected by TB by a factor of about 10. The combination of diseases puts these patients at risk of accelerated HIV-1 replication and mutation.\(^{35}\)

The WHO recommends counselling and voluntary HIV testing of TB patients.\(^{36}\)

Other co-morbidities

Major disturbance of glucose metabolism, and liver and renal function should be apparent from the history and routine blood tests. Tests for additional co-morbidities are done only if clinically indicated. (See also section 14.1.12.)

14.1.11 Pleural investigations\(^{22}\)

Tuberculous pleural fluid is an exudate with a lymphocyte predominance in 90% of cases. Other causes include malignancy, lymphoma, collagen vascular diseases and post-coronary artery bypass surgery. Early TB effusions may show neutrophils predominating. An eosinophilic pleural effusion is unusual in pleural TB, but is occasionally seen.\(^{37}\) A low pleural fluid glucose level is also typical.

The sensitivity of the pleural fluid TB culture (10–35%) is less than that of pleural biopsy culture (39–65%). Histology and culture of pleural biopsies can yield a diagnosis in up to 86%. Pleural biopsies are essential.

Studies of the value of adenosine deaminase (ADA) levels have been reported for more than a decade, but widespread acceptance of the diagnostic value has not been achieved. A recent study of ADA in subjects with various lymphocytic effusions showed only rare false-positive results using an ADA level of 40 U/L or more as a pointer to TB.\(^{38}\)

Thoracoscopic pleural biopsy specimens may be needed, especially when all other specimens (including sputum) fail to provide a diagnosis. This statement is particularly applicable to people from countries with a high incidence of TB and TB drug resistance, where the susceptibility pattern of the TB organism is essential information.

14.1.12 Lymph node TB

Fine-needle aspiration (FNA) of suspected tuberculous peripheral and mediastinal nodes is the first step toward the diagnosis. A CXR is always needed, as pulmonary TB coexists in about 70% of cases of supraclavicular and cervical lymph node TB. When pulmonary
disease is also present it may be easier to make the diagnosis with respiratory investigations.

Is an FNA a reliable test for diagnosing TB in New Zealand? A New Zealand study\textsuperscript{39} showed that FNA of tuberculous cervical and supraclavicular nodes gave the diagnosis in only 33\% of cases – lower than in many other studies. Two reasons for this finding may be the small number of subjects, or possibly because cases present and are investigated earlier in New Zealand than in non-Western countries, from which most other studies have been reported.

When an FNA is performed, FNA AFB smears are essential, and several FNA specimens should undergo mycobacterial culture. FNA cytology may point to TB if necrotic material, multi-nucleate giant cells and other components of granulomas are seen.

\textit{In a person without risk factors for drug resistance}, and a clinical situation in which TB adenitis seems virtually certain, the clinician may elect not to obtain further specimens, or to do another FNA and then start TB treatment.

\textit{If there are risk factors for drug resistance}, it is essential to obtain the organism and its drug susceptibility pattern.

1. If the FNA AFB smears are negative, the clinician might decide to do another FNA, or go straight to an excision biopsy.
2. If a repeat FNA is smear-negative, it is then essential to proceed to an excision biopsy, with mycobacterial culture as well as node imprints and histology.
3. If there is no clinical urgency, mycobacterial cultures could be awaited before deciding whether or not to perform an excision biopsy.
4. Do not start treatment until a positive culture has been obtained, or until an abnormal node has been excised and is being cultured for mycobacteria.

The principles discussed apply to both peripheral and mediastinal (or intra-abdominal) lymphadenopathy, where there is no easier way to obtain diagnostic material. In the case of mediastinal adenopathy where TB is strongly suspected, transtracheal or transbronchial needle aspirate may be done. CT or ultrasound-guided percutaneous FNA is also employed.\textsuperscript{40} If one of these is non-diagnostic, the patient should proceed to mediastinoscopy.

\begin{center}
\textbf{Practice point}
\end{center}

\begin{quote}
\textit{Always make a point of writing down for the surgeon all tests that the surgeon should arrange on excised biopsy specimens.}
\end{quote}

\section*{14.1.13 Routine laboratory tests}

There are a large number of abnormal results that may occur with TB.
A mild leukocytosis is common. Occasionally a leukemoid reaction or a leukopaenia may be seen. A raised monocyte or eosinophil count is occasionally seen.

Anaemia is common, especially with disseminated disease, and iron studies then usually show features indicative of chronic disease.

Pancytopenia occurs occasionally, and may indicate extensive bone marrow involvement.

Hyponatraemia is said to occur in about 10% of cases, and is due to the production of an anti-diuretic hormone-like substance in diseased tissue. Hypoadrenalism should also be excluded by a short synacthen test.

Hypercalcaemia occurs in about 5% of cases of TB. It is usually mild, and responds to treatment of the TB.

Mild hepatic dysfunction is common with moderately extensive TB. More severe hepatic dysfunction may also be the result of unrelated factors, such as alcohol or viruses that cause hepatitis.

Hypoalbuminaemia and other non-specific features of severe chronic disease are observed in disseminated TB.
14.2 Techniques to enhance the prediction of active TB

Attempts have been made to create methods of predicting:

- which subjects do not need isolation
- which subjects require isolation
- which subjects with smear-negative TB do actually have active pulmonary TB, and should be started on treatment before TB cultures are complete.

These are considered below, but it is important to recognise the limitations of the models discussed. In particular, local epidemiology is an important factor in determining the efficacy of the model. Local epidemiology also influences the situations in which models are needed. Both may change over time. Thus, in an area with a high incidence of TB, where there are many admissions with infectious TB and isolation facilities are limited, it may be very important to try to reduce needless episodes of isolation. Although prediction models may be useful in some settings, they may not always improve on the decisions of experienced clinicians.41 (See also section 14.5, ‘Future Developments’.)

In New Zealand the focus should be on models that:

- are appropriate to different clinical settings
- identify all infectious cases
- identify all active cases of TB, including smear-negative pulmonary, and extrapulmonary TB.

14.2.1 A decision tree to identify which subjects need isolation

This method was developed by El-Solh et al.42 The decision tree used is shown in Figure 14.1. The sensitivity of the decision tree was 100%. Its specificity was 48%, and the negative predictive value was 100%. Using the model, 248 out of 563 (44%) isolation episodes could have been prevented, and approximately $US34,400 in direct costs would have been saved over the 3.5 years of the study.
Figure 14.1: A decision tree to identify which subjects need isolation

Source: El-Solh et al.42
Note: PPV = positive predictive value for sputum positive for M. tuberculosis; n = number of patients; NA = not available.

14.2.2 A computerised artificial neural network to predict active pulmonary TB and the need for isolation43

The decision tree model in the preceding section has been extended using a neural network. Neural networks (NNs) are computation systems that process information in parallel, and identify patterns in the data entered. The authors state that NNs predict outcome more accurately than expert opinion or conventional statistical methods. They compared the results from their artificial NN (available at: http://bgrant.med.buffalo.edu/activetb/) with physicians’ predictions in subjects thought to be at risk of active pulmonary TB.

In prospective testing of a patient set in which 11 of 119 were proven to have active pulmonary TB, sensitivity and specificity were 100% and 69% with the NN, and 64% and 79% with physician assessments. The authors point out limitations of the method, including the fact that the model may not be applicable to locations with different epidemiology. Also, the present model may not be suitable for diagnosing extra-pulmonary TB.
Perhaps after further refinements and simplification, and then prospective testing in different centres, this methodology might be the basis of a future software computer program for improving the early diagnosis of TB.

14.2.3 Predicting the need for respiratory isolation

In this retrospective study from New York, clinical and radiographic data from two patient groups were compared. Data from 56 culture-positive pulmonary TB cases were compared with that from 56 age- and year-matched control subjects who had been isolated, but then shown not to have TB.

Points were allocated to clinical and radiographic variables according to the magnitude of the association (by multivariate analysis) between each factor and a positive culture for TB. Points (shown in brackets) were allocated to variables as follows: TB risk factors or chronic symptoms (4); positive PPD skin-test result (5); shortness of breath (-3); crackles noted during examination (-3); temperature, °C: < 38.5 (0), 38.5–39.0 (3), > 39.0 (6); upper lobe consolidation (6).

Based on the distribution of the final scores in cases and controls, a score of 1 or higher was chosen to indicate the need for respiratory isolation (98% sensitivity, 95% CI, 95–100%; 46% specificity, 95% CI, 33–59%). A higher value was associated with a higher risk of TB. Likelihood ratios were also calculated, but those results are not discussed here.

Had the methodology from this study been applied to 3000 isolation episodes at the study institution, 1400 patients (47%) would not have been unnecessarily isolated. Only one of the 56 infectious cases (1.8%) in this study would have been misclassified.

This method of prediction could be prospectively validated in New Zealand. If the method yielded reproducible results it would be a useful addition to clinical practice, because the data on which the prediction is based are available from routine information obtained at the time of admission.

14.2.4 Using the tuberculosis prediction score (TPS) to predict which smear-negative subjects have active pulmonary TB

There are large numbers of patients in whom sputum tests for TB are ordered, who turn out not to have TB. One estimate from Canada was that 125 people were tested for every one culture-confirmed case of TB.

The objective of the retrospective case-control chart review by Kanaya et al was to use the clinical demographic and radiological characteristics that identified smear-negative patients with active pulmonary TB, and to incorporate them into a tuberculosis prediction score (TPS). The charts and X-rays of 47 smear-negative patients with TB and 141 smear-negative, control subjects admitted with suspicion of pulmonary TB were examined.
The following table shows odds ratios of multivariate factors independently influencing the risk of a positive mycobacterial culture.

**Table 14.3:** Odds ratios of multivariate factors independently influencing the risk of a positive mycobacterial culture

<table>
<thead>
<tr>
<th>Positive predictive factors</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculin skin test (+)</td>
<td>4.8</td>
<td>2.0–11.9</td>
<td>.001</td>
</tr>
<tr>
<td>HIV (+) and mediastinal adenopathy</td>
<td>7.2</td>
<td>1.4–36</td>
<td>.02</td>
</tr>
</tbody>
</table>

Factors predictive of a decreased risk of a positive *M. tuberculosis* culture

<table>
<thead>
<tr>
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<td>0.1–0.7</td>
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* Lobar consolidation or a diffuse pattern on CXR.

Likelihood ratios were calculated, and a TB prediction score (TPS) was developed, based on the score assigned to the above variables. The score given varied according to an individual’s TB prevalence category. A companion editorial by Long46 was sceptical of the usefulness of this paper’s TPS because of the wide variety of clinical contexts in which it would be applied. Further validation studies are required before this technique can be widely used. Suitable computer software would be needed to enable the TPS to be calculated rapidly in clinical practice.
14.3 Assessment of TB activity, severity and extent

14.3.1 Active and inactive TB

Active TB

This is TB disease in which:

- an *M. tuberculosis*-complex organism* has been cultured, or identified in a culture by DNA probe. (Note that a positive PCR test on a tissue specimen, as distinct from secretions or other bodily fluids, does not distinguish between active and inactive TB.)
- clinical parameters are suggestive of activity, which include some of the following:
  - a changing radiological infiltrate (worsening or improving) which is compatible with TB, or an infiltrate compatible with active TB
  - other disease features suggestive of TB (eg, supraclavicular or cervical lymphadenopathy)
  - tissue histology compatible with TB
  - the Mantoux reaction is positive or has converted
  - the person has had contact with an infectious TB case
  - the person has risk factors for TB infection progressing to disease.

Inactive TB

This term refers to TB disease in which full investigation has been performed, other diagnostic possibilities considered, and:

- adequate specimens are smear- and culture-negative for TB
- radiological features are suggestive of inactivity (see Chapter 16: ‘Treatment of Tuberculosis’, section 16.1.2)
- clinical indices and tests do not suggest disease activity; for example:
  - fever and other systemic features of active TB are absent
  - the ESR is within normal limits or another clear-cut cause for a raised ESR is identifiable
  - the midstream urine does not show sterile pyuria
- if the person receives treatment, lack of radiological change after three months’ treatment also argues against disease activity.47

* *M. tuberculosis* complex includes the organisms *M. tuberculosis, M. bovis, M. bovis Bacille Calmette Guerin, M. microti, M. canetti and M. africanum.*
14.3.2 Severity of TB

Bacillary load, extent of disease and anatomical site are considerations in determining the severity of TB. This holds true whether judging the severity of current or past TB. Severe active disease is judged to be present if there is:

- acute threat to life (eg, pericardial TB), or
- risk of subsequent severe handicap: this is most likely to occur with the following types of TB disease:
  - pulmonary TB, with bilateral very extensive disease (eg, three or more lobes heavily involved) or widespread cavitatory disease (more than two lobes involved)
  - extra-pulmonary TB: spinal TB, TB meningitis, miliary TB, TB pericarditis, TB peritonitis, bilateral or extensive pulmonary effusion, intestinal, or genito-urinary TB

14.3.3 Extent of TB

Radiological extent of pulmonary disease

There is no widely accepted system of classifying extent of disease. The Harrison-Wells method (Auckland) has been validated, and has been modified here by adding one additional grade of extensive disease. The radiological grades of disease extent are:

- Grade 0: no disease
- Grade 1: trivial disease, where the total possible volume of old and/or active TB is equivalent to, or less than, one broncho-pulmonary segment
- Grade 2: intermediate disease, where the total possible TB volume is greater than one broncho-pulmonary segment but less than or equal to one lobe
- Grade 3: extensive disease, with the total TB volume greater than one lobe, and up to one lung field
- Grade 4: very extensive disease, exceeding one lung field.

Parenchymal disease should be categorised as unilateral or bilateral. The presence of lymphadenopathy, pleural disease or miliary abnormalities should also be noted.

Disseminated TB

This term refers to TB that involves multiple body systems. It is, by definition, extensive. Disseminated TB only occurs in about 3% of non-HIV TB cases in Western countries, but may carry an overall mortality rate as high as 38%. The absence of miliary changes on the chest radiograph, in the presence of pulmonary and multi-system TB, indicates a much higher mortality rate (around 85%). Malnutrition, if present, may need particular attention in people with severe or extensive TB.

* WHO does not specify criteria for disease extent. The classifications of extent shown in this section are arbitrary.
14.4 Investigation of TB in people from countries with a high incidence of TB

The incidence of TB in non-New Zealand-born people visiting or living in New Zealand is much higher than in European or Māori populations. Moreover, foreign-born individuals, particularly if non-European or of ‘Other’ ethnic origin, are more likely to have organisms that are resistant to one or more first-line anti-TB agents (see Chapter 1: ‘Epidemiology and Surveillance’).

Although this section primarily concerns the screening of refugees, immigrants and visitors, the same principles should be applied to evaluating disease risk in New Zealanders returning home from countries with a high incidence of TB, where they may have had a high risk of exposure.

14.4.1 Clinical investigation of suspected TB

The process of investigation does not differ from that for other groups, and is described above in section 14.1. There are some special considerations, however.

Language and cultural considerations

These should receive particular attention, both from a humane viewpoint and to promote co-operation. The latter is essential for the collection of accurate information and adherence with health measures.

Awareness of possible HIV/AIDS

Because some immigrants will be arriving from countries with a high prevalence of HIV infection, it is important to:

- maintain a high index of suspicion for HIV
- ask about personal risk factors
- have a low threshold for seeking permission to perform an HIV test
- do an HIV test if:
  - it is thought that treatment of LTBI or preventive treatment is appropriate, or
  - if active TB is suspected or discovered.

Only with X-ray abnormalities from trivial, healed TB should an HIV test be omitted.

A low threshold for obtaining bronchial specimens

This is appropriate, as positive exclusion of active TB is required. Table 14.2, above, gives details of radiological criteria for detailed mycobacteriological testing.

14.4.2 ‘Immigration clearance’ for TB

An ‘immigration clearance’ is often requested for non-New Zealand residents applying for permanent residence or a visa, when a CXR report describes an abnormality.
Who should pay for the immigration clearance?

An immigration medical followed by a detailed TB search is a costly exercise for immigrants. Currently the costs of all investigations and treatment for TB for non-residents are borne by the New Zealand taxpayer, if the medical officer of health considers the health care services to be compulsory (Direction Relating to Eligibility for Publicly Funded Personal Health and Disability Services in New Zealand). ‘Compulsory’ services are defined as those ordered when a letter is written by the medical officer of health to the patient under Section 9 of the Tuberculosis Act (Carol Hinton, personal communication, Ministry of Health, 17 May 1996 to Dr Lester Calder, Ministry of Health, Auckland).

Most medical officers of health would consider that any tests a physician considers necessary to clarify a diagnosis of TB would be sufficiently important to warrant making the investigations compulsory.

It is a matter for public policy debate whether it is acceptable that the New Zealand taxpayer continues to fund these services for non-residents. Many of the non-residents are poor and would not comply with investigation or treatment if they had to pay for the services themselves. However, it is not uncommon for fee-paying students or wealthy non-residents to receive free treatment under the current situation.

The only situation where TB-related costs would be borne by the non-resident is where they elect private medical assessment.

The role of the clinician in an immigration medical

Although the immigration focus is usually on excluding TB, the clinician must consider:

- if other diagnoses are possible (particularly lung cancer in current or past smokers, COPD or bronchiectasis)
- whether detailed mycobacteriological tests for TB are appropriate (see below)
- whether other investigations (eg, CT scan of the chest) or even no investigations are required
- if either treatment of latent TB infection, or full (preventive) treatment of inactive TB is required.

Indications and regimens for (preventive) treatment of inactive TB disease are discussed in Chapter 16: ‘Treatment of tuberculosis’, sections 16.1.2 and 16.4.

Items in the immigration medical

History

An interpreter should be used if the applicant cannot speak English sufficiently well. Key information required includes that concerning previous TB (and if so, details of treatment), contact with TB, and TB symptoms. Enquire into possible occupational exposure to TB through previous medical or dental occupations. A general medical history is also needed.
Physical examination

Ensure lymph node groups are examined.

A recent chest radiograph

If the person is asymptomatic, films taken three to four weeks earlier are satisfactory. Otherwise a repeat X-ray is needed. If chest or systemic symptoms of TB are present, the chest radiograph should not be more than about a week old. Always ask if previous films can be obtained for comparison if none are offered.

General tests

A full blood picture, ESR and midstream urine (MSU) test should be done. If the MSU result is abnormal, see section 14.1.5.

Is a Mantoux test needed?

A Mantoux is needed if the CXR appearance suggests a condition other than TB. A negative Mantoux will make it even less likely that TB is the cause of the X-ray abnormality. If the appearance is typical of current or old TB, a Mantoux test is not likely to add extra information, as clinical suspicion is already high. Sometimes a strongly positive Mantoux reaction will persuade the clinician or the client that some form of TB treatment is appropriate.

Indications for detailed mycobacteriological testing

The key indication is an abnormal CXR in which old or active TB is included in the differential diagnosis. The importance of full testing increases if there is suspicion of TB from a positive Mantoux or symptoms. (See Table 14.2 for radiological indications for detailed mycobacteriological investigations.)

Mycobacterial tests on bronchial specimens

1. Sputum tests (three specimens): these are only appropriate if the person has lower (not upper) respiratory tract secretions. This should be evident during the interview. If the person has very little or no sputum, other tests are necessary, as follows.

2. Induced sputum tests (three specimens): this is the procedure of choice in people who have little or no spontaneous sputum. Three specimens are needed, obtained under respiratory isolation conditions. Induced sputum testing is discussed in more detail earlier in section 14.1.6.

3. Bronchoscopy with broncho-alveolar lavage: if induced sputum facilities are not available, or are not available in the required time frame, bronchoscopy is the next best choice. The comparison with induced sputum testing is discussed above in section 14.1.6.
14.5 Future developments

14.5.1 Replacement of the Mantoux test
The Mantoux test has greater value in the detection of latent TB infection than it has in the
diagnosis of active TB, as discussed above in section 14.1.3 and in Chapter 2: ‘Mantoux
Testing’. Clinicians look forward to a serological test that is a reliable and reproducible
pointer to active TB.

14.5.2 Computer-based methods of predicting active TB and infectiousness
Computer methodology providing accurate prediction would be useful in the following
areas:
- predicting who is infected with live *M. tuberculosis* organisms
- predicting active TB
- predicting infectivity – which patients actually need isolation
- ability to make these predictions in general practice versus in hospital.

Existing methods have been discussed in 14.2. Improved practicality is needed before this
type of technology is widely available. Also, prediction models are not generalisable: they
need to be validated for the local epidemiological situation. Ongoing validation is needed,
as change in any of the parameters can cause marked differences in the performance of
such a model. There is the potential, however, for such methods to enable rapid
identification of infected individuals and infectious TB cases right from general practice.
References


Chapter 15: *M. Tuberculosis*, TB Medicines and Monitoring

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This chapter is endorsed by the Thoracic Society of Australia and New Zealand

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References
Summary

*M. tuberculosis* and the host response

- Characteristics of *M. tuberculosis* and the host response to TB are reviewed in the full text. Many aspects are pertinent to understanding certain characteristics of TB epidemiology, infection and disease, as well as clinical tests.

The eradication of TB with drug treatment

- The three phases in the eradication of TB are reviewed.

  Phase I: rapid bactericidal activity occurs. Actively multiplying organisms are killed in this stage. Isoniazid, alone or in combination, is much more bactericidal than rifampicin and other drugs in this phase.

  Phase II: this lasts up to two months. The rate of killing is slower, presumably because the remaining bacilli are metabolising more slowly. The decrease in the sputum colony counts is similar for different drug regimens (provided purely bacteriostatic drugs are not given alone), so there is no point adding more drugs to standard regimens in an attempt to shorten the period of infectivity when treating infectious cases with susceptible organisms.

  Phase III: the ‘sterilisation phase’. The drugs act on intracellular bacilli, including those that are mainly dormant but have brief periods of active metabolism – ‘persisters’ are eliminated. In this phase, rifampicin is much more bactericidal than isoniazid. Pyrazinamide is also important in eradicating this population of organisms.

- The early bactericidal and sterilising properties of the antituberculous drugs are summarised as follows (see Table 15.1 for details):
  - isoniazid has high early bactericidal activity, but is inefficient at achieving (TB) sterility
  - rifampicin and pyrazinamide are crucial in achieving sterilisation by killing persisting semi-dormant bacilli
  - with regimens containing rifampicin and isoniazid, there is no benefit from continuing pyrazinamide beyond two months; but with isoniazid resistance, pyrazinamide may be usefully continued throughout the full course of treatment
  - ethambutol is effectively devoid of sterilising activity (isoniazid/ethambutol in particular is a weak, ineffective regimen)
  - aminoglycosides are only actively bactericidal against rapidly growing organisms.

- Concentration-dependent and concentration-independent killing and post-antibiotic effects are discussed in the context of TB medicines in the full text.

Mechanisms of drug actions

- See Table 15.2 and accompanying discussion.

Drug resistance

- The main types of drug resistance are:
  - primary resistance: the organisms transmitted were resistant to one or more TB drugs
Naturally occurring resistance to anti-tuberculous drugs can also occur, and varies from drug to drug. Cavities contain approximately $10^8$–$10^9$ bacilli and there is a higher risk of naturally resistant organisms being present in TB cavities. Consideration should be given to adding additional drugs if there are other factors present for resistant organisms. A longer duration of treatment, compared with that for minor disease, is often appropriate.

Because of naturally occurring drug resistance, multiple drug therapy is essential for TB disease.

Secondary resistance to a particular drug is unlikely to occur within two months, if the drug in question has been taken as part of a multi-drug regimen, in which all doses have included all drugs and the organism is susceptible to most drugs in that regimen. Thus, stopping an effective regimen which has been taken regularly, prior to achieving a cure, should not predispose to the development of secondary resistance.

**Drug doses and administration**

- See Table 15.3 for dosage recommendations for anti-tuberculous 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 Chapter 17: ‘Treatment of Tuberculosis in Special Clinical Circumstances’.
- Ethambutol: the daily dose of ethambutol should be 15 mg/kg, unless there are good reasons for a higher (or lower) dose. The risk of optic neuritis is greater with higher doses.

**Use of pyridoxine**

- Always use pyridoxine when prescribing isoniazid for people at risk of peripheral neuropathy from other causes (eg, those with diabetes, chronic renal failure, malnourished people, alcoholics, those taking certain oncology agents and pregnant women).
- Many TB clinicians (including the chapter author) recommend routine use of pyridoxine 10–25 mg/day for everyone taking pyridoxine, as the development of peripheral neuropathy can occur without other risk factors. Moreover pyridoxine is cheap (especially with non-pharmacy brands) and easy to take.

**Drugs in fixed-dose combinations (FDCs)**

- See full text.

**Administration of ethambutol**

- Ethambutol and renal impairment: avoid using ethambutol with moderate and severe renal impairment. Doses for use in renal disease and dialysis are found in Chapter 17: ‘Treatment of Tuberculosis in Special Clinical Circumstances’ and Table 17.1.
- Ocular toxicity: this is the main potential side-effect of ethambutol.
  - Baseline assessment of visual acuity and red-green colour perception are needed.
  - Ophthalmological assessment should be obtained as a baseline before starting treatment in patients with abnormal visual acuity.
  - Patients must be advised to report visual deterioration: such complaints necessitate a semi-urgent ophthalmological opinion.
- Small children, the elderly, adults with already marked visual impairment or renal impairment and those who cannot be relied upon to report visual deterioration should all be offered another agent, if possible.
- Hospital and public health staff should each enquire every two months (as a minimum) about visual deterioration, particularly where communication difficulties are present.
- Opinions differ about the necessity to monitor visual acuity: testing every two months seems advisable, and this is the usual practice with the Green Lane Hospital TB Service.

Formal ophthalmological monitoring: where ethambutol is prescribed for people with comprehension or communication difficulties, formal ophthalmological assessment should be done regularly (eg, at monthly intervals). This is particularly important if renal impairment is present.

Administration of Amikacin

See Table 15.4 and accompanying discussion.

Pharmacological considerations with anti-tuberculous agents

1. Isoniazid

- Food and antacids may reduce the absorption of isoniazid, which is best taken on an empty stomach, or one to two hours before an antacid.
- The relevance of isoniazid acetylator status:
  - it is unlikely that slow acetylator status has much significance in most subjects; no guidelines recommend routine testing of acetylator status
  - fast acetylator status would only be a consideration if once/week regimens become available.
- Serum isoniazid levels may be appropriate where:
  - there is hepatotoxicity or other hypersensitivity reactions, and
  - the resistance pattern and/or other drug side-effects make reintroduction of isoniazid highly desirable.

2. Rifampicin

- Rifampicin is best taken on an empty stomach, wherever possible. The time at which the maximum serum concentration occurs is delayed from approximately two hours to six hours, and the peak serum concentration is reduced by a third if rifampicin is taken after a fatty meal.
- Antacids do not affect the absorption of rifampicin.
- Rifampicin is excreted in urine, sweat, tears and other bodily fluids, colouring them orange. Soft contact lenses may be permanently discoloured.

3. Rifabutin

- This drug should be taken straight after food, as serum concentrations of rifabutin are thereby enhanced.
4. *Ethambutol*
   - Absorption is unaffected by food.

5. *Pyrazinamide*
   - Food does not impair the absorption of pyrazinamide.

6. *Quinolones*
   - Ingestion with food delays the time to peak serum concentration by an additional one to two hours with these agents, but the extent of absorption is not changed.
   - Antacids or ferrous sulphate may interfere with the absorption of quinolones if both are taken together. See Table 15.8, Clinically important interactions with TB drugs.

7. *Directly observed therapy (DOT) – before or after food?*
   - In many subjects the timing is not critical.
   - When starting DOT, enquire about symptoms of malabsorption routinely. The combination of malabsorption and post-cibal administration of DOT containing rifampicin may result in treatment failure or the selection of rifampicin-resistant organisms.

**Monitoring**

**Monitoring infectivity**
   - Patients with positive pre-treatment sputum should have repeat sputum tests at fortnightly intervals until conversion is documented.
   - In people who are strongly acid-fast bacilli (AFB) smear-positive, it seems likely that two weeks of treatment is not sufficient to lower the infectious potential to a minimal level (ie, to a level of infectiousness equivalent to people with smear-negative, culture-positive TB). Isolation should continue until non-infectiousness can be virtually guaranteed, and usually this will mean the person is smear-negative. See Chapter 9: ‘Infection Control’.

**Radiological monitoring**
   - Failure of the chest radiograph to show improvement after three months of treatment requires consideration of the following possibilities:
     - the diagnosis is not TB: re-investigation is needed
     - the TB had produced scarring prior to treatment
     - mixed pathology may be present: TB and other condition(s)
     - non-adherence to the medication programme has occurred
     - drug resistance was present from the outset, or has developed.
   - Chest CT scanning is useful for monitoring mediastinal lymph node TB which is advanced or extensive initially. Consider giving longer treatment if a necrotic node appearance persists, or nodes do not diminish greatly in size during treatment.
Monitoring for adverse drug reactions

- Baseline haematology and biochemistry tests should be done on adults about to start TB treatment. Initial abnormalities need follow-up.
- Repeat blood tests two to three and six to eight weeks after adults start regimens containing hepatotoxic agents. Ongoing blood tests are unnecessary after the first two months of treatment if results are normal and no new symptoms develop.
- Symptoms of possible drug toxicity are an indication for appropriate blood tests.
- With pre-existing mild hepatic disease, or with substantial alcohol intake, it is prudent to monitor liver function (e.g., fortnightly for the first month, monthly for the next two months, and two-monthly thereafter). See also Chapter 17: ‘Treatment of Tuberculosis in Special Clinical Circumstances’.
- Nursing review (including a pill count) once a month is the minimum acceptable for patients on TB treatment. Instruct patients to watch for common drug reactions.
- Medical review every two to three months is acceptable, provided there are no risk factors for poor compliance, the patient can be relied on to report symptoms, and monthly review by a public health nurse is being carried out.

Therapeutic drug monitoring

- Improvements are needed in the methods of testing, the reliability of results, turnaround time, and the range of drugs available for testing. This will only occur if there is increased awareness and more frequent – but appropriate – requests for testing by clinicians.
- For situations where therapeutic drug monitoring may be indicated with first-line drugs, see section 15.6.4.

Drug side-effects

Common drug side-effects

- These are listed in Table 15.5.

Dermatological side-effects

- Pyrazinamide is the most common cause of dermatological side-effects with TB drugs.
- Isolated skin rash is very uncommon with isoniazid, but rash commonly occurs as part of a wider hypersensitivity reaction to this drug.
- Skin rash due to rifampicin is usually mild and can take a variety of forms.
- Ethambutol rarely causes dermatological side-effects.
- Photosensitivity can occur with pyrazinamide and the fluoroquinolones.

Hepatotoxicity from TB-drug treatment

- Treating TB involves giving several potentially hepatotoxic drugs – isoniazid, rifampicin and pyrazinamide. Ethambutol very rare causes hepatic dysfunction.
- Chronic hepatitis B carriers tolerate isoniazid well.
Isoniazid hepatotoxicity is associated with increasing age (see Table 15.6) and daily alcohol consumption. Time of onset: 15% during the first month, 30% during the second month, and 54% 2–11 months after starting isoniazid.

Rifampicin is the usual cause of a cholestatic pattern. There is no evidence that hepatotoxicity with rifampicin is age-related.

The hepatotoxicity with rifampicin and isoniazid seems to be additive rather than synergistic.

Pre-existing hepatic dysfunction and its management is discussed in Chapter 17, section 17.2.

Amikacin toxicities

See full text.

Paradoxical reactions to TB treatment

A paradoxical reaction to TB treatment is defined as ‘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.

Paradoxical reactions may have local or systemic components, or both. They occur more frequently in HIV-infected subjects who are on TB treatment and then commence anti-retroviral agents.

The differential diagnosis of apparently 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 secondary drug resistance or development of primary drug resistance
- drug reaction
- concurrent infection or malignancy.

The diagnosis of paradoxical reactions may be difficult. Investigation aims at detecting other possible causes of deterioration at sites of previous TB. Tissue sampling is particularly important in severely ill people and in those with major immunosuppression.

The management of paradoxical reactions

Once the 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 incising, though this would rarely be indicated.

Management of drug reactions

Always consider the need for a new, temporary regimen
**Stopping all anti-tuberculous treatment**

- Whenever considering stopping anti-tuberculous treatment, particularly if planning to give an oral steroid to counteract treatment side-effects, consideration must always be given to covering the TB with a new, temporary regimen. This regimen should continue until full doses of all drugs in the definitive regimen have been started.

- The duration of any period off all TB treatment (while awaiting resolution of TB-drug side-effects) depends on the clinical situation.
  - A person who is acutely ill with TB, or is infectious, should be given an alternative regimen immediately on stopping treatment.
  - For a non-infectious, well person there are no absolute rules. However, a period of four weeks is an arbitrary maximum period off all treatment, based on the fact that the opportunity for the development of infectiousness, or the spread of disease to other sites is possible after this length of time.

**Progressive, but non-effective partial regimens**

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

**Repeated periods on partial or no treatment:**

- These are particularly to be avoided. A second episode of no or partial treatment is an indication for starting a temporary regimen and continuing it for several weeks, until there is certainty that the difficulties have been fully resolved.

**Agents in the temporary regimen**

- These could include amikacin or streptomycin, ciprofloxacin, ethambutol and ethionamide (or prothionamide).

**Rules for managing TB drug side-effects**

- See ‘Practice points’ box, section 15.8.1.

**Other items in this section**

- See full text for discussion of drug challenges, drug densitisation and the management of skin side effects, hepato-toxicity and uncontrollable vomiting.

**Interactions with anti-tuberculous drugs**

- The interaction between rifamycins and oral contraceptives, and management of contraception, are discussed in Chapter 17: ‘Treatment of Tuberculosis in Special Clinical Circumstances’.

- The rifamycin–warfarin interaction is extremely important. There is the potential for:
  - sub-therapeutic anticoagulation occurring when a person on warfarin starts rifampicin
- a dangerous degree of anti-coagulation occurring when rifampicin is stopped, thereby effectively reducing the hepatic metabolism of warfarin.

Allopurinol and pyrazinamide taken concurrently may result in acute attacks of gout. Manoeuvres to avoid this are given in the full text.

For other drug interactions see Table 15.8.
Introduction

This chapter addresses the scientific background to the treatment of TB disease. It also provides information about anti-tuberculous drugs and their use. However, neither this nor the other treatment chapters attempts to be a comprehensive guide to the use of TB medications. Treatment regimens for active and inactive TB are discussed in Chapter 16: ‘Treatment of Tuberculosis’. The use of TB medicines in special clinical situations is the subject of Chapter 17, and their use in HIV is reviewed in Chapter 18.
15.1 **M. tuberculosis and the host response**

15.1.1 **Characteristics of M. tuberculosis**

*Mycobacterium tuberculosis* has a number of features that are important to its ability to survive and cause disease. Several are directly relevant to difficulties with treatment. These features include the fact that it:

- is a strictly aerobic bacterium
- has a long replication time (16–18 hours)
- possesses a thick, lipid-containing cell wall, which is the source of much of its virulence and persistence (e.g., the cell wall structure prevents it drying out and disintegrating quickly). Several antibiotics act via an effect on the cell wall
- has the ability to survive and multiply intra-cellularly
- has the ability to switch off metabolic activity and lie dormant for prolonged periods
- has resistance to conventional antibiotics and a (low) level of natural resistance to TB antibiotics (see section 15.4).

15.1.2 **The host response to TB**

The body’s responses to *M. tuberculosis* are important, and have a direct bearing on the clinical type of disease that results. This is a complex and expanding topic which is beyond the scope of this chapter. Key aspects of the immune response to *M. tuberculosis* include the following.

- *M. tuberculosis* binds to macrophages and monocytes – the alveolar macrophage is the body’s initial defence against this organism. Strain virulence, complement and cytokine release influence the initial binding of the organism to these cells. To become active against mycobacteria, macrophages must be activated. Activating factors include IFN-γ and TNF-α (see below), and also Vitamin D. Certain Vitamin D receptor polymorphisms may be associated with susceptibility to TB.¹

- Phagocytosis of the organism occurs – inside the macrophage a variety of complex killing mechanisms come into play, as a result of interaction between phagocytic cells and lymphocytes. Some bacilli are killed within the macrophage, but some survive and multiply.

- Although many T-lymphocytes play a part in defence against TB, there is no doubt that the CD4+ T-lymphocyte is the main effector cell in the cell-mediated immunity against TB. CD 8+ T-lymphocytes are also important.

- Interferon-γ (IFN-γ) is an important part of the defence against mycobacteria. It is released from CD4+ T-lymphocytes and natural killer (NK) T-lymphocytes. An important role of IFN-γ against TB is in the activation of macrophages. Children with defective receptors for IFN-γ or interleukin-12 (IL-12) are susceptible to TB.

- There is a complex array of interleukins and cytokines which activate and inactivate macrophages. Malnutrition unrelated to TB can markedly affect cytokine production, as can TB treatment.
Tumour necrosis factor (TNF-α) produced by macrophages may play a dual role, helping macrophage activation on the one hand, while greater production resulting in increased plasma levels has been associated with deterioration in patients with severe TB. This cytokine, like IL-12, also facilitates the production of IFN-γ by NK cells, and subsequently by T-lymphocytes.

Apoptosis (programmed cell death) of macrophages reduces the viability of mycobacteria contained within them.

*M. tuberculosis* has a number of strategies that enable it to avoid being killed by macrophages. By altering the pattern of cytokine release from infected macrophages, it reduces macrophage activation and T-cell recruitment. The severity of the disease can affect the cytokine response.

Some CD4+ T-lymphocytes differentiate into memory T-lymphocytes, and these mediate delayed hypersensitivity – the process that underlies the reaction to tuberculin in the Mantoux test (see Chapter 2: ‘Mantoux Testing’).

The ‘atypical’ clinical picture of TB seen in AIDS (see Chapter 18: ‘Tuberculosis and HIV’) and occasional cases of TB that are unresponsive to appropriate TB medicines are examples of the direct clinical relevance of understanding the host response to TB. For further reading, see.1–5
15.2 The eradication of TB with drug treatment

15.2.1 The three phases in the eradication of TB

These are relevant to the phases of TB treatment, as discussed in Chapter 16: ‘Treatment of Tuberculosis’. These are theoretical concepts based on animal models and studies in humans, and the duration of the phases are not exact.

**Phase I**

Phase I is said to last about two days, during which time rapid bactericidal activity occurs. The organisms being killed are actively multiplying at this stage, and they are thought to comprise 90% of the bacterial population (see also 15.2.2). There are large differences between drug regimens with respect to the speed with which colony counts decrease. Isoniazid, alone or in combination, is much more bactericidal than rifampicin and other drugs in this phase. It is likely that this phase does not stop abruptly on day three, but rather becomes less important as the bacterial number decreases with time. The effectiveness of drugs in reducing colony counts during this two-day phase is called their early bactericidal activity (or EBA).

**Phase II**

Phase II lasts up to two months. The rate of killing is slower, presumably because the remaining viable bacilli are metabolising more slowly. During this phase the decrease in the sputum colony counts is similar for different drug regimens (provided purely bacteriostatic drugs are not given alone). For this reason there is no point in adding more drugs to standard regimens in an attempt to shorten the period of infectivity, when treating infectious cases with susceptible organisms.

**Phase III**

In Phase III, or the ‘sterilisation phase’, the drugs act on intracellular bacilli, including those that are mainly dormant but have brief periods of active metabolism. In this third phase, ‘persisters’ (which demonstrate very occasional bursts of metabolic activity) are eliminated, and rifampicin is much more bactericidal than isoniazid for this population of organisms.

Although three phases can be identified, they probably all start at the commencement of treatment. Despite the fact that most replicating bacteria are killed rapidly during the first one to two weeks of treatment, there is no known relationship between EBA and the outcome of treatment. Time to sputum sterilisation is a very important predictor of outcome.11

15.2.2 The early bactericidal and sterilising properties of the anti-tuberculous drugs

**Table 15.1:** Grading of anti-tuberculous drugs

<table>
<thead>
<tr>
<th>Extent of activity</th>
<th>Prevention of drug resistance</th>
<th>Early bactericidal activity</th>
<th>Sterilising activity</th>
</tr>
</thead>
</table>

Guidelines for Tuberculosis Control in New Zealand 2003
Chapter 15: *M. Tuberculosis, TB Medicines and Monitoring*
Isoniazid
Isoniazid has high early bactericidal activity and kills rapidly growing bacilli in lesions. It is thought to be responsible for killing about 95% of these organisms during the first two days of treatment. However, it is inefficient at ultimately sterilising these lesions.\(^\text{13}\)

Rifampicin and pyrazinamide
These are crucial in achieving sterilisation by killing persisting semi-dormant bacilli. Their use in daily treatment regimens is discussed in Chapter 16: ‘Treatment of Tuberculosis’, section 16.4. Rifampicin is the most important anti-TB drug from a sterilising viewpoint. Rifabutin is the best of the rifamycins at cell penetration, and is an excellent sterilising drug, killing intra-cellular bacilli.

It used to be thought that pyrazinamide worked by killing organisms within macrophages in an acidic environment. However, the intra-cellular environment around bacilli is not acidic. It is now believed that this drug kills both extra-cellular, semi-dormant organisms whose growth is slowed by an acidic environment, and those within macrophages.\(^\text{12}\)

Pyrazinamide is a pro-drug, the active agent being pyrazinoic acid. The latter is formed by the action of the enzyme pyrazinamidase – which is identical with nicotinamidase – on pyrazinamide. Amidase activity is present in \textit{M. tuberculosis} organisms susceptible to pyrazinamide, but not in those resistant to it. The gene encoding for this amidase, \textit{pncA}, has been identified.\(^\text{14}\) It remains to be seen whether resistance to pyrazinamide can occur by a mechanism other than by \textit{pncA} mutation.

With regimens containing rifampicin and isoniazid there is no benefit from continuing pyrazinamide beyond two months, because by then there is insufficient acute inflammation and insufficient acidity for pyrazinamide to be bactericidal. There are also concerns about continuing pyrazinamide beyond two months because this drug has been found to antagonise the bactericidal activity of isoniazid and rifampicin in macrophages.\(^\text{15}\) With isoniazid resistance, however, pyrazinamide may still be useful in the continuation phase of treatment.
**Ethambutol**

Ethambutol is very useful for preventing the development of drug resistance, but ‘is effectively devoid of sterilizing activity’. High relapse rates occurred with 12-month regimens of isoniazid/ethambutol, despite two initial weeks of daily streptomycin.

**Amikacin**

Even with serum levels that are well in excess of the minimal inhibitory concentration (MIC) of *M. tuberculosis*, amikacin has ‘only just detectable’ early bactericidal activity. This contrasts with *in vitro* studies in which amikacin and other aminoglycosides have been shown to be highly bactericidal. Possible explanations for this paradox include:

- aminoglycoside activity is critically dependant on pH, with greatly lessened activity at an acidic pH
- there is poor penetration of all aminoglycosides into bronchial secretions, concentrations there being only 15–20% of that in the bloodstream.

Aminoglycosides are only actively bactericidal against rapidly growing organisms; they are not active against occasionally metabolically active ‘persisters’. Consequently, aminoglycosides do not have useful sterilising ability. These agents are most likely to be useful against mycobacteria in phase II of treatment (as discussed in 15.2.1), when the degree of inflammation has subsided as a result of other multi-drug treatment. Donald et al 2001 conclude that the role of aminoglycosides, like that of ethambutol, is probably mainly in preventing the emergence of resistance to other drugs.

**15.2.3 Concentration-dependent and concentration-independent killing**

**Bactericidal agents active against the cell wall of aerobic bacteria**

These agents exhibit saturable bacterial killing at concentrations above the MIC. In other words, drugs working on the cell wall have a concentration-independent pattern of action. For these agents, the aim should be to maintain plasma drug concentrations above the MIC for the entire administration interval.

TB antibiotics that are active against the mycobacterial cell wall (see Table 15.2) probably include ethambutol, isoniazid, ethionamide, prothionamide and thiacetazone.

**Bactericidal agents with intra-cellular targets**

Agents in this category exhibit non-saturable (or concentration-dependent) killing. ‘Concentration-dependent killing’ means that increasing doses above the organism’s MIC induces more rapid killing of the pathogen. Optimal antibacterial effects with these agents require:

- *either* high maximum plasma concentrations in relation to the MIC
- *or* a long period of antimicrobial exposure (ie, the time in which ‘the area under the curve vs plasma concentration,’ is above the MIC).

TB drugs with intracellular targets include aminoglycosides, fluoroquinolones, the rifamycins and possibly pyrazinamide (see Table 15.2). While Ciprofloxacin has useful
early bactericidal activity, its sterilising ability after two months is inferior (in combination with isoniazid, rifampicin) to isoniazid, rifampicin, pyrazinamide, ethambutol, with sterilising rates of 67% with isoniazid, rifampicin, ciprofloxacin \( n = 11 \) and 100% with isoniazid, rifampicin, pyrazinamide, ethambutol \( n = 9 \). The role of ciprofloxacin in combination regimens appears to be as a bactericidal rather than as a sterilising agent.\(^{20}\)

### 15.2.4 Post-antibiotic effect

The ‘post-antibiotic effect’ refers to the persistent inhibitory bactericidal effect against organisms that is seen after the drug has been eliminated from the blood stream. It probably represents the time required for the organism to recover from cellular injury. At present the only clinical relevance of the post-antibiotic effect is the ability to use aminoglycosides in a once-a-day dosage. This is associated with reduced renal toxicity. Fluoroquinolones have a prolonged post-antibiotic effect against most gram-negative pathogens. Whether this effect occurs with mycobacteria seems not to have been studied.\(^{21}\)
### 15.3 Mechanisms of drug actions

Table 15.2: Mechanisms of action of the anti-tuberculceous drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Poorly understood: may involve depletion of nicotinamide-adenine dinucleotide, inhibition of mycolic acid synthesis, and/or inhibition of mycobacterial catalase activity; most likely inhibits cell-wall structural integrity</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Interferes with mycobacterial mRNA synthesis by binding to DNA-dependent RNA polymerase</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>Inhibits synthesis of arabinogalactan and lipoarabinomannan, thereby interfering with cell-wall structure</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Poorly understood: activity depends on its conversion to pyrazinoic acid by mycobacterial pyrazinamidase/nicotinamidase*</td>
</tr>
<tr>
<td>Amikacin and other aminoglycosides</td>
<td>Inhibition of protein synthesis at the ribosomal level</td>
</tr>
<tr>
<td>Fluoro-quinolones</td>
<td>Inhibit DNA gyrase</td>
</tr>
<tr>
<td>Prothionomide</td>
<td>Bactericidal effect by inhibiting mycolic acid synthesis (resistance to prothionomide is unrelated to inhibition of catalase enzyme activity, as occurs with isoniazid)</td>
</tr>
<tr>
<td>Capreomycin</td>
<td>Inhibits ribosomal protein synthesis</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Cycloserine is a structural analogue of D-alanine. It competitively blocks enzymes involved in the synthesis of the dipeptide D-alanine:D-alanine. Thus it inhibits mycobacterial cell wall synthesis.</td>
</tr>
<tr>
<td>Para-aminosalicylic acid</td>
<td>PAS is a structural analogue of PABA, competitively blocking the conversion of PABA into folic acid (an essential purine needed for DNA synthesis).</td>
</tr>
</tbody>
</table>

* See section 15.2.2.
** PABA = para-aminobenzoic acid.
15.4 Drug resistance

15.4.1 Types of drug resistance

There are two types of drug resistance: primary and secondary.

- Primary resistance refers to the fact that the organisms transmitted were resistant to one or more TB drugs.
- Secondary resistance means that new resistance developed as a result of inadequate drug treatment.

General bacterial mechanisms of drug resistance include barrier mechanisms (affecting permeability), degrading or inactivating enzymes, and genetic drug target modification. The last is the main mechanism of resistance to TB drugs, and is due to endogenous chromosomal mutation, and not to acquired resistance from an exogenous genetic source such as plasmids.

Limited studies suggest that the development of resistance may, in some instances, come at a physiological cost to the organism, in the form of reduced virulence or ‘fitness’.

15.4.2 ‘Natural’ drug resistance

There is a degree of naturally occurring resistance to anti-tuberculous drugs, which 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 both isoniazid and rifampicin.

Cavities contain approximately $10^8 - 10^9$ bacilli and so there is a significantly higher risk of naturally resistant organisms being present in cavitary TB. Consideration should be given to adding additional drugs (if there are other factors present for resistant organisms). A longer duration of treatment, compared with that for minor disease, is often appropriate.

Because of naturally occurring drug resistance it is essential to give multiple drug therapy for TB disease. With TB infection, because of the small number of infecting organisms, monotherapy is successful. In treating TB infection, knowledge of the susceptibility of the organism from the index case is enormously helpful. Treatment of TB infection is the subject of Chapter 3: ‘Latent Tuberculosis Infection’.
15.4.3 The molecular basis of drug resistance

The molecular basis of drug resistance is well described for all the first-line agents, the aminoglycosides and the quinolones. Resistance to pyrazinamide was covered in section 15.3.

Rapid and reliable genotypic methods of detecting TB drug resistance may be available in the future. This is most likely to be useful with rifampicin resistance, where mutations occur in a relatively small part of the TB genome, corresponding to the β sub-unit of the RNA polymerase. In contrast, with isoniazid resistance, multiple genes may be involved, and molecular biological testing is more complex.

15.4.4 Development of resistance

Secondary resistance to a particular drug is unlikely to occur within two months, if the drug in question has been taken as part of a multi-drug regimen, in which all doses have included all drugs, and the organism is susceptible to most drugs in that regimen. Stopping an effective regimen which has been taken regularly, prior to achieving a cure, should not predispose to the development of secondary resistance.
15.5 Drug doses and administration

15.5.1 Drug doses

Table 15.3 shows dosage recommendations for anti-tuberculous medicines. The following notes should be taken into account when using that table.

**Isoniazid**

**Children**

10 mg/kg/day is generally recommended for treatment of TB disease in children. A dose of 5 mg/kg/day may be adequate for treatment of latent tuberculosis infection (LTBI) in children. Douglas and McLeod point out that doses of ‘5 mg/kg/day achieve serum concentrations 60–100 times the MIC and produce satisfactory clinical outcomes’.19

**Adults**

5 mg/kg/day is the accepted daily dose for adults. Higher doses are not required for tuberculous meningitis or miliary tuberculosis: a higher dosage may increase the risk of adverse reactions.

**Obese patients**

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 Chapter 17: ‘Treatment of Tuberculosis in Special Clinical Circumstances’.

**Ethambutol**

The daily dose of ethambutol should be 15 mg/kg, as noted later in this section (15.5.3), unless there are good reasons for a higher (or lower) dose. The risk of optic neuritis is greater with higher doses. The maximum daily dose of ethambutol is 2.5g/day. Higher doses are appropriate with intermittent therapy.

**Pyrazinamide**

The maximum daily dose of pyrazinamide is 2.0 g. Higher doses are appropriate with intermittent therapy.
Table 15.3: Dosage recommendations for anti-tuberculous agents

### A. First-line agents

<table>
<thead>
<tr>
<th>Medication</th>
<th>Daily dose (mg/kg)</th>
<th>Twice-weekly dose</th>
<th>Thrice-weekly dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Child† Adult</td>
<td>Child† Adult</td>
<td>Child† Adult</td>
</tr>
<tr>
<td>Isoniazid</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max dose/day</td>
<td>5–10</td>
<td>20–40</td>
<td>20–40</td>
</tr>
<tr>
<td>Max dose/week**</td>
<td>300 mg</td>
<td>900 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td></td>
<td>600 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Guidelines not complete</td>
<td>5 mg/kg safe</td>
<td>300–600 mg/ day effective</td>
</tr>
<tr>
<td>Max dose/day</td>
<td>10–20</td>
<td>10–20</td>
<td>10–20</td>
</tr>
<tr>
<td>Max dose/week</td>
<td>600 mg</td>
<td>600 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td></td>
<td>600 mg</td>
<td>1.8 g</td>
<td>1.8 g</td>
</tr>
<tr>
<td>Rifampicin††</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max dose/day</td>
<td>10–20</td>
<td>10–20</td>
<td>10–20</td>
</tr>
<tr>
<td>Max dose/week</td>
<td>600 mg</td>
<td>600 mg</td>
<td>600 mg</td>
</tr>
<tr>
<td></td>
<td>600 mg</td>
<td>1.8 g</td>
<td>1.8 g</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max dose/day</td>
<td>20–35</td>
<td>50–70</td>
<td>50–70</td>
</tr>
<tr>
<td>Max dose/week</td>
<td>2 g</td>
<td>4 g</td>
<td>3 g</td>
</tr>
<tr>
<td></td>
<td>6 g</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### B. Second-line agents

<table>
<thead>
<tr>
<th>Medication</th>
<th>Daily dose (mg/kg)</th>
<th>Twice-weekly dose</th>
<th>Thrice-weekly dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Child† Adult</td>
<td>Child† Adult</td>
<td>Child† Adult</td>
</tr>
<tr>
<td>Prothionamide and Ethionamide‡</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max dose</td>
<td>15–20</td>
<td>45–50</td>
<td>25–30</td>
</tr>
<tr>
<td></td>
<td>15–25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluoroquinolones</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>500–1000</td>
<td>500–1500 mg</td>
<td></td>
</tr>
<tr>
<td>Oxofloxacin</td>
<td>1500 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moxifloxacin</td>
<td>800 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Streptomycin IM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Max dose/day</td>
<td>20–40</td>
<td>25–30</td>
<td>25–30</td>
</tr>
<tr>
<td>Max dose/week</td>
<td>1 g</td>
<td>1.5 g</td>
<td>1.5 g</td>
</tr>
<tr>
<td></td>
<td>1 g</td>
<td>3 g</td>
<td>3 g</td>
</tr>
<tr>
<td>Amikacin</td>
<td>15</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Max dose IM, IV</td>
<td>1 g</td>
<td>1 g</td>
<td></td>
</tr>
<tr>
<td>Kanamycin</td>
<td>15–30</td>
<td>15–30</td>
<td></td>
</tr>
<tr>
<td>Max dose, IM, IV</td>
<td>1 g</td>
<td>1 g</td>
<td></td>
</tr>
<tr>
<td>Capreomycin</td>
<td>15–30</td>
<td>15–30</td>
<td></td>
</tr>
<tr>
<td>Max dose IM</td>
<td>1 g</td>
<td>1 g</td>
<td></td>
</tr>
<tr>
<td>Cycloserine</td>
<td>15–20</td>
<td>15–20</td>
<td></td>
</tr>
<tr>
<td>Max dose</td>
<td>1 g</td>
<td>1 g</td>
<td></td>
</tr>
</tbody>
</table>

* American Thoracic Society
** Bednall et al
† Child: less than 12 years of age
†† An intravenous form of Rifampicin is available
‡ Prothionamide and ethionamide are given in divided doses.
See also Chapter 17, sections 17.1 and 17.3.
15.5.2 Use of pyridoxine

It is essential to give pyridoxine when prescribing isoniazid for people at risk of peripheral neuropathy from other causes (eg, those with diabetes, chronic renal failure, malnourished people, alcoholics, those taking certain oncology agents and pregnant women). Many TB clinicians (including the chapter author) recommend routine use of pyridoxine 10–25 mg/day for everyone taking pyridoxine, as the development of peripheral neuropathy can occur without other risk factors. Moreover, pyridoxine is cheap (especially with non-pharmacy brands) and easy to take.

Drugs in fixed-dose combinations (FDCs)

General

FDC tablets contain two or more medicines within the same tablet or capsule. The main advantages are reduced risk of resistance developing to the drugs in the event of missed doses, potentially fewer medication errors, and fewer prescription items to order. However, a key disadvantage of many FDC formulations is reduced bioavailability of some drugs – in particular rifampicin. Another is that the number of tablets is not reduced, and the flexibility in obtaining an optimal dose of some agents, such as pyrazinamide, may be lost by using FDCs. Only those FDCs that have been proven to provide unaltered bioavailability of the component drugs should be used.35

Rifinah

The numbers in the names ‘Rifinah 150’ and ‘Rifinah 300’ refer to the dose (mg) of the rifampicin component. The dose of isoniazid in these two preparations is 100 and 150 mg respectively. Thus, in order to provide a satisfactory dose of isoniazid, ‘Rifinah 150’ should be used in persons weighing under 50 kg, while ‘Rifinah 300’ should be used in those over 50 kg.

Rifater

This FDC, which is widely used in many parts of the world, contains rifampicin, isoniazid and pyrazinamide. Unaltered bioavailability of the component drugs has been proven. Rifater is not available in New Zealand because it would be economically unprofitable for the supplier.

Drug suspensions (syrups)

See Chapter 17: ‘Treatment of Tuberculosis in Special Clinical Circumstances’, section 17.5.5.

15.5.3 Administration of ethambutol

Doses

Standard doses are listed above in 15.5.1. Briefly, a dose of 15 mg/kg/day is usual, unless severe or drug-resistant TB necessitates 25 mg/kg/day. The higher dose should not be given for longer than two months. Ideal weight should be used in calculations for obese people. The maximum daily dose is 2.5 gm/day.
**Ethambutol and renal impairment**

Ethambutol should be avoided in the presence of renal impairment. This is not always possible, and the doses for use in renal disease and dialysis are found in Chapter 17: ‘Treatment of Tuberculosis in Special Clinical Circumstances’, section 17.3 and Table 17.1.

**Ocular toxicity**

Ocular toxicity is the main potential side-effect of ethambutol. Baseline assessment of visual acuity and red–green colour perception are needed. Ophthalmological assessment should be obtained as a baseline before starting treatment in patients with abnormal visual acuity. Patients must be advised to report visual deterioration. Such complaints necessitate a semi-urgent ophthalmological opinion.

Enquiring every two months (as a minimum) about visual deterioration is essential. Hospital and public health staff should both enquire, particularly where communication difficulties are present. Opinions differ about the need to monitor visual acuity: testing every two months seems advisable, and this is the usual practice with the Green Lane Hospital TB Service.

**Formal ophthalmological monitoring**

Where ethambutol is prescribed for people with comprehension or communication difficulties, formal ophthalmological assessment should be done regularly – for instance, at monthly intervals (level III evidence). This is particularly important if renal impairment is present.

When to avoid ethambutol

Relative contraindications to ethambutol are: small children, the elderly, adults with already marked visual impairment or renal impairment, and those who cannot be relied on to report visual deterioration. All these should be offered another agent, if possible.

**15.5.4 Administration of Amikacin**

**General**

Aminoglycoside administration has traditionally been by multiple dosing, usually every 8 to 12 hours. There is now a large body of experience which supports the use of extended-interval or once-daily dosing of aminoglycosides for most indications. This approach results in a high peak serum concentration, which declines over a 24-hour period to essentially result in a drug-free period at the end of the dosing interval. Advantages of once-daily dosing include reduced toxicity and increased convenience.

*See Chapter 16, Introduction, for an explanation of levels of evidence.
Doses with normal weight and renal function

Dosing of amikacin is based on body weight and must also be adjusted for renal insufficiency. The weight used to calculate the dose should be the actual bodyweight for non-obese individuals. For these subjects the usual daily dose is 15 mg/kg, given by IV infusion (or rarely, IM).

Dosing weight

Obese people (those with an actual bodyweight greater than 25% above lean body weight) require a dose adjustment because aminoglycosides are primarily distributed into extracellular fluid. Doses based on actual body weight in the obese may lead to excessively high serum levels, while doses calculated using ideal (lean) body weight will result in inadequate concentrations. The method of calculating the dosing weight in obesity is discussed in Chapter 17: ‘Treatment of Tuberculosis in Special Clinical Circumstances’, section 17.1.

Doses with (stable) renal impairment

Modifications are required to the dose and/or dosing interval when significant renal impairment is present. The first step is estimation of creatinine clearance, but only if the serum creatinine is stable:

\[
\text{Estimated creatinine clearance (ml/min)} = \frac{(140 - \text{age}) \times \text{lean body weight (kg)}}{815 \times \text{serum creatinine (mmol/L)}}
\]

Note that:
1. this value should be multiplied by 0.85 in women
2. this equation may overestimate creatinine clearance in severe liver disease and malnutrition.

Once the estimated creatinine clearance has been calculated, and the correct dosing weight is known, an appropriate amikacin dose can be calculated. A variety of methods have been proposed, such as that shown in Table 15.4, but prescribers are advised to consult their local guidelines, hospital pharmacist or clinician experienced in the use of aminoglycosides.

Table 15.4: Amikacin dosing and renal function

<table>
<thead>
<tr>
<th>Creatinine clearance</th>
<th>&gt; 80 ml/min</th>
<th>50–80 ml/min</th>
<th>10–50 ml/min</th>
<th>&lt; 10 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin dose</td>
<td>15 mg/kg</td>
<td>75%</td>
<td>50%</td>
<td>25%</td>
</tr>
<tr>
<td>Dose interval</td>
<td>Q 24 h</td>
<td>Q 24 h</td>
<td>Q 24 h</td>
<td>Q 24–48 h</td>
</tr>
</tbody>
</table>

Prolonged treatment with amikacin and normal renal function

Depending on the severity of the TB, amikacin is generally given daily for 14 days, five days per week for another 14 days and then thrice weekly thereafter, if still required.
**Administration method**

See amikacin in section 15.5.6.

**Monitoring**

*Serum amikacin trough levels* should be measured just before a dose. Trough levels only are required with once-a-day dosing. The trough level should be < 1 mg/L if toxicity is to be avoided. If the estimated creatinine clearance is < 50 ml/min or serum creatinine is increasing, then trough levels should be monitored frequently.

*Plasma creatinine concentration:*

- normal renal function: monitor creatinine every one to three weeks.
- with long-term dosing: fortnightly creatinine clearance is recommended.

*Monitoring ototoxicity and vestibular dysfunction:* with long-term dosing, fortnightly audiometry should be done. Electronystagmography is usually only carried out if vestibular symptoms develop.

**Amikacin toxicity**

See section 15.7.

**15.5.5 Nebulised aminoglycoside treatment**

This should be regarded as an unproven treatment.

Nebulised aminoglycoside was reported to diminish the period of sputum smear-positivity, and thus the period of infectivity, in 13 of 19 subjects in South Africa. Gentamicin sulphate (80 mg in 2–3 ml saline) or kanamycin sulphate in the same dose and dilution were nebulised eight-hourly in subjects who were sputum smear- and culture-positive after a mean period of two months of appropriate conventional treatment. The *M. tuberculosis* organism displayed some degree of drug resistance in 12 out of 19 subjects.

The median interval between instituting aerosol therapy and the first negative sputum smear was 23 days among patients who converted to negative smears. Follow-up sputum smears remained negative in five out of seven subjects whose sputum was retested one month or longer after smear conversion. No side-effects were reported.

This initial report therefore suggests that patients with prolonged sputum smear-positivity may have a shortened period of infectivity, if nebulised aminoglycoside is added to their oral regimen. Treatment could be started in patients with extensive pulmonary disease (particularly with extensive cavitary disease) without waiting for the response to two months of standard treatment.

This form of treatment is regarded as experimental at the time of publication of these guidelines. Further studies are required. Standard safety monitoring should be performed with this form of administration, as detailed in section 15.6.
15.5.6 Pharmacological considerations with anti-tuberculous agents

Isoniazid

Absorption

Food and antacids may reduce the absorption of isoniazid, which is best taken on an empty stomach, or one to two hours before an antacid.\(^{38}\)

Acetylator status and elimination

Tri-modal rather than bimodal elimination of isoniazid is now accepted. The eliminator phenotypes are classed as fast acetylator, slow acetylator and intermediate acetylator. The intermediate acetylator genotype is constituted of co-dominant fast and slow alleles. Differences between fast and slow acetylation of isoniazid mean that:

- fast acetylators acetylate isoniazid 5–10 times faster than slow acetylators
- the elimination half-life in fast acetylators is approximately 50% of that of slow acetylators\(^{19}\)
- the peak serum level (C\(_{\text{max}}\)) is lower in fast acetylators;\(^{19}\) the mean daily isoniazid exposure (AUC) in fast acetylators is half that of slow acetylators
- the hydazine metabolite reaches a lower level and persists at a lower level in the serum than in slow acetylators.\(^{39}\)

Testing acetylator status

Acetylator status is not easily determined, as sulphamethazine, the agent traditionally employed in the sulphamethazine test, is not available. Acetylator phenotype may be determined by measuring the ratio of the acetylated and parent drugs in urine.\(^{40}\) For further reading, see Pea et al and Parkin et al.\(^{39,41}\)

Hepatotoxicity and acetylator status

A number of large studies found no association between acetylator status and susceptibility to isoniazid hepatotoxicity.\(^{42-45}\)

More recently, acetylator status has been reported to be a factor affecting the incidence of hepatotoxicity from combined treatment with isoniazid and rifampicin.\(^{46}\) In a prospective study, 77 Japanese subjects were classified according to their N-acetyltransferase 2 (NAT2) genotype. This was determined by PCR-RFLP testing of peripheral blood lymphocytes. Hepatotoxicity was observed in slow acetylators: the degree was not clinically important in this group, but might become relevant with concurrent pyrazinamide, alcohol, other medications or illness.

Practice points

i. The relevance of isoniazid acetylator status

- It is unlikely that slow acetylator status has much significance in most subjects. No guidelines recommend routine testing of acetylator status.
Fast acetylator status would only be of consideration if once per week regimens become available.

**Serum isoniazid levels** may be appropriate where reintroduction of isoniazid is highly desirable:

- hepatotoxicity or other hypersensitivity reactions, and
- resistance pattern and/or other drug side-effects make management difficult without isoniazid.

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**Rifampicin**

Rifampicin is best taken on an empty stomach, wherever possible. The time at which the maximum serum concentration occurs is delayed from approximately two hours to six hours, and the peak serum concentration is reduced by one-third, if rifampicin is taken after a fatty meal. (The importance of high peak levels was explained earlier: see section 15.2.3). Lesser reductions are seen with carbohydrate meals.

Only free rifampicin, and not plasma protein-bound rifampicin (which accounts for 75% of the total serum rifampicin level) is available to interact with mycobacteria. Hence, in order 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, despite post-cibal administration of this drug.\textsuperscript{47,48} Antacids do not affect the absorption of rifampicin.\textsuperscript{48}

Rifampicin is excreted in urine, sweat, tears, and other bodily fluids, colouring them orange. Soft contact lenses may be permanently discoloured.

**Rifabutin**

This drug should be taken straight after food, as serum concentrations of rifabutin are thereby enhanced.\textsuperscript{49} This is the opposite of the effect of food on rifampicin blood levels.

**Ethambutol**

Absorption is unaffected by food.\textsuperscript{50} Major caution is needed with this drug in the presence of renal impairment (with and without dialysis). For more information, see 15.5.1. This drug should be avoided with renal impairment whenever possible.

**Pyrazinamide**

Food does not impair the absorption of pyrazinamide.

**Prothionamide and ethionamide**

These drugs have a narrow therapeutic-side effect profile. They are well absorbed after food. The effect of antacids is uncertain.
**Quinolones**

Ingestion with food delays the time to peak serum concentration by an additional one to two hours with these agents, but the extent of absorption is not changed. Antacids or ferrous sulphate may interfere with the absorption of quinolones if both are taken together. See Table 15.8.

**Streptomycin**

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

**Amikacin**

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

**Directly observed therapy (DOT) – before or after food?**

In many subjects the timing is not critical, and most DOT treatment is successful despite little attention being paid to this point. For the convenience of all concerned this is fortunate. However, caution is required. As discussed above (see section 15.5.6), rifampicin levels are lower when the drug is taken after food – especially after a fatty meal, and appropriate advice should be given to people who are to take DOT.

When starting people on DOT the prescriber must remember and enquire about symptoms of malabsorption routinely. The combination of malabsorption and post-cibal administration of DOT containing rifampicin may result in treatment failure or the selection of rifampicin-resistant organisms.52
15.6 Monitoring

15.6.1 Monitoring infectivity

Patients with positive pre-treatment sputum should have repeat sputum tests at monthly intervals until conversion is documented. Eighty-five percent of these patients are expected to be smear- and culture-negative after two months of treatment. Special measures are needed for those who remain sputum-positive, and a clinical TB expert should be consulted.

Documenting sputum conversion to negative is important epidemiologically. The WHO use sputum conversion data as an indicator of the effectiveness of a TB control programme.

The infectious potential of sputum smear-positive people on treatment remains controversial. Many clinicians worldwide either ignore this possibility, or follow the generally held opinion that the majority of infectious patients pose no public health risk after two weeks of full treatment. A study of this subject, using time for cultures to become positive as a surrogate for infectivity, was conducted at Green Lane Hospital, Auckland. The following points are relevant from that study.

- When sputum remained smear-positive it was always culture-positive. Even after two months of treatment the organisms were still viable.
- With sputum smear-negative, culture-positive TB the median time for cultures to become positive was 14 days.
- When sputum contained 10–100 (or more) acid-fast bacilli (AFB) per high-powered field after two weeks of treatment, the median time for cultures to become positive was 10 days (AC Harrison, A Morris, L Calder, personal communication).

Thus, in people who are strongly AFB smear-positive, it seems likely that two weeks of treatment is not sufficient to lower the infectious potential to a minimal level (ie, to a level of infectiousness equivalent to people with smear-negative, culture-positive TB). How long these people should be held in isolation is discussed in Chapter 9: ‘Infection Control’.

15.6.2 Radiological monitoring

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. Failure of the chest radiograph to show improvement after three months of treatment requires considering the following possibilities:

- the diagnosis is not TB: re-investigation is needed
- the TB had produced scarring prior to treatment
- mixed pathology may be present – TB and other condition(s)
- non-adherence to the medication programme occurred
- drug resistance was present from the outset, or has developed.
**Chest CT scanning** is useful for monitoring the progress of mediastinal lymph node TB which is advanced or extensive initially. Comparison of a before / early treatment-CT with another done just before planned completion of treatment may lead to revising the treatment cessation date. A longer length of treatment may be appropriate if lymph nodes continue to have a necrotic appearance, or have not diminished greatly in size during treatment (level III evidence* – ie, expert opinion).

**Serial imaging and extrapulmonary sites:** the need for and the frequency of repeat imaging will depend on:

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

### 15.6.3 Monitoring for adverse drug reactions

**Pre-treatment blood tests**

Baseline haematology and biochemistry tests should be done in adults who are to be given treatment for TB (level III evidence: Ministry of Health Tuberculosis Working Group). Initial abnormalities need follow-up.

**Routine blood testing during treatment**

Expert opinion in New Zealand recommends repeating blood tests two to three and six to eight weeks after adults start taking regimens containing hepatotoxic agents. Ongoing blood tests are unnecessary after the first two months of treatment if results are normal and no new symptoms develop. Overseas experts recommend clinical monitoring, *without* regular blood tests, in people who are asymptomatic – even in the elderly, who have a higher incidence of hepatotoxicity.

The New Zealand recommendation to monitor liver function is based on the following:

- serious hepatic dysfunction can develop before patients develop symptoms
- even an occasional death from TB-drug induced hepatitis is unacceptable
- iatrogenic hepatic failure necessitating liver transplantation is also unacceptable.

Symptoms suggesting possible drug toxicity are an indication for appropriate blood tests.

**Monitoring and hepatic dysfunction**

In people with pre-existing mild hepatic disease, or those with substantial alcohol intake, it would be prudent to monitor liver function; for example, fortnightly for the first month, monthly for the next two months, and two-monthly thereafter. Monitoring and treatment for those with severe hepatic dysfunction is discussed in Chapter 17: ‘Treatment of Tuberculosis in Special Clinical Circumstances’, section 17.2.

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* See Chapter 16, Introduction, for an explanation of levels of evidence.
**Monitoring by a nurse**

Nursing review (including a pill count) once a month is the minimum acceptable for patients receiving self-administered anti-tuberculous treatment. Patient education about TB includes instruction to watch for common drug reactions.

**Medical appointments**

Medical review every two to three months is acceptable, provided there are no risk factors for poor compliance, the patient can be relied on to report symptoms, and monthly review by a public health nurse is being carried out.

**Monitoring with drugs causing specific toxicities**

For precautions with ethambutol, see section 15.5.3.

Use of an aminoglycoside necessitates pre-treatment and follow-up (eg, fortnightly) audiology testing and creatinine clearance estimations. Monitoring drug levels is discussed in the next section.

**15.6.4 Therapeutic drug monitoring**

**Monitoring amikacin levels**

See section 15.5.4.

**Laboratory methods**

Colorimetric methods are often used to measure TB drug levels for clinical purposes. Not all drugs can be tested accurately with this method.

Chromatography techniques (eg, high-pressure liquid chromatography, or HPLC) are probably the best, but if levels are only required occasionally, the costs of setting up the methodology and time lost by interrupting other HPLC tests to occasionally measure the level of an anti-tuberculous drug become important disadvantages. Measurement of TB drug levels by HPLC is being set up at the Biochemistry Department (Toxicology Division) at Auckland Hospital during 2002.

Immunoassay methods would be convenient, but the present low frequency of testing would mean that the reagents would deteriorate within six months. Thus immunoassay methods could not be justified on a cost basis unless batches were measured several times a month.
Indications for, and use of, therapeutic drug monitoring

Therapeutic drug monitoring may be required if the disease does not show the expected improvement, and also if, for other reasons, non-adherence or malabsorption are suspected. Malabsorption is particularly likely in patients with HIV infection, cystic fibrosis or diabetes mellitus. In HIV patients there may be up to 70% reduction in serum TB drug concentrations compared with control subjects. Sub-therapeutic drug concentrations indicate significant risk of drug resistance developing.

There should be a low threshold for checking ethambutol levels in patients with renal impairment, though recommendations in Chapter 17: ‘Treatment of Tuberculosis in Special Circumstances’, section 17.3, will usually allow effective dosing.

Other indications for therapeutic drug monitoring are:
- unexpectedly slow improvement of TB disease
- possible lack of adherence to treatment
- malabsorption
- ascites (see Chapter 17, section 17.2)
- drug side-effects, especially if re-introduction of the offending drug is desired
- risk factors for drug toxicity are present
- severe obesity (eg, BMI > 30) (see Chapter 17, section 17.1).

Unfortunately, therapeutic drug monitoring has not advanced greatly in recent years, and this limits clinicians’ ability to identify individuals who may require higher doses of anti-tuberculous medicines, and to ascertain whether toxicity is dose-related, or idiosyncratic.

Improvements are needed in the methods of testing, the reliability of results, turnaround time, and the range of drugs available for testing. This will only occur if there is increased awareness, and more frequent – but appropriate – requests for testing by clinicians.
15.7 Drug side-effects

Common drug side-effects are listed in Table 15.5.

**Table 15.5: Adverse effects of TB medicines**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse side-effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td>Ototoxicity (lowest incidence with streptomycin); renal damage, skin rashes, fevers, circum-oral paraesthesiae, neuromuscular blockade</td>
</tr>
<tr>
<td>(amikacin, capreomycin,</td>
<td></td>
</tr>
<tr>
<td>kanamycin, streptomycin)</td>
<td></td>
</tr>
<tr>
<td>Para-aminosalicylic acid</td>
<td>Gastrointestinal effects, hepatitis, fever, rash and hypothyroidism</td>
</tr>
<tr>
<td>Cycloserine</td>
<td>Dose-related CNS 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 TB expert.</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Isoniazid hepatotoxicity: see above, and also Table 15.6. Hypersensitivity reactions are unusual. Peripheral neuropathy, optic neuritis, fever, hepatitis, ataxia, euphoria, convulsions, tinnitus, insomnia, hyperglycaemia, gynaecomastia, dry mouth, epigastric discomfort, urinary retention, anaemia, arthralgias. Contraindicated in manic states and porphyria. Idiosyncratic reactions may include a (usually reversible) lupus-like syndrome (fever, arthritis, pleuritis, pericarditis, positive rheumatoid factors, etc), and, very rarely, a rheumatoid arthrits-like syndrome, and agranulocytosis. Very rare hypersensitivity reactions can include eosinophilia, angitis, toxic psychosis, and meningo-encephalitis. Toxic doses decrease the synthesis of the inhibitory neurotransmitter, GABA. CNS depression or stimulation may result.</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>Gastrointestinal side effects, hyperuricaemia, hepatotoxicity, fever, anorexia, nausea and vomiting; precipitation of gout (see section 15.9); arthralgias, urticaria, sideroblastic anaemia.</td>
</tr>
<tr>
<td>Rifabutin</td>
<td>Rash, gastrointestinal disturbance, neutropaenia; uveitis, particularly in combination with macrolide antibiotics.</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Gastrointestinal disturbance, cholestatic hepatic dysfunction, transient elevation of hepatic enzymes. Danger with intermittent therapy – flu-like syndrome, shock, acute renal failure, death. Rare reports of rifampicin-induced light chain proteinuria and renal failure, attributed to dehydration associated with fluid restriction for SIADH.</td>
</tr>
<tr>
<td>Thiacetazone</td>
<td>Nausea, vomiting and diarrhoea, bone marrow depression, vertigo, ataxia, tinnitus and occasional liver toxicity. Cutaneous hypersensitivity can occur.</td>
</tr>
</tbody>
</table>
15.7.1 Dermatological side-effects

Dermatological side-effects of various anti-TB drugs are as follows.

- Pyrazinamide is the most common cause of dermatological side-effects with TB drugs, accounting for 26 of 31 (84%) of all rashes in 1317 patients in one study.\(^{55}\) It also often causes facial flushing or transient pruritis.

- Isolated skin rash occurs in about 2% of people taking isoniazid, and can take a variety of forms. However, rash commonly occurs as part of a wider hypersensitivity reaction to this drug. A dose-related skin response can occur with isoniazid.

- Skin rash due to rifampicin is usually mild, and can take a variety of forms.

- Ethambutol rarely causes dermatological side-effects.

- Photosensitivity can occur with pyrazinamide and the fluoroquinolones.

The management of dermatological problems caused by TB treatment is discussed in section 15.8. Oral or topical corticosteroid treatment may be required for severe adverse skin reactions.

15.7.2 Hepatotoxicity from TB drug treatment

Treating TB involves giving several potentially hepatotoxic drugs – isoniazid, rifampicin, and pyrazinamide. Ethambutol very rarely causes hepatic dysfunction.

Isoniazid hepatotoxicity is associated with increasing age (see Table 15.6) and daily alcohol consumption. It has a time of onset of 15% during the first month, 30% during the second month, and 54% 2 to 11 months after starting isoniazid.\(^{56}\) The possibility that slow isoniazid acetylator status may predispose to hepatotoxicity from combined treatment with rifampicin and isoniazid is discussed in section 15.5.6. Chronic hepatitis B carriers tolerate isoniazid well.

Rifampicin is the usual cause of a cholestatic pattern. There is no evidence that hepatotoxicity with rifampicin is age-related.\(^{57,58}\) The hepatotoxicity with rifampicin and isoniazid seems to be additive rather than synergistic.

There are very rare reports of hepatotoxicity with ethambutol. Most reviews and reports make no mention of this side effect.

For the monitoring of liver function during the first two months of treatment, see section 15.6.3; and for the management of drug-induced hepatotoxicity, see section 15.8.5.

Oral corticosteroid treatment may sometimes be tried in order to speed up the resolution of very slowly resolving drug-induced hepatitis (see Chapter 16: ‘Treatment of Tuberculosis’, section 16.10.7.)
Table 15.6: Age and frequency of hepatotoxicity with isoniazid

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>Rare</td>
</tr>
<tr>
<td>20–34</td>
<td>&lt; 0.3</td>
</tr>
<tr>
<td>35–49</td>
<td>&lt; 1.2</td>
</tr>
<tr>
<td>≥ 50</td>
<td>&lt; 2.3</td>
</tr>
</tbody>
</table>

Source: Van Scoy and Wilkowske 1987.\(^5^9\)

15.7.3 Amikacin toxicities

**Auditory and vestibular toxicity**

Amikacin can cause both auditory and vestibular toxicity. Auditory effects are greater than vestibular ones with amikacin. Damage begins in the basal end and progresses to the apical end of the cochlea. Symptomatic hearing loss begins with high frequency loss, and as administration continues lower frequency loss occurs. In at least 50% of cases auditory toxicity is irreversible. Vestibular damage may be reversible, however. Early detection helps prevent hearing loss in the frequency range that can affect communication. Testing high-frequency ranges is essential for the reason just discussed.

High trough serum levels and advanced age are the most important predisposing factor to ototoxicities. Other factors include the duration of administration, total dosage, high fever and bacteraemia, dehydration, and prior renal or ear disease. Ototoxicity occurs quite independently of nephrotoxicity. Some studies show that ototoxicity can develop at non-toxic serum levels, but is more likely to occur if serum levels exceed the recommended range.\(^6^0\)

**Nephrotoxicity**

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

15.7.4 Paradoxical reactions to TB treatment

A paradoxical reaction to TB treatment is defined as ‘worsening of disease at a pre-existing site, or the development of new tuberculosis lesions following initiation of appropriate treatment’.\(^6^1\) These reactions generally occur about one to three months after the start of treatment.

They are thought to result from:

1. an immunological host response to mycobacterial products, which have been released as a result of treatment-induced bacterial cell death and dissolution
2. 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-infected people. However, they occur more frequently in HIV-infected subjects who are on TB treatment and then commence anti-retroviral agents. Tuberculin skin-test conversion has been described as being associated with the onset of paradoxical TB reactions.

TB-related paradoxical reactions and immune reconstitution syndrome in the context of HIV are discussed in Chapter 18, ‘TB and HIV Infection’, section 18.4.2.

The differential diagnosis of apparently paradoxical reactions

The differential diagnosis includes:

- incorrect or inadequate treatment, with worsening of the TB, through non-adherence with drug treatment, malabsorption of TB drugs, the presence of secondary drug resistance or development of primary drug resistance
- drug reaction
- concurrent infection or malignancy.

The diagnosis of paradoxical reactions

This may be difficult, depending on the site of involvement and whether or not immunosuppression is part of the clinical situation. Investigation is aimed at detecting other possible causes of deterioration at sites of previous TB, as discussed in section 15.4. Tissue sampling is particularly important in severely ill people and in those with major immunosuppression.

The management of paradoxical reactions

Once the 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 incising, though this would rarely be indicated.
15.8 Management of drug reactions

15.8.1 Always consider the need for a new, temporary regimen

Stopping all anti-tuberculous treatment

Whenever considering stopping anti-tuberculous treatment – particularly if planning to give an oral steroid to counteract treatment side-effects – consideration must always be given to covering the TB with a new, temporary regimen. This regimen should continue until full doses of all drugs in the definitive regimen have been started.

The duration of any period off all TB treatment (while awaiting resolution of TB-drug side-effects) depends on the clinical situation.

- A person who is acutely ill with TB, or is infectious, should be given an alternative regimen immediately on stopping treatment.
- For a non-infectious, well person there are no strict rules. However, a period of four weeks is an arbitrary maximum period off all treatment, based on the fact that the opportunity for the development of infectiousness, or the spread of disease to other sites, is possible after this length of time.

Progressive but non-effective partial regimens

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

Repeated periods on partial or no treatment

These are particularly to be avoided. A second episode of no or partial treatment is an indication for starting a temporary regimen and continuing it for several weeks, until there is certainty that the difficulties have been fully resolved.

Agents in the temporary regimen

These could include amikacin or streptomycin, ciprofloxacin, ethambutol and ethionamide (or prothionamide).
### Practice points

**Rules* for managing TB drug side-effects**

1. **Maximum period off all drugs** *(infectiousness could develop during this time)*: 4 weeks
2. **Maximum period on a partial regimen**: 10 days
3. **Temporary regimen**: include at least three of the following – amikacin or streptomycin, ethambutol, ciprofloxacin, prothionamide.

*These are not based on direct evidence. See text.

### 15.8.2 Drug challenges

When troublesome side-effects occur, the offending agent(s) need(s) to be identified. Firstly, all treatment must be stopped and the reaction allowed to resolve. Drugs are then re-introduced sequentially, allowing 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, building up to the full dose over several days.

This procedure may necessitate covering the patient with additional agents to prevent resistance emerging during the challenge period.

If there is no reaction the process is repeated with the next drug selected. With less severe reactions it is occasionally possible to introduce full doses. If a clinician is unfamiliar with conducting drug challenges they may wish to consult a clinical TB expert with more experience.

#### Table 15.7: Drug challenge doses for mild-to-moderate reactions

<table>
<thead>
<tr>
<th>Drug</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Days 3 and 4</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 1989.63

### 15.8.3 Drug desensitisation

Rapid desensitisation protocols have been published for use in patients sensitive to rifampicin and ethambutol,64 and isoniazid.65 The methodology is based on protocols for treating penicillin allergy. So far only small numbers of patients have been studied, with greater success reported for rifampicin and ethambutol than for isoniazid hypersensitivity.

Desensitisation should be carried out cautiously, with full resuscitation resources available. The procedure should only be considered when suitable replacement drugs are not available.
15.8.4 Management of skin side-effects

Minor rash and itch are common with anti-tuberculous drugs. It should be noted that sometimes the skin side-effects are only short-lived and the treatments listed below might only be needed for a matter of days to weeks. The TB drugs may not have to be stopped, or if they are, it is sometimes possible to resume them successfully. Some of the following measures may be helpful.

- **Soap:** before assuming that TB drugs are the cause of the symptoms, check that the patient has not recently changed their usual brand of soap. Some soap brands are more prone to cause irritation than others, and it may be worth using:
  - a ‘simple’ soap containing no perfumes or other additives to try to minimise side effects (eg, Dove soap)
  - a soap substitute (eg, BK liquid soap substitute, or Cetaphil bar or lotion).

- **Skin moisturisers** may be useful for dry, itchy skin, for example:
  - ung simplex (paraffin ointment)
  - a barrier cream (eg, containing dimethicone)
  - refer to *New Ethicals Catalogue*, Guide to OTC section, Dermatological products.

- **Hydrocortisone 1% ointment in ung simplex:** this should be the starting point for trying steroid ointments, unless very severe reactions necessitate more potent steroid treatment.

- **Pruritis:**
  - antihistamines: a non-sedating antihistamine such as loratidine might be tried, although older, non-sedating antihistamines may also be successful, and at a lesser cost, if tolerated
  - Pinetarsol gel or solution may be a useful anti-pruritic cleansing preparation
  - BK bath oil or lotion may also have anti-pruritic properties
  - a number of other over-the-counter remedies are available.

15.8.5 Management of drug-induced hepatotoxicity

Cross-sensitivity may occur between drugs that are chemically related, such as the rifamycins. Other examples include isoniazid and ethionamide (both of which are derivatives of iso-nicotinic acid). Generally, drugs that are closely chemically related should not be used if marked hepatotoxicity occurs with one of them. However, rifabutin may be tried cautiously after recovery from rifampicin hepatotoxicity, where clinically indicated.

Mild, transient and asymptomatic increases in serum hepatic enzyme concentrations (eg, to three times the upper limit of normal) occur in about 20% of people during the early weeks of treatment. Treatment should not be interrupted because of these changes.
Authors vary in the degree of ‘transaminitis’ that is accepted and drug therapy allowed to continue. In general, if the person is asymptomatic, levels that are five-fold higher than the normal range can simply be watched while treatment continues. Van den Brande et al recommend that a five- to tenfold rise in transaminase levels, in the absence of symptoms, can be compatible with continuation of treatment. In that study, 10% of their patients showed a normalisation of transaminase levels despite continuation of isoniazid and rifampicin.53

If clinical hepatitis occurs – with anorexia, nausea, vomiting, hepatic tenderness and/or jaundice – all drugs should be stopped. Any correctable factors (such as prolonged bleeding time) should be corrected.

Often it is sufficient just to wait and see how rapidly the hepatotoxicity settles. Progressive, rapid improvement often occurs. On the other hand, it sometimes takes many weeks for abnormal liver function to return to normal, and this may be a situation where oral steroid treatment is required and/or a temporary regimen is prescribed (see section 15.8.1).

Clinical judgement is needed to decide whether to try to reinstitute 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 in several.66

15.8.6 Uncontrollable vomiting

Although nausea is not uncommon with TB drug treatment, it can be managed with usual agents. Theoretically it is possible that agents such as metoclopramide, which stimulate gastric emptying, may have an effect on TB drug levels. However, there is no literature available on this subject. It may be preferable to use prochlorperazine (Stemetil) or cyclizine (Marzine) if prolonged administration is needed.

Persistent vomiting may necessitate a drug challenge and elimination of the offending agent, once other causes have been excluded.

Very severe vomiting is uncommon with anti-tuberculous drug treatment. In one extreme case, where multiple drug-resistant TB was present, persistent vomiting caused sub-therapeutic drug levels. A percutaneous gastrojejunostomy tube was placed, and crushed tablets were administered through it. Clinical cure was achieved. Pharmacokinetic studies showed that drug levels peaked and began to decline earlier than is observed with oral administration. The practical importance of this is that blood levels needed to be taken an hour after this method of administration, instead of at two hours, which is the usual recommended sampling time after oral doses.67
15.9 Interactions with anti-tuberculous drugs

The interaction between rifamycins and oral contraceptives, and management of contraception, are discussed in Chapter 17: ‘Treatment of Tuberculosis in Special Clinical Circumstances’, section 17.4.3.

The rifamycin–warfarin interaction is extremely important. There is the potential for:

- *sub-therapeutic anticoagulation* occurring when a person on warfarin starts rifampicin.68 Patients who are taking both agents, and who have an absolute indication for anticoagulation, need monitoring at least weekly. If therapeutic anticoagulation proves difficult, consider the use of low molecular weight heparin.

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

Allopurinol may paradoxically increase serum urate levels if given with pyrazinamide.69 Pyrazinamide may have to be avoided in patients with troublesome gout, as it can precipitate acute attacks of gout in those disposed to such 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 0.6 mg BID. If this manoeuvre is successful, the colchicine should be continued, and stopped when the pyrazinamide is discontinued.

For other drug interactions, see Table 15.8.

### Table 15.8: Clinically important interactions with TB drugs

<table>
<thead>
<tr>
<th>TB drug</th>
<th>Interacting agent</th>
<th>Effect</th>
<th>Advice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Isoniazid</strong></td>
<td>Antacids, containing aluminium</td>
<td>Reduced absorption of isoniazid.</td>
<td>As for Cipro + antacids</td>
</tr>
<tr>
<td><strong>Anti-epileptics:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Carbemazepine</td>
<td>Inhibition of carbemazepine hepatic metabolism has been described.</td>
<td>Monitor carbemazepine blood levels</td>
<td></td>
</tr>
<tr>
<td>- Phenytoin</td>
<td>Inhibition of phenytoin hepatic metabolism; phenytoin toxicity may develop over days to weeks.</td>
<td>Monitor phenytoin levels and symptoms</td>
<td></td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Plasma haloperidol may increase</td>
<td></td>
<td>Adjust dose if needed</td>
<td></td>
</tr>
<tr>
<td><strong>Anxiolytics and hypnotics</strong></td>
<td>Possible delayed metabolic clearance of diazepam and triazolam, causing prolongation of their effects</td>
<td>Monitor effects</td>
<td>Decrease dose if necessary</td>
</tr>
<tr>
<td><strong>Anti-fungals:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Ketoconazole</td>
<td>The antifungal blood level may be decreased</td>
<td>No problem using Fluconazole</td>
<td></td>
</tr>
<tr>
<td><strong>Cyclosporin</strong></td>
<td>Marked rise in cyclosporin levels</td>
<td>Monitor cyclosporin blood levels</td>
<td></td>
</tr>
<tr>
<td><strong>Disulfiram</strong></td>
<td>About 30% of people on both get CNS toxic effects of Disulfiram</td>
<td>Reduce dose or discontinue Disulfiram</td>
<td></td>
</tr>
<tr>
<td><strong>TB drug</strong></td>
<td><strong>Interacting agent</strong></td>
<td><strong>Effect</strong></td>
<td><strong>Advice</strong></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</td>
<td>Avoid concurrent use of these two agents. More likely in isoniazid rapid acetylators</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>Dietary advice; if necessary, give antihistamine</td>
<td></td>
</tr>
<tr>
<td>Tyramine-rich foods</td>
<td>Red wine, cheese, yeast extract</td>
<td>Due to slight monoamine oxidase effect of isoniazid. Dietary advice</td>
<td></td>
</tr>
</tbody>
</table>

**Rifampicin and rifabutin**

- **a. Reduced levels of:**
  - Antiarrhythmics
    - Disopyramide
    - Mexilitine
    - Propafenone
    - Quinidine
  - Antifungals
    - Itraconazole
  - Fluconazole
  - Ketoconazole
  - Anti-retrovirals
    - Nevirapine*
  - Clarithromycin (and possibly other macrolides)
  - Corticosteroids
    - Gluco- and mineralocorticoids
  - Diazepam, Nitrazepam
  - Digitalis preparations
  - Immunosuppressive agents
    - Cyclosporin
    - Tacrolimus
  - p-aminosalicylic acid (PAS)

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<tr>
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**Rifampicin and rifabutin**

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    - Nevirapine*
  - Clarithromycin (and possibly other macrolides)
  - Corticosteroids
    - Gluco- and mineralocorticoids
  - Diazepam, Nitrazepam
  - Digitalis preparations
  - Immunosuppressive agents
    - Cyclosporin
    - Tacrolimus
  - p-aminosalicylic acid (PAS)
**TB drug** | **Interacting agent** | **Effect** | **Advice**
--- | --- | --- | ---
Phenytoin concurrent isoniazid | Markedly reduced anti-epileptic effect especially in fast acetylators<br>Further reduction in phenytoin isoniazid counteracts covering of serphenybin by rifampicin |  |
Sulphonylureas<br>• tolbutamide<br>• possibly others<br>(eg, glibenclamide) |  | Monitor diabetic control
Warfarin<br>*See text also* | Markedly reduced anticoagulation | Warfarin dose may need to be doubled or tripled at the start, and be similarly reduced when the rifamycin is stopped (*see text*)
Ethambutol | No interactions of note |  |
Pyrazinamide | Allopurinol (*see text also*) | Acute gout | Avoid allopurinol; try colchicine instead<br>May need to abandon use of pyrazinamide
Ciprofloxacin | Antacids, containing aluminium, calcium and magnesium | Reduced absorption of Ciprofloxacin | Avoid antacids; or give ciprofloxacin two hours before or four hours after antacid
Warfarin | Occasional, unpredictable prolonged prothrombin time | Monitor anticoagulation carefully if starting or stopping ciprofloxacin
Iron and zinc | As for Cipro + antacids |  |
Sucralfate | As for Cipro + antacids |  |
Ethionamide and prothionamide | Increased risk of hepatotoxicity with rifampicin, isoniazid and pyrazinamide |  | * Ribera et al 2001<sup>70</sup>  ** Centers for Disease Control and Prevention 1998<sup>71</sup>
References

Chapter 16: Treatment of Tuberculosis

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This chapter is endorsed by the Thoracic Society of Australia and New Zealand

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16.10.6 Renal-tract stenoses

16.10.7 Oral steroid in the management of drug side-effects

References
Summary

Indications for anti-tuberculous treatment

Active TB

- Proof or strong suspicion of active TB is an absolute indication for treatment. The timing of starting treatment will depend on the clinical circumstances.
- Notification should not be delayed until treatment is commenced.

Inactive TB

- People with inactive pulmonary TB have an annual risk of developing active disease, which is at least 2.5 times greater than those with latent TB infection (LTBI) and a normal radiograph.
- Decisions about whether or not to treat persons with inactive TB, and also the treatment regimen to be used, are guided by several factors, including:
  - the extent of the radiological abnormalities
  - the nature of the radiological abnormalities:
    a) Features of healed, primary TB (calcified solitary pulmonary nodules, calcified hilar lymph nodes) and apical or basal pleural thickening do not by themselves present significant risk of TB reactivation and do not require treatment. The presence of other risk factors and the size of the Mantoux reaction guide the need for treatment of LTBI when these radiological abnormalities are present.
    b) Nodules and fibrotic scars may contain slowly multiplying tubercle bacilli. These have greater priority for treatment of LTBI or full preventive treatment than minor primary TB abnormalities.
    c) Multiple and/or non-calcified nodules suggest the process is not inactive TB, and they require investigation. Treatment may also be indicated.
  - the presence or absence of risk factors for reactivation of disease
  - the age of the patient, and their general condition
  - past treatment of TB or past chemoprophylaxis: it may be preferable to keep these patients under review, rather than re-treating them.
- Obtaining a second opinion from a clinical TB expert may be appropriate if there is uncertainty about the best management.

Management principles in treating TB

- Wherever possible, investigations should be undertaken that give the best possible chance of identifying the organism and its sensitivity pattern. This is particularly important where drug resistance is possible.
- The drugs must be taken regularly.
- Re-treatment, suspicion of poor compliance and multi-drug resistance are indications for directly observed therapy (DOT).
- Completion of therapy is based on the total number of doses administered – not the duration of therapy alone.
- Regimens must contain multiple drugs to which the organisms are susceptible.
- Single agents must never be added to an existing treatment regimen, and particularly not to a failing regimen.
If drug resistance is suspected, treatment should be modified accordingly. Clinicians should notify (to the medical officer of health) all people who are treated for TB disease or infection. Infectious cases of TB must be isolated to prevent further spread of disease.

**Treatment of inactive TB in people with past, untreated TB on chest radiograph**

**Investigation before starting treatment**

- People with past TB disease on chest radiograph must have microbiological testing before they are started on treatment – especially if single-drug treatment is planned. This statement does not apply to people with radiographs that show only one or two calcified pulmonary nodules.
- Acid-fast bacilli (AFB) tests on sputum are appropriate only if the person has a productive cough. Others must undergo induced sputum or bronchoscopy.

**Treatment regimens for trivial, inactive pulmonary TB**

- These regimens are discussed in Chapter 3: ‘Latent Tuberculosis Infection’.

**Treatment of moderately extensive, inactive pulmonary TB**

See Table 16.1.

**Treatment of extensive, inactive pulmonary TB**

- Treat as for active TB. See Table 16.1.

(Usually) no follow-up of untreated, inactive TB

- Sound education (using interpreters as needed) about having a low threshold for reporting symptoms is recommended, rather than serial CXRs.
- There are exceptions to this advice, and follow-up should be done if:
  - there are major risk factors for reactivation of TB, and treatment is not given
  - other diagnoses are possible.
- Clinical judgement should be exercised regarding the need for follow-up radiographs.

**Daily treatment regimens for active TB**

- All treatment regimens suggested in this chapter represent the minimum number of medications to be used and the minimum period of treatment required to achieve cure.
- Clinicians should consider increasing the number of medications and/or the duration of treatment for:
  - extensive TB
  - cavitative TB
  - slow clinical or radiological improvement on treatment
  - patients who are being re-treated.
**Drug resistance not suspected**

- There is just one proven regimen which requires only a six-month daily treatment period for culture-positive fully sensitive TB: 2RHZ/4RH.* No other agents can be substituted.
- Note that in the USA and Australia, ethambutol is recommended as a fourth initial drug (RHZE) if the susceptibility pattern is not known. In New Zealand, however, we recommend this only for foreign-born cases since drug resistance is uncommon in New Zealand-born people.
- For other regimens that may be used in this category, see Table 16.1.

**Daily treatment when single-drug resistance is proven**

- In general, treatment needs to continue for at least six months after sputum cultures become negative. Treatment periods suggested are thus only a guide and represent the *minimum* duration of treatment. See Table 16.1 for treatment regimens in the categories below.
- Isoniazid-resistant TB:
  - Regimens that should *not* be used in subjects with, or at risk of, isoniazid resistance: 2RHEZ / 4RH or 2RHEZ / 4HE.
  - It is unclear whether isoniazid should be used in the treatment of isoniazid-resistant TB. Many TB experts would give isoniazid in the treatment of multi-drug resistant TB, but ensure that sufficient other drugs to which the organism is sensitive are also given.
- Rifampicin-resistant TB:
  - Resistance to rifampicin is far more serious than resistance to isoniazid.
  - Generally, at least three drugs to which the organism is still susceptible are needed.
  - Regimens are shown in Table 16.1.
  - Rifabutin has been shown to be as effective as rifampicin: proof of susceptibility is needed before giving rifabutin when rifampicin resistance is present.
- *Mycobacterium bovis* is naturally resistant to pyrazinamide.

**Drug resistance suspected**

- If cultures are negative, see Table 16.2.
- Initial phase of treatment: start with 2RHEZ. Additional drugs may be necessary in re-treating TB in people previously treated.
- Maintenance phase:
  - If all initial cultures are negative: 4RH (ie, total treatment duration = six months).
  - If resistance to H is identified: 4RHEZ or 7RHE (or 7RE).
  - If resistance to R is identified: 18–24HE. 12RbHE may be appropriate (but is unproven) provided the organism has been shown to be sensitive to rifabutin.
  - If resistance to ethambutol is identified: 4RH.

* See Introduction (at the beginning of the full text) for an explanation of the abbreviations used in this chapter.
Multi-drug resistant TB (MDR-TB)

Treatment considerations

1. Resistance to rifampicin and isoniazid (which is the definition of MDR-TB) eliminates the two most important TB drugs from the treatment regimen.

2. It is essential that a clinical TB expert is involved in management.

3. If resistance to rifampicin and isoniazid is identified after the patient has already been started on RHEZ, additional cultures must be taken in case further resistance has developed. These results will guide eventual treatment.

4. If the patient is taking RHEZ and MDR is then identified, while continuing EZ two, or preferably three, of the following drugs must be added: an aminoglycoside (streptomycin, amikacin, kanamycin or capreomycin), prothionamide, ciprofloxacin, or rifabutin (if sensitivity to rifabutin is confirmed). Other possible agents are discussed below. Some would continue isoniazid in this situation.

5. Surgery may well be appropriate in these cases if the disease is sufficiently localised to permit resection of the bulk of the diseased lung.

6. DOT is mandatory for MDR-TB. At this time daily DOT is the only option, as no regimens for intermittent DOT for MDR-TB are recommended.

The outcome of treating MDR-TB

The majority of cases of MDR-TB can be cured in developed countries: cure rates of the order of 85% should be achievable. Adverse effects of treatment are common.

Additional agents to consider with very severe, multiple-drug-resistant TB

1. An aminoglycoside and a quinolone.

2. See full text for details of the following:
   - para-aminosalicylic acid
   - thiacetazone
   - cycloserine
   - beta-lactams
   - thioridazine or methdilazine – phenothiazines: possible agents, on theoretical grounds, but there are no clinical reports, let alone trials
   - inhaled interferon–gamma
   - subcutaneous interleukin-12
   - thalidomide
   - vaccination with *M. vaccae*.
Directly observed treatment (DOT)

Definition, and alternatives to DOT

See full text of this chapter, but more especially Chapter 5: ‘Directly Observed Therapy’, and Chapter 4: ‘Adherence to Treatment’.

DOT regimens for fully sensitive organisms

1. 2RH/4H3R3 or 2RH/4H2R2: add E if resistance suspected.
2. Two weeks RHZE, then: Six weeks R2H2Z2E2, then: 16 weeks R2H2
   Omit E if resistance has been excluded or is highly unlikely.
3. 6R3H2Z3E3.
4. 1 or 2 RH/8R2H2: add E if there are any risk factors for resistance. Add Z and E if drug resistance is proven.

Note:
- An aminoglycoside can be used, replacing E in protocols 2 and 3.
- Longer durations of treatment are advisable in the presence of widespread disease or major cavitatory TB.
- These regimens are unproven in the treatment of extra-pulmonary TB, where longer duration may also be advisable.

DOT for drug-resistant organisms

No protocols have been agreed upon. Thrice-weekly treatment should be the minimum frequency of administration.

6R3H3E3Z3 is acceptable for H resistance, provided smears and cultures are negative after three months of treatment.

Duration of treatment for extra-pulmonary TB

The minimum treatment periods for fully sensitive organisms are shown below. Longer duration of treatment should be considered in the presence of:
- severe or extensive disease
- drug resistance
- intermittent (DOT) treatment
- clinical or radiological progress which is slower than expected, or
- imaging showing major residual shadowing which is thought to be the result of TB.

Immunosuppressive factors, such as HIV or diabetes mellitus, are not in themselves indications to prolong treatment.

A longer duration of treatment is essential if pyrazinamide is not included in the regimen.

Six months' treatment is suitable for minor-to-moderate disease involving:
- lymph node TB
- pleural effusion
- genito-urinary organs*
- pericardial effusion
- bone and joint TB
- skin.

Twelve months’ treatment:
- miliary, meningeal and intra-cerebral TB.

Management of central nervous system TB

- Isoniazid and pyrazinamide penetrate best into the cerebrospinal fluid (CSF), and are therefore the most important drugs in the treatment of tuberculous meningitis and intra-cerebral TB.
- Rifampicin is also an excellent agent if the meninges are inflamed.
- Where drug resistance is suspected, an aminoglycoside can be used if the meninges are inflamed. If there is no inflammation, prothionamide is probably the next best agent as this does penetrate into the CSF.
- Intra-thecal antibiotic treatment for CNS TB: this is used exceedingly rarely, and there are few reports. See full text for one recent report.
- See 16.7.3 for the use of anti-tuberculous drugs in CNS TB.

Corticosteroid treatment in the management of TB

See Table 16.4, which shows a summary of indications for corticosteroid treatment in TB.

TB meningitis and intra-cerebral TB

- The following recommendations are based on level II evidence.
  - Early, mild TB meningitis: oral steroid is of no benefit in asymptomatic patients.
  - TB meningitis of intermediate severity (e.g., drowsiness, single cranial nerve paresis or hemiparesis): oral steroid treatment for ‘four weeks to months’ is beneficial.
  - TB meningitis with coma has a poor prognosis; steroid treatment is unlikely to improve it.
  - With intra-cerebral tuberculomas, most authors accept the need for steroid treatment if there is evidence of raised intra-cranial pressure (level III evidence).
  - It is possible that oral steroid treatment may improve the blood–brain barrier and reduce the effectiveness of rifampicin and ethambutol, as they penetrate the CSF relatively poorly.

* Prostatic TB is uncommon. General infections at this site tend to be difficult to eradicate. It may be advisable to consider 9–12 months’ treatment for prostate TB.

+ See Introduction for an explanation of levels of evidence.
Tuberculous pleural effusion

- Recommendations for managing TB pleural effusions are as follows.
  - Steroid treatment is not routinely indicated for tuberculous pleural effusions, despite the fact that pleural thickening with impaired ventilatory function can occur.
  - 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.
  - Full drainage of tuberculous effusions is very desirable. Usually this can be achieved by repeated thoracentesis.
  - 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.

Tuberculous ascites

- No well-controlled studies are available. In the absence of evidence to support steroid treatment for tuberculous pleural effusion, it is difficult to recommend it for tuberculous ascites.

Tuberculous pericarditis

- Placebo-controlled trials of corticosteroids in conjunction with anti-tuberculous chemotherapy for acute tuberculous pericarditis have shown reduced mortality, reduced requirement for subsequent pericardectomy and reduced need for pericardiocentesis or open surgical drainage. Therefore, oral corticosteroid (initially prednisone 60 mg/day and tapering to zero over 11 weeks) is recommended (along with TB treatment) for acute tuberculous pericarditis.

Miliary TB, very advanced TB and suspected hypo-adrenalism

- There is level I–II support for steroid treatment in these situations.
- These circumstances are associated with an incidence of unexpected death. The cause(s) of this are discussed in the full text.

Indications for corticosteroid treatment (TB treatment being taken)

- See Table 16.4.
- Because of the small risk from steroid treatment and the potential benefit, steroid treatment (eg, 20–60 mg/day) should be given:
  - where the patient is very ill from TB (level I evidence, showing faster general improvement, weight gain and early CXR improvement)
  - where the CXR shows a miliary appearance (level III evidence)
  - to reduce the mass effects and obstructive complications from mediastinal lymphadenopathy (level I evidence)
  - where there are clinical or laboratory features compatible with hypo-adrenalism (if adrenal insufficiency is suspected, 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 those with radiologically very advanced disease, steroid cover should commence immediately. The duration of steroid treatment will be judged by the clinical circumstances, but may well continue for several weeks.
Renal-tract stenoses

In the past, oral steroid has been used with anti-tuberculous drugs for the treatment of tuberculous renal-tract stenoses. Severe TB cystitis has often been managed in the same way. However, benefits are unproven in both situations.

Oral steroid in the management of drug side-effects

This should only be undertaken by a clinician who is an expert in the treatment of TB.

Usually, steroid treatment is not needed to control drug side-effects. The offending drug(s) can be identified and then eliminated. See also Chapter 15: ‘M. tuberculosis, TB Medicines and Monitoring’, section 15.8.

Nevertheless, steroid treatment is indicated in the following situations:
- to speed up the resolution of severe side-effects: such as marked hepatic toxicity, severe dermatological and/or systemic side-effects, including troublesome fever. However, other causes for these problems must be sought before starting steroid treatment. This is also true when steroid treatment is required for severe paradoxical reactions to TB treatment.
- to control these same problems while continuing treatment: there is no information about the risks or safety of this latter practice, particularly in relation to ongoing hepatotoxicity that is partially controlled by steroid.

People with TB should not receive oral steroid without concurrent anti-tuberculous treatment. This rule must be observed always with severe TB. However, there may be occasional instances in mild, non-infectious forms of TB where treatment is stopped and oral corticosteroid treatment is given for up to two weeks. This may speed up resolution of side-effects, thereby enabling earlier drug challenge testing and earlier resumption of effective treatment (level III recommendation).

See Chapter 15, section 15.8.1, especially the 'Practice points', 'Rules for managing TB drug side-effects'. These discuss giving a new, temporary regimen if TB treatment is stopped, or is reduced to a partial regimen. A temporary regimen is most important if steroid treatment is given when the treatment regimen is compromised.
Introduction

This chapter deals with indications for treatment of TB, treatment regimens and their duration. Pharmacological issues and other matters relating to individual drugs are the subject of Chapter 15: ‘M. tuberculosis, TB Medicines and Monitoring’. Treatment in special situations is discussed in Chapter 17: ‘Treatment of Tuberculosis in Special Clinical Circumstances’, and Chapter 18: ‘Tuberculosis and HIV’.

The chapters on the treatment of TB do not form a comprehensive guide to the management of this disease. TB is a complicated condition, management is frequently not straightforward, and there is a high incidence of drug side-effects. Failure to prescribe an appropriate regimen or to obtain adherence with medication will compound patient and community problems. Adherence is covered in detail in Chapter 4: ‘Adherence to Treatment’.

Those not familiar with TB and its management, or who are not regularly involved in TB care, should not be tempted to use the information in this chapter in a ‘cookbook’ fashion, but instead are advised to refer patients to a clinician experienced in the field.

Definitions

Case definitions of TB relapse, reactivation and infection can be found in Chapter 1: ‘Epidemiology and Surveillance’, which also covers notification.

Active and inactive TB are defined in Chapter 14: ‘Clinical Investigation and Assessment of Tuberculosis’.

The evaluation of people with TB includes assessing and documenting the severity and extent of disease, regardless of whether the process is active or inactive. These factors affect the treatment regimens required for cure. Definitions of severe and extensive disease are given in Chapter 14.

Levels of evidence and strength of recommendations

Throughout this document, quality of evidence and the strength of recommendations drawn from the evidence are cited wherever possible. The categories within each are explained as follows.

Quality of evidence

I. At least one randomised trial with clinical endpoints.
II. Clinical trials that are either not randomised or were conducted in other populations.
III. Expert opinion.
Strength of the recommendation

A. Preferred; should generally be offered.
B. Alternative; acceptable to offer.
C. Offer when preferred or alternative regimens cannot be given.
D. Should generally not be offered.
E. Should never be offered.

Abbreviations for the names of TB drugs

In this chapter the names of many of the drugs used in the treatment of TB are abbreviated, especially when presented in multi-drug regimens. The following is a guide to the abbreviations.

R = rifampicin  H = isoniazid  E = ethambutol
Z = pyrazinamide  Rb = rifabutin  S = streptomycin
A = amikacin  C = ciprofloxacin  M = moxifloxacin
Cap = capreomycin  P = prothionamide  Ethi = ethionamide

Abbreviations for TB regimens

Phases of treatment

Treatment of active TB usually comprises:
¶ an initial phase of treatment (when more drugs are used) = the bactericidal phase
¶ a maintenance phase (with fewer drugs) = the sterilisation phase.

In a regimen such as 2HRZ/4HR, the number and letters before the slash refer to the initial phase and those after it refer to the maintenance phase. The letters in each case indicate the medicines used (see abbreviations above), while the numbers refer to the number of months that particular regimen is given.

Frequency of doses

A further abbreviation is found in regimens given intermittently, such as 6R3H3E3Z3. The subscript numerals (in this case, number 3) refer to the number of times per week the medication is be given.

Thus, 2HRZ/4H3R3 indicates an initial phase of two months taking HR and Z each day; and a maintenance phase of four months taking H and R (isoniazid and rifampicin) three days per week.

The absence of a subscript indicates that the drug is taken daily.
16.1 Indications for anti-tuberculous treatment

16.1.1 Active TB

Proof or strong suspicion of active TB is an absolute indication for treatment. The timing of the commencement of treatment – immediately, or delaying until culture results are available – will depend on the clinical circumstances.

Notification should not be delayed until treatment is commenced. Public health investigation of contacts, or the search for a source case, should start immediately after active TB is clinically obvious or is proven. (See Chapter 1: ‘Epidemiology and Surveillance’, section 1.3.3.)

16.1.2 Inactive TB

Past TB may be evident on examination or on chest radiographs. It is not possible to confidently determine the activity of apparent past pulmonary TB on the basis of a single film. The radiological criteria for performing detailed microbiological investigations on cases who either have no sputum or have smear- and culture-negative sputum, but where TB is suspected or needs exclusion, are given in Chapter 14: ‘Clinical Investigation and Assessment of Tuberculosis’, Table 14.2.

People with inactive pulmonary TB have an annual risk of developing active disease which is at least 2.5 times greater than those with latent TB infection (LTBI) and a normal radiograph.¹

Factors which influence the need for treatment of inactive TB

Decisions about whether or not to treat people with inactive TB, and also the treatment regimen to be used, are guided by the following factors.

1. The likelihood of M. tuberculosis having been responsible for the abnormalities: this is increased if there is a positive Mantoux reaction, if the radiographic features are typical of past TB, the person has lived in a country with a high incidence of TB, or has had known close contact in the past with TB.

2. The extent of the radiological abnormalities: ‘trivial’ radiological extent of disease suggests a low initial burden of M. tuberculosis organisms. These radiological abnormalities in themselves indicate a low risk of reactivation in the future. ‘Extensive’ past TB, with extensive scarring and shadowing in several lobes, conversely implies a very high initial burden of organisms, and a higher risk of reactivation.

3. The nature of the radiological abnormalities: evidence suggestive of healed primary TB (calcified solitary pulmonary nodules, calcified hilar lymph nodes) and apical or basal pleural thickening does not by itself present significant risk of TB reactivation,¹ and does not require treatment.² The presence of other risk factors and the size of the Mantoux reaction guide the need for treatment of LTBI when these radiological abnormalities are present.
‘Nodules and fibrotic scars may contain slowly multiplying tubercle bacilli with substantial potential for future progression to active TB.’ These have greater priority for treatment of LTBI than the abnormalities in the previous paragraph. Multiple and/or non-calcified nodules suggest the process is not inactive TB, and they require investigation. Treatment may also be indicated.

The presence or absence of risk factors for reactivation of disease

The age of the patient and their general condition
Young people are likely to have been relatively recently infected (which carries a higher risk of active disease than remote past infection), and they have a long future period in which past TB may reactivate. They therefore continue to have priority for preventive treatment. The elderly may have more risk factors, but a much shorter period in which reactivation may occur.

In elderly people with features of extensive past TB on chest radiograph, the decision whether or not to treat can be difficult. It is reasonable not to treat when there are no risks for reactivation. The decision to give treatment is straightforward when marked risks for reactivation are present, comprehensive testing for TB is negative, and the person’s general condition is good. However, if the person’s health indicators point to the period of possible reactivation being relatively short, it may be preferable to withhold treatment. In this situation the person should have ongoing clinical surveillance, with a low threshold for performing further bacteriological tests and chest radiographs.

Past treatment of TB or past chemoprophylaxis
If past treatment has been given, regardless of whether the details of the regimen are known or not, there are only two possibilities: it was curative or it was not.

If it was curative, further treatment is unnecessary. (‘Curative treatment’ means a regimen as outlined below in sections 16.4 and 16.7.) If past treatment was not curative, then there is a significant chance that drug-resistant organisms may persist. In this situation, further treatment without knowledge of the organism’s susceptibility pattern carries risks of not being curative and, at the same time, of compounding the degree of drug resistance. Consequently, it may be (and almost always is) preferable to keep these patients under review rather than re-treating them.

Obtaining a second opinion from a clinical TB expert may be appropriate if there is uncertainty about the best management.
16.2 Management principles in treating TB

Wherever possible, investigations should be undertaken that give the best possible chance of identifying the organism and its sensitivity pattern. This is particularly important where drug resistance is possible (see ‘Risk factors for drug-resistant TB’ below).

The drugs must be taken regularly, so patient co-operation is essential in the successful treatment of TB. It is essential that each person who is prescribing TB medicines, or who is otherwise involved in the care of TB patients, is familiar with the content of Chapter 4: ‘Adherence to Treatment’ and Chapter 5: ‘Directly Observed Therapy’.

Directly observed therapy (DOT) is indicated with re-treatment, suspicion of poor compliance and multi-drug resistance.

‘Completion of therapy is based on the total number of doses administered – not on the duration of therapy alone.’2 Although this statement was made in relation to treatment of LTBI, it is also true of the treatment of active TB.

Treatment regimens must contain multiple drugs to which the organisms are susceptible. Single agents must never 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. If drug resistance is suspected (see ‘Risk factors for drug-resistant TB’ below), treatment should be modified accordingly.

Clinicians should notify all people 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 9: ‘Infection Control’.

Risk factors for drug-resistant TB

The following are risk factors for drug-resistant TB:
¶ reactivation following previous treatment.
¶ prolonged residence in a country outside Western Europe, North America and Australasia
¶ contact with a case with known drug resistance
¶ contact with groups at risk of drug-resistant TB, such as patients with HIV infection from New York
¶ partial regimens lasting weeks (eg, during a prolonged drug challenge, where a temporary regimen is not used). See 15.8.
16.3 Treatment of inactive TB in people with past, untreated TB on chest radiograph

16.3.1 Investigation before starting treatment

People with past TB disease on chest radiograph must have microbiological testing before they are started on treatment – especially if single-drug treatment is planned. This statement does not apply to people with radiographs that show only one or two calcified pulmonary nodules. The radiological features for which testing is needed are discussed above in section 16.1.2, and in Chapter 14, Table 14.2.

Acid-fast baccilli (AFB) tests on sputum are appropriate only if the person has a productive cough. Individuals who are not producing sputum from the lower respiratory tract must undergo induced sputum or bronchoscopy.

16.3.2 Treatment regimens for trivial, inactive pulmonary TB

The regimens for infected people who require treatment, and have trivial radiological features of inactive TB on chest radiograph, are the same as those for people with LTBI. These regimens are discussed in Chapter 3: ‘Latent Tuberculosis Infection’.

16.3.3 Treatment of moderately extensive, inactive pulmonary TB

See also Table 16.1.

4RH (level II evidence)

A four-month course of self-administered daily RH is reported to be as efficacious as a 12-month course of isoniazid by Jasmer and colleagues from San Francisco. There were 477 people in the RH group, and they were compared with 545 people who had taken 12RH in previous years; 93% of all subjects were born outside the USA. Completion rates (about 80%) and side-effects (in about 5%) were similar in each arm. The radiographic features of prior TB were confined to ‘apical fibro-nodular infiltrations, often with volume loss’. Even comparing nine months of H with this four-month RH regimen, cost savings favoured the shorter programme ($92 per patient). In a population with 10% isoniazid resistance, the incremental cost-benefit would have been $288 per patient.

Dutt and colleagues earlier conducted an open study of 4RH, and 414 subjects completed the course. During a median of 44 months’ follow-up, five subjects (1.2%) relapsed: three out of 126 who had showed radiographic and/or clinical improvement during treatment, and two among the non-responders.
4RHEZ (level II evidence)

4RHEZ, taken daily as self-supervised treatment, was compared with 12H in a report from Seattle. The ethnicities of subjects were similar to those in the study of 4RH. Fifty-three subjects who took 4RHEZ were compared with an historical cohort of 108 people who received 12H. Completion rates were similar, but side-effects were more frequent with RHEZ (30% compared with 11%). The cost of the four-drug regimen was almost four times greater than the isoniazid regimen.

2RH(E)Z/2RH

This regimen can be used for smear-negative, culture-negative people with evidence of inactive TB on chest radiograph, or Mantoux reactors with silicosis.

16.3.4 Treatment of extensive, inactive pulmonary TB

Extensive radiological scarring should prompt the selection of a regimen for the treatment of active TB, rather than one for the treatment of inactive disease.

Table 16.1: Treatment regimens for non-extensive pulmonary TB

<table>
<thead>
<tr>
<th>Disease activity</th>
<th>Regimen</th>
<th>Level of evidence</th>
<th>Recommendation rating</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inactive TB</td>
<td>4RH</td>
<td>II</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>4RHEZ</td>
<td>II</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>2RH(E)Z/2RH</td>
<td></td>
<td>B</td>
</tr>
<tr>
<td>or use a regimen for active TB</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Active TB</td>
<td>2RHZ/4RH</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>9RH</td>
<td>II</td>
<td>C</td>
</tr>
<tr>
<td></td>
<td>2RHE/7RH</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>H resistance</td>
<td>6RHEZ</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td></td>
<td>6RHSZ</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>2R(H)EZ/7RE</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td></td>
<td>12RE</td>
<td>III</td>
<td>C</td>
</tr>
<tr>
<td>R resistance and susceptible to Rb</td>
<td>2RbHEZ/4RH</td>
<td>II</td>
<td>A</td>
</tr>
<tr>
<td>Resistance to R and Rb</td>
<td>2HEZ/16HE</td>
<td>III</td>
<td>B</td>
</tr>
<tr>
<td>Z resistance</td>
<td>2RHE/7RH</td>
<td>III</td>
<td>A</td>
</tr>
</tbody>
</table>

Notes:
These regimens may be appropriate for some forms of extra-pulmonary TB: see below, section 16.8.
Extensive TB – whether pulmonary or multi-system – requires a longer duration of treatment than the total periods shown in this table.
For definitions of evidence levels and recommendations, see Introduction.
(Usually) no follow-up of untreated, inactive TB

Serial CXR follow-up is no longer recommended for people with (presumed) inactive disease who do not receive treatment, for the following reasons.

- There are no studies to show that X-ray follow-up is an effective strategy.
- A Canadian study calculated that the cost of preventing a case of TB was $24,225 for cases identified by screening all immigrants at entry, and $65,126 for those cases detected by ongoing surveillance of inactive TB.
- Sound education (using interpreters as needed) about having a low threshold for reporting symptoms is now recommended.

There are exceptions to this advice, and follow-up should be done if:

- there are major risk factors for reactivation of TB, and a decision is taken not to give preventive treatment
- the chest radiograph appearance and a history of smoking raise the possibility of lung cancer; at times, fine-needle aspirate (FNA) may give a false negative impression of benign disease
- other diagnoses are possible (eg, fungal infection).

Clinical judgement should be exercised when considering the need for follow-up radiographs.
16.4 Daily treatment regimens for active TB

All treatment regimens suggested in this chapter represent the minimum number of medications to be used and the minimum period of treatment required to achieve cure. Clinicians should consider increasing the number of medications and/or the duration of treatment for:

- extensive TB
- cavitatory TB
- slow clinical or radiological improvement on treatment
- patients who are being re-treated.

Drug regimens are summarised in Table 16.1.

16.4.1 Drug resistance not suspected

There is just one proven regimen that requires only a six-month daily treatment period for culture-positive fully sensitive TB: 2RHZ/4RH.\(^9\) No other agents can be substituted in either the initial or the maintenance phase of treatment as this will decrease the efficacy of the regimen, and a longer duration of therapy will be required.

Note that in the USA and Australia, ethambutol is recommended as a fourth initial drug (RHZE) if the susceptibility pattern is not known. In New Zealand, however, we recommend this only for foreign-born cases since drug resistance is uncommon in New Zealand-born people.

9RH is as effective as the above six-month regimen (level II evidence).\(^10\) The longer duration of treatment may be a disadvantage and is more expensive.

2RHE/7RH may also be used when pyrazinamide is not tolerated, or the organism is resistant to it (level III evidence).\(^11\)

16.4.2 Daily treatment when single-drug resistance is proven

The duration of treatment needs to be re-evaluated during the course of treatment when drug resistance is encountered. In general, treatment needs to continue for at least six months after sputum cultures become negative. The following treatment periods are thus only a guide and represent the minimum duration of treatment.

Isoniazid-resistant TB

6RHSZ (or 6RHEZ) is a proven and accepted regimen (level I evidence).\(^12\) 2R(H)EZ/7RE is an alternative (level I evidence).\(^13\) 12RE may also be used (level III evidence).\(^14\)

Regimens that should not be used in subjects with, or at risk of, isoniazid resistance are 2RHEZ/4RH or 2RHEZ/4HE.\(^15\)

There are conflicting data about whether isoniazid should be used in the treatment of isoniazid-resistant TB.\(^16\) It is often included in this situation, 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. British Thoracic Society Guidelines state: ‘we consider it safer practice to stop isoniazid and change the regimen as above’ (ie, give 2REZ + 7RE (level A recommendation) or 2REZ + 12RE (level C recommendation)). On the other hand, many TB experts would give isoniazid in the treatment of multi-drug-resistant TB, but ensure that sufficient other drugs to which the organism is sensitive are given.

*Rifampicin-resistant TB*

The Hong Kong studies indicate that resistance to rifampicin is far more serious than resistance to isoniazid. Generally, at least three drugs to which the organism is still susceptible are needed. 2HEZ/16HE may be used (level III evidence).

An exception to the three-drug requirement may be very minor disease extent, when 18-24HE may be satisfactory. Note: see 15.2.2 ‘Ethambutol’ section, for comments on the use of HE and its weak efficacy.

When the organism is sensitive to rifabutin but resistant to rifampicin, rifabutin may be used. (Note that proof of susceptibility is needed before giving rifabutin when rifampicin resistance is present.) Rifabutin has been shown to be as effective as rifampicin in a study that provided level II evidence. In this study, two groups took two months of daily treatment (RbHEZ or RHEZ), followed by four months of twice-weekly treatment (RbH or RH, respectively). Differences in bacteriological conversion rate, time to conversion, and relapse rate over a further 24 months were not significant.

*Pyrazinamide-resistant TB*

*Mycobacterium bovis* is naturally resistant to pyrazinamide. 2RHE/7RH (or 9RH for minor extent of disease) is appropriate here.

### 16.4.3 Drug resistance suspected

If cultures are negative and previous treatment of unknown adequacy has been given, see Table 16.2.

**Initial phase of treatment**

Start with 2RHEZ. Additional drugs may be necessary in re-treating TB in people previously treated.

**Maintenance phase**

1. If all initial cultures are negative, use 4RH (ie, total treatment duration = six months).
2. If resistance to isoniazid is identified, use 4RHEZ or 7RHE (or 7RE).
3. If resistance to rifampicin is identified, use 18–24HE. 12RbHE may be appropriate (but is unproven) provided the organism has been shown to be sensitive to rifabutin.
4. If resistance to ethambutol is identified, use 4RH.
Table 16.2:  Treatment regimens for culture-negative TB in people with prolonged residence in a country with a high incidence of TB and drug resistance

<table>
<thead>
<tr>
<th>Radiological features</th>
<th>Previous treatment: either inadequate regimen or no details known</th>
<th>Suggested (preventive) treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor pleural thickening, trivial parenchymal abnormality, or normal CXR</td>
<td>No 4</td>
<td>Consider no treatment, or LTBI regimen</td>
</tr>
<tr>
<td></td>
<td>Yes 4</td>
<td>No treatment</td>
</tr>
<tr>
<td>Moderate TB scarring</td>
<td>No</td>
<td>2RHEZ/2RH</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>No treatment</td>
</tr>
<tr>
<td>Severe TB scarring</td>
<td>No</td>
<td>2RHEZ/4-7RH</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>No treatment unless high risk of reactivation, or of active disease</td>
</tr>
</tbody>
</table>

Note: this table shows empirical decisions based on:

- a moderately aggressive approach using only treatments likely to produce cure (which lesser regimens than those shown have not been proven to do)
- a reluctance to give treatment to people previously treated. If their previous treatment was inadequate, drug-resistant organisms are likely. The addition of a conventional four-drug regimen may result in worsening of the resistance pattern.

When severe TB scarring is present, with no information about the adequacy of previous treatment, induced sputum testing or bronchoscopy is required. If cultures are negative, a careful decision must be made whether to:

- give no treatment and follow with serial CXRs, or
- treat with RHEZ and risk compounding any pre-existing drug resistance, or
- treat with a six-drug regimen (eg, RHEZ plus ciprofloxacin and prothionamide).
16.5 Multi-drug resistant TB (MDR-TB)

MDR-TB is defined as TB with resistance to rifampicin and isoniazid. Resistance to other drugs may be present or not. However, as rifabutin is as efficacious as rifampicin, the definition should probably be changed to resistance to rifampicin, rifabutin and isoniazid. As yet there have been no trials of treatment of rifabutin with other agents in the treatment of MDR-TB.

Multi-drug resistance and multiple drug resistance are not interchangeable terms. ‘Multiple resistance’ simply means there is resistance to more than one TB drug, without any particular agents being specified. ‘Multi-drug resistance’ specifies the two drugs to which the organism is resistant – rifampicin and isoniazid.

16.5.1 Treatment considerations

Resistance to rifampicin and isoniazid eliminates the two most important TB drugs from the treatment regimen: their roles in modern drug treatment are discussed in Chapter 15: ‘M. tuberculosis, TB Medicines and Monitoring’, sections 15.2 and 15.3.

A clinical TB expert must be involved in the management: it is essential that those treating MDR-TB are familiar with the actions and limitations of the remaining drugs.

If resistance to rifampicin and isoniazid is identified after the patient has already been started on RHEZ, additional cultures must be taken in case further resistance has developed. These results will guide eventual treatment. If the patient is taking RHEZ and multi-drug resistance is then identified, while continuing EZ, two, or preferably three, of the following drugs must be added: an aminoglycoside (streptomycin, amikacin, kanamycin or capreomycin), ethionamide, ciprofloxacin, or rifabutin (if sensitivity to rifabutin is confirmed). Other possible agents are discussed in section 16.5.

Surgery may well be appropriate in these cases if the disease is sufficiently localised to permit resection of the bulk of the diseased lung.

DOT is mandatory for MDR-TB. At this time daily DOT is the only option, as no regimens for intermittent DOT for MDR-TB are recommended.

16.5.2 The outcome of treating MDR-TB

The majority of cases of MDR-TB can be cured in Western countries: cure rates of the order of 85% should be achievable. Adverse effects of treatment are common. However, they should not prevent cure, unless there is major combination of multiple drug resistance and intolerance. Management of TB drug side-effects is discussed in Chapter 15: ‘M. tuberculosis, TB Medicines and Monitoring’, section 15.8.
16.5.3 Prevention of MDR-TB

There are no strategies of proven efficacy. However, the two most important principles in preventing the development of MDR-TB are:

- careful selection of the treatment regimen, keeping in mind risk factors for drug resistance (see ‘Risk factors for drug-resistant TB’, in section 16.2)
- careful follow-up, bearing in mind:
  - factors contributing to treatment failure (see below)
  - the causes and prevention of non-adherence to treatment (see Chapter 4: ‘Adherence to Treatment’).

Factors contributing to failure of TB chemotherapy

The following factors contribute to the failure of TB chemotherapy:

- patient non-adherence
- prescription of an inadequate regimen (‘physician non-adherence’) or dispensing errors
- adverse drug reactions resulting in not taking part of the regimen
- drug-resistant organisms
- immunosuppressed patient
- inadequate absorption of drugs (eg, secondary to gastrointestinal disease)
- inadequate penetration of drugs into diseased tissues (eg, CNS).
16.6 Additional agents to consider with very severe, multiple-drug-resistant TB

Aminoglycosides and quinolones

These agents are discussed in Chapter 15, ‘M. tuberculosis, Medications and monitoring’.

Para-aminosalicylic acid (PAS)

A new granule formulation of PAS became available in the USA in 1999. Twice-daily dosing achieves serum concentrations above the MIC of M. tuberculosis throughout the dosing interval.\textsuperscript{21}

Thiacetazone

This is a bacteriostatic drug whose mechanism of action remains unknown. Adverse side-effects are common, especially gastro-intestinal symptoms. It crosses the placenta and is excreted in breast milk. Cutaneous side-effects, including Stevens-Johnson Syndrome, are common in HIV infection.

Cycloserine

This drug inhibits enzymatic production of cell wall precursors, thereby causing reduction in cell growth, and possibly cell death by lysis. Toxicity occurs in up to 15% of patients taking cycloserine – seizures are the most frequent side-effect. There is a narrow margin between toxicity and therapeutic effect. Adverse effects are more frequent in alcoholics, patients with a history of neurological or psychiatric disorders, and those with renal impairment.

Beta-lactams

M. tuberculosis produces a penicillinase which is inhibited by beta-lactamase inhibitors. The latter drugs inhibit the growth of mycobacteria \textit{in vitro}. However, it is known that beta-lactam antibiotics penetrate poorly into mammalian cells, and this may limit their effectiveness in the treatment of TB. Successful treatment of MDR-TB has been reported in two patients who received amoxycillin-clavulanic acid, 2 g daily, along with ethionamide, cycloserine, capreomycin or streptomycin.\textsuperscript{22}

Inhaled interferon–gamma

Interferon-gamma (IFN-\(\gamma\)) probably activates macrophages by inducing nitric oxide synthetase, thereby increasing nitric oxide production and killing M. tuberculosis. There may be other mechanisms by which IFN-\(\gamma\) stimulates intra-macrophage killing of M. tuberculosis. At present there is only one report of five patients with pulmonary MDR-TB in whom IFN-\(\gamma\) delivered by aerosol was associated with a substantial clinical response. Relapse is likely to occur after IFN treatment is discontinued, unless other agents are able to achieve control of infection at the same time. Expense is the main factor limiting the use of IFN-\(\gamma\).
Subcutaneous interleukin-12

There is a single case report of successful treatment of refractory, fully sensitive TB with subcutaneous interleukin-12, along with appropriate anti-tuberculous drugs. Malabsorption had been excluded, the person had not responded to subcutaneous IFN-γ and in vitro demonstration of the ability of the person’s peripheral blood mononuclear cells to release IFN-γ in response to interleukin-12 was performed before the interleukin was administered. The dose given was 300 ng/kg SC twice weekly for a total of eight months.24

Thalidomide46

Although Thalidomide was banned throughout the world in the early 1960s because of its teratogenicity, research with this agent continued because of its anti-inflammatory and immuno-modulatory properties. It modifies the host response to TB (which is discussed in Chapter 15, section 15.1.2) in several ways. It has been shown (in both HIV + and – TB patients) to curb the inflammatory response by suppressing TNF-α production by macrophages. At the same time, the production of certain cytokines is enhanced – there is increased INF-γ production by T cells, and IL-12 production is stimulated. Thalidomide is a potent co-stimulator of primary human T lymphocytes, with greater effect on CD8+ than CD4+ T cell proliferation.

Clinical studies are incomplete. Reported effects vary with respect to immunological and clinical parameters and the development of negative sputum cultures. However, there are several reports of benefit in CNS TB, where reduction in the cytotoxic response may reduce raised intracranial pressure and be accompanied by healing of cerebral TB. The drug is apparently well tolerated, even in young children. Strict precautions are required to prevent pregnancy. Thalidomide may become an important adjuvant in TB treatment.

Thioridazine or methdilazine – phenothiazines

Phenothiazines are derivatives of methylene blue, which was described by Paul Ehrlich in the 19th century as rendering bacteria immobile. Since then, phenothiazines have been shown to be active against a wide variety of viruses, bacteria, mycobacteria and protozoa. Pulmonary macrophages concentrate chlorpromazine 100-fold above the concentration found in plasma. Thioridazine is probably the mildest of the phenothiazines and is effective in vitro against all encountered strains of M. tuberculosis, irrespective of antibiotic susceptibility. In desperate circumstances it may be worth considering using this agent, which has not been studied in clinical trials.23

Vaccination with M. vaccae

M. vaccae is a rapid-growing mycobacterium that was isolated from the environment in central Uganda. It is not known to cause disease in humans. Published results do not support the use of M. vaccae immunotherapy for TB.25
16.7 Directly observed treatment (DOT)

16.7.1 General

Adherence to the medication programme is an important topic, and is the subject of Chapter 4: ‘Adherence to Treatment’, which should be read in conjunction with this chapter. Alternatives to DOT are also discussed in Chapter 4. DOT itself is discussed in detail in Chapter 5: ‘Directly Observed Therapy’.

DOT should be considered whenever there are risk factors for poor adherence with self-medication. These include:

- long duration of treatment course
- TB drug side-effects
- attitude suggests denial of having TB, and therefore resistance to treatment.
- lack of understanding about disease and health
- antagonistic to prescribed medication
- previous poor adherence
- life stresses and poor or absent social support
- alcohol or any substance abuse
- feeling unwell
- previous treatment for TB (e.g., in the last 10 years).

All patients with multi-drug-resistant TB should receive DOT.

A public health nurse (preferably), a community-based nurse or another health worker trained in DOT administration must directly observe the administration of every dose of medication to meet the DOT definition. In some instances a reliable relative may be able to take over supervision. However, if supervision is carried out by someone who has not been specifically trained to administer DOT, it would mean the patient would not be considered to be on DOT, according to the definition (see Chapter 5).

A degree of patient co-operation is required, even with DOT. Patients may conceal tablets in the mouth or try to avoid taking medications in other ways. Careful vigilance is required by the person administering therapy throughout the whole treatment period.

Self-administration of DOT-type intermittent treatment is not acceptable (see Chapter 5).

16.7.2 Directly observed treatment regimens for fully sensitive organisms

1. 2RHZ/4H₂R₃ or 2RHZ/4H₂R₂: add E if resistance suspected.

2. Two weeks RHZE, then:
   - six weeks R₂H₂Z₂E₂, then:
   - 16 weeks R₂H₂,
   - Omit E if resistance has been excluded or is highly unlikely.
3 6R₃H₃Z₃E₃.
4 1 or 2 RH/8R₂H₂:
   ¶ add E if there are any risk factors for resistance
   ¶ add Z and E if drug resistance is proven.

Note:

i  An aminoglycoside can be used, replacing E in protocols 2 and 3.
ii Longer durations of treatment are advisable in the presence of widespread disease or major cavitatory TB.
iii These regimens are unproven in the treatment of extra-pulmonary TB, where longer duration may also be advisable.

16.7.3 Directly observed treatment for drug-resistant organisms

No protocols have been agreed on. Thrice-weekly treatment should be the minimum frequency of administration. 6R₃H₃E₃Z₃ is acceptable for isoniazid resistance, provided smears and cultures are negative after three months of treatment.
16.8 Duration of treatment for extra-pulmonary TB

The minimum treatment periods for fully sensitive organisms are shown below. Longer
duration of treatment should be considered in the presence of:

- severe or extensive disease
- drug resistance
- intermittent (DOT) treatment
- clinical or radiological progress which is slower than expected, or
- imaging showing major residual shadowing which is thought to be the result of TB.

Immunosuppressive factors, such as HIV or diabetes mellitus, are not in themselves
indications to prolong treatment. A longer duration of treatment is essential if
pyrazinamide is not included in the regimen.

Six months’ treatment is suitable for minor-to-moderate TB disease involving:

- lymph node
- pleural effusion
- genito-urinary organs
- pericardial effusion
- bone and joint TB
- skin.

Give 12 months’ treatment for miliary, meningeal and intracerebral TB.

A report published in 2001 reviewed previous studies of TB meningitis and concluded that
a six-month treatment regimen is sufficient for TB meningitis with fully susceptible
organisms.47

---

* Prostatic TB is uncommon, and receives little mention in the literature. General infections at this site tend to be
difficult to eradicate, and perhaps this indicates that antibiotic penetration is difficult. It may be advisable to
consider 9–12 months’ treatment for prostate TB.
16.9 Management of central nervous system (CNS) TB

Table 16.3 shows that isoniazid and pyrazinamide penetrate best into the cerebrospinal fluid (CSF), and are therefore the most important drugs in the treatment of tuberculous meningitis and intra-cerebral TB. Rifampicin is also an excellent agent if the meninges are inflamed.

Where drug resistance is suspected (noting that isoniazid is the most common agent to which there is resistance, worldwide), an aminoglycoside can be used if the meninges are inflamed. If there is no inflammation, prothionamide is probably the next best agent, as this does penetrate into the CSF.

There is little information about intra-thecal antibiotic treatment for CNS TB. One exception is a report by Berning and colleagues, who used a frontally located Ommaya reservoir for intra-thecal drug administration, and an indwelling epidural drain for pharmacokinetic measurements. Their patient was successfully treated for multi-drug-resistant TB meningitis with intra-thecal lecofloxacin and amikacin. Oral drug treatment had failed, but oral medications were continued, and prednisone 25 mg was added once intra-thecal treatment had been established.

Thalidomide may have a limited role in the treatment of CNS TB, but further studies are needed. This is not a recognised treatment at this stage. See Section 16.6.

Table 16.3: Treatment of tuberculous meningitis and intra-cranial TB

<table>
<thead>
<tr>
<th>Drug penetration across the blood/brain barrier:</th>
<th>R</th>
<th>H</th>
<th>Z</th>
<th>E</th>
<th>S</th>
</tr>
</thead>
<tbody>
<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 CNS 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>20–35 mg/kg</td>
<td>20 mg/kg IM (max 1 g)</td>
<td></td>
</tr>
</tbody>
</table>

No dose increase needed for CNS TB

Oral steroid** Include if there is impaired consciousness, or neurological signs

Duration of TB medicines 12 months for children 9–12 months for adults

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* Doses for children: see Chapter 15, section 15.5, Table 15.3.
** Girgis et al. 1991. See also section 16.10, which follows.
16.10 Corticosteroid treatment in the management of TB\textsuperscript{35–37}

See Table 16.4, which shows a summary of indications for corticosteroid treatment in TB.

16.10.1 TB meningitis and intra-cerebral TB

For further information, see the review by Dooley et al.\textsuperscript{37} The following recommendations are based on level II evidence.

For early, mild TB meningitis oral steroid is of no benefit in asymptomatic patients. With TB meningitis of intermediate severity (eg, drowsiness, single cranial nerve paresis or hemiparesis), oral steroid treatment for ‘four weeks to months’ is beneficial. Severe disease (ie, coma) has a poor prognosis, which steroid treatment is unlikely to improve.

A Cochrane review of TB meningitis “found some evidence that corticosteroids help to reduce the frequency of death ... and neurological disability”, but concluded that larger studies, which include patients with HIV infection, are required.\textsuperscript{48}

There are no useful reports on the usefulness of steroids in the treatment of intra-cerebral tuberculomas. However, most authors accept the need for steroid treatment if there is evidence of raised intra-cranial pressure (level III evidence).

The possibility has been raised that oral steroid treatment may, by restoring the blood–brain barrier to normal, reduce the effectiveness of rifampicin and ethambutol, as these agents penetrate the CSF relatively poorly.\textsuperscript{38}

16.10.2 Tuberculous pleural effusion

Level I and II evidence shows that oral corticosteroid is no longer routinely recommended for tuberculous pleural effusion, despite the fact that 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.\textsuperscript{39}

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 was used or not.\textsuperscript{40}

Similarly, level I evidence from Wyser et al\textsuperscript{41} 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.
Practice points
Recommendations for managing TB pleural effusions

1. Steroid treatment is not routinely indicated for tuberculous pleural effusions, despite the fact that pleural thickening with impaired ventilatory function can occur.
2. Large, loculated effusions that cannot be adequately drained may benefit from steroid treatment. Any benefit is unlikely to occur after two months on steroid.
3. Oral steroid may be required to obtain early control of symptoms (pain, fever or malaise).
4. Full drainage of tuberculous effusions is very 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. There is no evidence for or against this possibility with concurrent modern chemotherapy.
5. 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.

16.10.3 Tuberculous ascites

No well-controlled studies are available, but in order to minimise adhesions, corticosteroid treatment has been commonly used in this situation. In the absence of evidence to support steroid treatment for tuberculous pleural effusion, it is difficult to recommend it for tuberculous ascites.

16.10.4 Tuberculous pericarditis

Level II evidence supports the use of steroid treatment in acute tuberculous pericarditis. Although uncommon, pericarditis is a dire complication of TB. TB 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-tuberculous therapy are very important in preventing the development of constriction.

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

The efficacy of corticosteroid treatment in TB pericarditis may be different for different stages of the disease (effusive, effusive-constrictive and constrictive). Many reports do not distinguish these stages in their subjects. It seems unlikely that oral steroid stops the progression from any stage to constrictive pericarditis, but it does reduce the need for surgery.
Placebo-controlled trials of corticosteroid in conjunction with anti-tuberculocid chemotherapy (rifampicin, isoniazid, pyrazinamide and streptomycin) for acute tuberculocid pericarditis have shown reduced mortality, reduced requirement for subsequent pericardectomy and reduced need for pericardiocentesis or open surgical drainage. Therefore, oral corticosteroid (initially prednisone 60 mg/day and tapering to zero over 11 weeks) is recommended, along with TB treatment, for acute tuberculocid pericarditis.

16.10.5 Miliary TB, very advanced TB and suspected hypo-adrenalism

There is level I–II support for steroid treatment in these situations. The circumstances listed in the heading of this section are associated with an incidence of unexpected death. The cause(s) of this 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 (as discussed in Chapter 17: ‘Treatment of Tuberculosis in Special Clinical Circumstances’, section 17.4.3)
- the Jaresch-Herxheimer reaction, occurring soon after starting TB treatment
- sudden death from myocardial TB has been described
- other common medical complications may be additive and contribute to cardiac arrythmias and death in people with advanced TB, including:
  - electrolyte disturbances (from TB, from other conditions or from their treatment)
  - hypoxaemia caused by pulmonary TB or concurrent chronic air-flow obstruction
  - coronary artery disease.

<table>
<thead>
<tr>
<th>Type of disease</th>
<th>Other considerations</th>
<th>Give oral steroid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleural effusion</td>
<td>Fully drained</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Loculated, or extensive thickening</td>
<td>Yes</td>
</tr>
<tr>
<td>Pericardial effusion or thickening</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Ascites</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Meningitis</td>
<td>Intermediate severity only</td>
<td>Yes</td>
</tr>
<tr>
<td>Other major disease from TB</td>
<td>See text below</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Because of the small risk from steroid treatment and the potential benefit, steroid treatment (eg, 20–60 mg/day) should be given:

- where the patient is very ill from TB (level I evidence, showing faster general improvement, weight gain and early CXR improvement)
- where the CXR shows a miliary appearance (level III evidence)
- to reduce the mass effects and obstructive complications from mediastinal lymphadenopathy (level I evidence)
where there are clinical or laboratory features compatible with hypo-adrenalism (if adrenal insufficiency is suspected, 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 those with radiologically very advanced disease, steroid cover should commence immediately. The duration of steroid treatment will be judged by the clinical circumstances, but may well continue for several weeks.

16.10.6 Renal-tract stenoses

In the past, oral steroid has been used with anti-tuberculous 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 TB cystitis has often been managed in the same way. However, benefits are unproven in both situations. Steroid treatment is only likely to be helpful if narrowing is due to acute inflammation caused either by a hypersensitivity response to tuberculo-protein or to the infection.

16.10.7 Oral steroid in the management of drug side-effects

This should only be undertaken by a clinician who is expert in the treatment of TB.

There is surprisingly little literature about the management of TB drug side-effects with oral steroid treatment. Usually, steroid treatment is not needed to control drug side-effects. The offending drug(s) can be identified and then eliminated. The process involves stopping treatment and, when appropriate, testing for sensitivity by progressively adding drugs one at a time. See also Chapter 15: ‘M. tuberculosis, TB Medicines and Monitoring’, section 15.8.2.

Nevertheless, steroid treatment is indicated in the following situations:

- to speed up the resolution of severe side effects – such as marked hepatic toxicity, severe dermatological and/or systemic side-effects, including troublesome fever. However, other causes for these problems must be sought before starting steroid treatment. This is also true when steroid treatment is required for severe paradoxical reactions (see Chapter 15, section 15.7.4)

- to control these same problems while continuing treatment – there is no information about the risks or safety of this latter practice, particularly in relation to ongoing hepatotoxicity that is partially controlled by steroid.

People with active TB should not receive oral steroid without concurrent anti-tuberculoc treatment. This is a most important rule, and doing otherwise always puts the patient, and perhaps others, at risk. This rule must be observed always with severe TB. However, there may be occasional instances in mild, non-infectious forms of TB where treatment is stopped and oral corticosteroid treatment is given for up to two weeks. This may speed up resolution of side-effects, thereby enabling earlier drug challenge testing and earlier resumption of effective treatment (level III recommendation).
Chapter 16: ‘Treatment of Tuberculosis’, section 16.8.1 and Chapter 15, section 15.8.1, ‘Practice points’ box, entitled ‘Rules for managing TB-drug side-effects’ discuss giving a new, temporary regimen if TB treatment is stopped, or is reduced to a partial regimen. A temporary regimen is very important if steroid treatment is given when the treatment regimen is compromised.
References


Chapter 17: Treatment of Tuberculosis in Special Clinical Circumstances

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This chapter is endorsed by the Thoracic Society of Australia and New Zealand

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Summary

Obesity and TB drug doses

- Obesity is associated with a number of physiological changes with potential flow-on effects for antimicrobial pharmacokinetics.

Doses of the first-line TB medicines in obesity

- Maximum doses of the standard TB medicines are shown in Chapter 15: ‘M. tuberculosis, TB Medicines and Monitoring’, Table 15.3. Always check that these have not been exceeded in obese people.
- With short obese people (including obese children), 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.
- Calculation of lean body weight (LBW), or ideal body weight (IBW):
  - women: 45 kg + 0.9 kg per cm of height above 150 cm
  - men: 50 kg + 0.9 kg per cm of height above 150 cm.
- In a single case report in which doses of rifampicin, streptomycin, ethambutol and pyrazinamide were given on the basis of IBW, therapeutic blood and cerebrospinal levels were obtained with these agents in an adult subject weighing 190% of his ideal body weight.

Doses of second-line agents in obesity

- The Devine formula is recommended for use with aminoglycosides and quinolones. The formula is:
  \[ \text{Daily dosing weight} = \text{IBW} + \text{DWCF}(\text{ABW} - \text{IBW}) \text{ kg} \]
  where:
  - IBW = ideal body weight (see 15.2.2)
  - ABW = actual body weight
  - DWCF = dosing weight correction factor, which is different for different drugs (as discussed below).
- Determining the daily dose for aminoglycosides using ABW may result in higher than desirable serum concentrations in obese people. Doses based on IBW may lead to sub-therapeutic serum levels. The larger volume of distribution and subsequent prolongation of elimination half-life offset the higher clearance of aminoglycosides in obesity. Alteration in dosage interval is not necessary in the presence of obesity.
- In the Devine formula, the DWCF for amikacin = 0.38. Thus, the dosing weight to be used in calculating the daily dose of amikacin = IBW + 0.38(ABW – IBW) kg. Thus, the daily dose of amikacin in obesity = 15 mg x (IBW + 0.38(ABW – IBW)).
- Quinolones are distributed less to adipose tissue than to other tissues. Consequently, doses calculated using ABW may overestimate the dose required. Studies by Ellard and colleagues have led to a recommendation to use the Devine formula with quinolones in the presence of obesity. The DWCF for ciprofloxacin is 0.45. Therefore the daily dosing weight recommended for ciprofloxacin = IBW + 0.45(ABW – IBW) kg.
Hepatic dysfunction, ascites and TB treatment

- This section covers hepatic dysfunction prior to starting TB treatment. The hepatotoxicity of TB drugs and the management of that problem are discussed in Chapter 15, sections 15.7.2 and 15.8.5.
- If hepatic dysfunction prior to TB treatment is due to TB, the abnormal results should improve within the first few weeks of treatment.
- Drugs being taken on presentation also need to be considered as a possible cause of the abnormalities.

Tests before starting treatment:

- Tests to determine the cause of hepatic dysfunction will depend on the severity and the pattern of the hepatic dysfunction (e.g., virus antibodies, abdominal ultrasound).

Serial liver function testing during treatment

- Usually liver function tests are not done for several weeks after starting treatment. However, when abnormal liver function is present before treatment starts, close clinical evaluation and repeat liver tests are needed (e.g., weekly, or even more often).

Regimens when major liver disease is present prior to treatment

- When major hepatic dysfunction is present it makes sense to start treatment with an effective non-hepatotoxic regimen such as amikacin, ethambutol* and ciprofloxacin. If these do not cause side-effects in the first three to four days, consider adding some of the potentially hepatotoxic agents.
- Rifampicin would be the next agent of choice to add (see Chapter 15, section 15.2.2). Consultation with a TB clinical expert is strongly recommended.

TB drug clearance in the presence of hepatic failure

- In this situation there will be decreased total body clearance of isoniazid and rifampicin, resulting in drug accumulation and higher serum levels. Their elimination half-life may increase by 30–100% in hepatic failure.
- Significant accumulation of pyrazinamide has been described in icteric patients.
- Although 50% of ciprofloxacin clearance occurs via the liver, its serum concentration is not substantially altered in hepatic disease.
- Transaminase levels usually do not correlate with the ability or inability of the liver to metabolise drugs.

* Ethambutol has been described to cause hepatotoxicity, but this is a rare occurrence. It should be noted that ethambutol has weak bactericidal and sterilising abilities. (See Chapter 15, sections 15.7.2 and 15.2.2.)
Ascites

TB drugs that distribute freely into water will display a larger volume of distribution and therefore a longer elimination half-life. Therapeutic drug monitoring should be done in people with persistent ascites.

Renal impairment and treatment of TB

Isoniazid, rifampicin, pyrazinamide, ethionamide and prothionamide are eliminated almost entirely by non-renal routes (ie, by metabolism or biliary secretion). For a summary of antituberculous drug doses and renal impairment, see Table 17.1.

Renal impairment, without dialysis

- **Isoniazid**: standard doses of isoniazid should be given in renal failure. If side-effects occur, therapeutic drug monitoring is appropriate.
- **Rifampicin**: no dosage adjustment is required.
- **Ethambutol**: approximately two-thirds of the ingested dose of ethambutol is excreted unchanged in the urine. The frequency of dosage may be reduced according to the severity of renal impairment: 25 mg/kg three times per week with creatinine clearance of 50–100 ml/min, 25 mg/kg twice a week if creatinine clearance is 30–50 ml/min. Alternatively, the daily dosage adjustment can be based on the glomerular filtration rate (GFR) (see Table 17.1). However, the following should be noted.
  - 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 while the serum creatinine remains normal.
  - Once renal failure is established and the serum creatinine is significantly elevated (> 0.2–0.3 mmol/L, depending on muscle mass), then 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.

Doses used in conjunction with haemodialysis are discussed below (see Haemodialysis).

- **Pyrazinamide** is 97% metabolised by the liver: 3% appears unchanged in the urine and 30–40% as pyrazinoic acid. Mild to moderate degrees of renal impairment do not require any adjustment of dose or frequency of administration. For severe renal impairment, the recommendations listed below in the sections on haemodialysis are appropriate. In severe renal impairment, taking into account its concentration-dependent mechanism of action (see Chapter 15, section 15.2.3), reduced frequency of administration is more appropriate than reduced dose.

- **Quinolones**: the mode of excretion varies among the quinolone family, and drug management therefore varies in the presence of renal impairment. With:
  - grepafloxacin and trovafloxacin, which have preferential hepatic metabolism, no dose adjustment is needed
  - moxifloxacin, which is excreted both by renal (20–30%) and biliary pathways, no dose adjustment is needed (there are no pharmacokinetic data available for people on dialysis).
- Levofoxacin and ofloxacin, which are cleared entirely by renal excretion, dose adjustment is recommended if the creatinine clearance is less than 50 ml/min
- Ciprofloxacin and sparfl oxacin, ‘moderate adjustment’ are necessary.

- **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, if possible.

- **Thiacetazone and p-aminosalicylic acid (PAS):** these are partly excreted unchanged in the urine. The difference between the toxic and therapeutic dose of thiacetazone is small. PAS has the potential to exacerbate acidosis in patients with renal impairment. For all these reasons these agents should be avoided when significant renal impairment is present. (Note: Thiacetazone is not available in New Zealand; it is used overseas.)

**Peritoneal dialysis (CAPD)**

- **Rifampicin:** give the normal dose.
- **Isoniazid:** give the normal dose, even in slow acetylators.
- **Pyrazinamide:** give thrice-weekly, using 40 mg/kg; or twice-weekly, using 60 mg/kg.
- **Ethambutol:** give 15 mg/kg every 48 hours. Ethambutol is removed by peritoneal dialysis and by haemodialysis to a lesser extent.

**Haemodialysis**

- Isoniazid, rifampicin and ethambutol are not significantly removed by haemodialysis.
- Isoniazid and rifampicin can be given in their usual daily doses. Conventional doses (300 mg) are safe and effective.
- Blood levels of ethambutol can vary between patients in chronic renal failure because of variable absorption. This may be the result of pre-dialysis fluid overload. Better absorption may be achieved with post-dialysis dosing.
- Recommended doses of ethambutol with haemodialysis are:
  - 15–25 mg/kg given three times per week, after dialysis, when dialysis is given at that same frequency
  - when the frequency of haemodialysis is not thrice-weekly, other authors have suggested 45 mg/kg twice weekly for twice-weekly dialysis, and 90 mg/kg once each week for once-weekly dialysis.
- Monitoring serum levels of ethambutol is highly desirable. Regular ophthalmology tests are essential if ethambutol is used.
- Pyrazinamide is significantly removed by haemodialysis. Doses of 25–30 mg/kg must be given after haemodialysis, thrice-weekly. Pyrazinoic acid, which is the primary metabolite of pyrazinamide, is partially removed by haemodialysis, but the extent of removal is uncertain.
- Rifampicin/isoniazid/ethambutol (RHE) may be administered after haemodialysis, and this may facilitate directly observed therapy.
- Ethionamide and PAS: see full text.
Pregnancy, lactation and oral contraceptive use

Pregnancy

- Pregnancy does not increase the risk of developing TB, and there is no evidence that pregnancy alters the tuberculin response. Most authorities believe that with appropriate treatment of TB, the prognosis for mother and baby should be excellent. For a discussion of congenital TB, see 17.5.3.

- Many anti-tuberculous drugs, including isoniazid, rifampicin and ethambutol, cross the placental barrier and are present in low concentrations in human foetal fluids and tissue. There is no evidence that these three drugs are unsafe during pregnancy: abortion is not justified on medical grounds.

- If active disease is present, treatment must start immediately. In pregnant women with inactive, past TB, where preventive treatment is indicated, initiation of therapy may be delayed until after the first trimester. In situations where active disease is suspected but not proven despite investigations, treatment should start after the first trimester, where possible.

- Treatment of latent TB infection with isoniazid should be postponed until after delivery. Exceptions are women who have been recently infected, or those with medical conditions placing them at high risk of developing disease, such as HIV infection.

- Pyridoxine should be used for all pregnant women receiving isoniazid in order to prevent neurotoxicity in the foetus.

- The general use of pyrazinamide in pregnancy cannot be supported because of inadequate data on teratogenicity. In cases with severe drug resistance, the risk of taking pyrazinamide is less than the risk of not curing TB, and pyrazinamide use should be considered in this situation.

- Streptomycin, capreomycin and kanamycin are potentially ototoxic to the foetus and should be avoided. This ototoxicity is independent of the ‘initial period’ early in embryogenesis, which is important in teratogenesis produced by other drugs.

- Ethionamide and prothionamide are considered potentially teratogenic and should not be used during pregnancy. There is inadequate information on cycloserine, and this drug should also be avoided.

- Initial anti-tuberculous therapy should consist of isoniazid, rifampicin and ethambutol. The minimum duration of treatment with these agents is of course nine months (in the absence of pyrazinamide), as explained in Chapter 16: ‘Treatment of Tuberculosis’, section 16.4.1.

Lactation

- Only small quantities of rifampicin and isoniazid appear in breast milk, and generally do not produce toxicity in the breastfed newborn: breastfeeding is not contraindicated while taking standard TB treatment.

- TB drugs in breast milk have no therapeutic effect in a baby with TB infection or TB disease.

- Despite ethambutol levels in breast milk being the same as those in maternal serum, its use is still regarded as being compatible with breastfeeding.

- Very low amounts of pyrazinamide are transferred in breast milk. Its slow metabolism by neonates adds a theoretical risk of accumulation in the newborn.
Hormonal contraceptives

- Rifamycins induce certain hepatic cytochrome P450 enzymes. Both oestrogens and progesterones are metabolised through this pathway: their elimination is accelerated by rifampicin or rifabutin, and contraceptive efficacy is lost.

- The induction of liver enzymes commences six days after the commencement of rifampicin and can be observed for up to one month after cessation of the drug.

- Another contraception method should be used during rifampicin therapy and for one month after completing rifampicin, even if rifampicin treatment is taken for less than a week. Barrier devices such as condoms may also be used, possibly in combination with a spermicidal agent.

- The only effective administered contraceptive is the injectable progesterone, depot medroxyprogesterone acetate. Although 12-weekly injection is the standard dosing interval, when rifampicin is being taken it is safer to reduce the dose interval of medroxyprogesterone from 12 to 10 weeks.

TB in children

Clinical differences with adult TB

- The basic principles of TB and its treatment in children are essentially the same as for adults. The three clinically important differences are:
  - post-primary TB is usual in children, and open cavities are rare, so infectious TB in a child is most unusual because of the smaller size of the bacillary population in children, they are considered to be at low risk of developing acquired drug resistance during treatment
  - the risk of developing extra-pulmonary disease, particularly miliary or meningeal TB, is greater than in adults.
  - TB in children aged under four years is more likely to disseminate and to be fatal: childhood TB requires prompt and vigorous treatment.

Management of TB in infants and children

- Use appropriately adjusted doses of the drugs.

- The regimen for most forms of TB is the same as in adults, and six months is the minimum duration. Longer durations are recommended for children with miliary, meningeal and bone and joint disease (9–12 months).

- Limited data are available for intermittent regimens in children, but experience suggests they are equally efficacious in children as adults.

- Medication-taking can be difficult in children. This should be worked through carefully, with close supervision from a public health nurse.

Management of neonates

- Congenital TB is rare.

- Infants born to mothers with TB are not contagious and do not need isolation.

* Rifabutin is a less potent enzyme inducer than rifampicin.
The stage of the mother’s TB at the time of delivery determines the appropriate management of the neonate. See full text for advice in the following situations:
- mother with latent TB infection but no disease
- mother with active pulmonary TB
- mother with extra-pulmonary TB disease.

**Basic principles of treating TB in children**

The two main differences in TB treatment in children, compared with adults, are:
- due to different pharmacokinetics, children tolerate large doses of drugs/kg and are less likely to develop side-effects than adults
- lack of specific drug formulations for children can result in difficulties with administering medication.

In the young child there can be considerable difficulties with the taking of multiple medications. Trained people experienced in this should be involved with the family early to resolve these issues. If it is not dealt with early and adequately, significant delays and interruptions in therapy can result which may effect adequacy of treatment.

**Drug preparations**

TB medications are primarily formulated for adults. As a result, crushed tablets and unstandardised suspensions may need to be used in children.

It is preferable to use crushed tablets and proprietary suspensions (rifampicin) before considering the use of non-proprietary suspensions. Tablets can be crushed and given mixed in small amounts of syrup or food as long as the child takes the entire amount. The majority of children will tolerate medication given this way.

Non-proprietary suspensions:
- are prepared extemporaneously for multiple use, are based on non-validated formulae, and use non-funded excipients
- should rarely be needed (occasionally they may need to be used in the very young or the child receiving medication via a naso-gastric tube).

Rifampicin, isoniazid and pyrazinamide should never be put in a suspension together because the rifampicin becomes unstable.

Products containing vitamin C should be used with caution if added to any suspensions, as it may reduce the concentration of the anti-tuberculous drug. Reduced serum levels have also been found when giving isoniazid suspension with apple sauce.

**Pyridoxine**

Most children do not require pyridoxine supplementation, as isoniazid peripheral neuritis is rare in children.

Pyridoxine (25–50 mg/day) should be given to any:
- breastfeeding infant
- adolescent (rapidly growing)
- malnourished individual
- children with inadequate dietary intake (eg, meat- or milk-deficient diets)
- breastfed infants whose mother is taking isoniazid
- children who develop paraesthesiae.

**Monitoring**

1. *Monitoring disease progression*: children with pulmonary TB usually have no sputum or are smear-negative, so bacteriology has little role in follow-up during treatment. Clinical and radiological follow-up is the mainstay of evaluating response to treatment.

2. *Monitoring drug side-effects*: side-effects from TB medicines are uncommon. Clinical monitoring for symptoms and signs of hepatotoxicity is the only follow-up required. Ethambutol should be avoided in the young child due to difficulties in monitoring ocular toxicity.
Introduction

In this chapter the discussion of TB treatment is extended to situations where treatment must be modified and/or special care is required. Specifically, this chapter deals with TB treatment in those with severe obesity, with liver and renal dysfunction, during pregnancy and lactation, and with contraceptive use. The treatment of TB in children is also discussed. HIV and TB are covered in Chapter 18.
17.1 Obesity and TB drug doses

Antimicrobial dosing in obese patients is a complex and poorly understood topic. The following points are derived from a comprehensive review by Wurtz et al.\textsuperscript{1}

Obesity is associated with a number of physiological changes with potential flow-on effects for antimicrobial pharmacokinetics. Some of these factors are interactive. They 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.

17.1.1 Doses of the first-line TB medicines in obesity

Maximum doses of the standard TB medicines are shown in Chapter 15: \textit{M. tuberculosis, Medicines and Monitoring’}, Table 15.3. Always check that these have not been exceeded in obese people. With short obese people (including obese children), 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.

Calculation of lean body weight (LBW), or IBW is carried out as follows:

- women : $45 \text{ kg} + 0.9 \text{ kg per cm of height above 150 cm}$
- men : $50 \text{ kg} + 0.9 \text{ kg per cm of height above 150 cm}$.

Surprisingly there is only a single case report in which doses of rifampicin, streptomycin, ethambutol and pyrazinamide were given on the basis of ideal body weight. Therapeutic blood and cerebrospinal fluid levels were obtained with these agents in an adult subject weighing 190\% of his ideal body weight.\textsuperscript{2}

17.1.2 Doses of second-line agents in obesity

\textit{The Devine formula}

This is recommended for use with aminoglycosides and quinolones. The formula is:

\[
\text{Daily dosing weight} = \text{IBW} + \text{DWCF(ABW – IBW)} \text{ kg}.
\]

where:

- IBW = ideal body weight (see 15.2.2)
- ABW = actual body weight
- DWCF = dosing weight correction factor, which is different for different drugs, as discussed below.
**Aminoglycosides**

Aminoglycosides are primarily distributed into extra-cellular fluid. Determining the daily dose using actual body weight may result in higher than desirable serum concentrations in obese people. Doses based on ideal body weight may lead to sub-therapeutic serum concentrations. The larger volume of distribution and subsequent prolongation of elimination half-life offset the higher clearance of aminoglycosides in obesity. Alteration in dosage interval is not necessary in the presence of obesity. Some studies have noted more nephrotoxicity in obese subjects despite serum concentrations being maintained in the recommended range. A confounding factor may be the greater likelihood of these subjects to receive frusemide.

**Daily dosing weight recommended for amikacin**

In the Devine formula, the DWCF for amikacin = 0.38. Thus, the dosing weight to be used in calculating the daily dose of amikacin = IBW + 0.38(ABW-IBW) kg. Thus, the daily dose of amikacin in obesity = 

$$15 \text{ mg} \times (\text{IBW} + 0.38[\text{ABW-IBW}]).$$

**Quinolones**

Quinolones are distributed less to adipose tissue than to other tissues. Consequently, doses calculated using actual body weight may overestimate the dose required. Studies by Ellard and colleagues have led to a recommendation to use the Devine formula with quinolones in the presence of obesity.

The DWCF for ciprofloxacin is 0.45. Therefore, the daily dosing weight recommended for ciprofloxacin = 

$$\text{IBW} + 0.45(\text{ABW} – \text{IBW}) \text{ kg.}$$
17.2 **Hepatic dysfunction (and ascites) and TB treatment**

This section discusses hepatic dysfunction prior to starting TB treatment. The hepatotoxicity of TB drugs and the management of that problem are discussed in Chapter 15: *M. tuberculosis*, TB Medicines and Monitoring*, sections 15.7.2 and 15.8.5.

17.2.1 **Cause(s) of abnormal liver function**

Hepatic dysfunction prior to starting TB treatment may be due to TB. In this case the abnormal results should improve within the first few weeks of treatment. Drugs being taken on presentation also need to be considered as a possible cause of the abnormalities.

17.2.2 **Tests before starting treatment**

Before starting treatment, and after appropriate clinical evaluation, tests may be needed if the cause of the dysfunction is uncertain. These will depend on the severity and pattern of the hepatic dysfunction. It may be appropriate to arrange tests for viral hepatitis; or, if an obstructive pattern is present, to do an upper abdominal ultrasound.

17.2.3 **Serial liver function testing during treatment**

Usually, liver function testing is not done for several weeks after starting TB treatment. However, when abnormal liver function is present before treatment starts, close clinical evaluation and repeat liver tests weekly (or even more often) may be required.

17.2.4 **Regimens when major liver disease is present prior to treatment**

No strategies are currently recommended. However, if a person with active TB has major hepatic dysfunction, it makes sense to start treatment with an effective, non-hepatotoxic regimen such as amikacin, ethambutol* and ciprofloxacin. If these do not cause side-effects in the first three to four days, one could consider adding some of the potentially hepatotoxic agents.

Rifampicin would be the next agent of choice to add (see also Chapter 15: *M. tuberculosis*, TB Medicines and Monitoring*, section 15.2.2). Consultation with a TB clinical expert is strongly recommended.

17.2.5 **TB drug clearance in the presence of hepatic failure**³

In this situation there will be decreased total body clearance of isoniazid and rifampicin, resulting in drug accumulation and higher serum levels. Their elimination half-life may increase by 30–100% in hepatic failure.

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* Ethambutol has been described to cause hepatotoxicity, but this is a rare occurrence. It should be noted that ethambutol has weak bactericidal and sterilising abilities. (See Chapter 15: *M. tuberculosis*, TB Medicines and Monitoring*, section 15.2.2).
Significant accumulation of pyrazinamide in icteric patients has also been described.

Although 50% of ciprofloxacin clearance occurs via 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. Transaminase levels usually do not correlate with the ability/inability of the liver to metabolise drugs.

17.2.6 Ascites
This presents a problem with a number of anti-tuberculous 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 should be done in people with persistent ascites. See Chapter 15: ‘M. tuberculosis, TB Medicines and Monitoring’, section 15.6.4.

17.2.7 Hepatitis B carriers
Chronic hepatitis B carriers generally tolerate isoniazid well.
17.3 Renal impairment and treatment of TB

Isoniazid, rifampicin, pyrazinamide, ethionamide and prothionamide are eliminated almost entirely by non-renal routes (ie, by metabolism or biliary secretion).

17.3.1 Renal impairment, without dialysis

Isoniazid

Ellard\(^4\) has estimated that 5–6 mg/kg/day given to a slow acetylator with severe renal impairment would be equivalent to 7–9 mg/kg/day in a normal subject. His recommendation is still current – namely, that standard doses of isoniazid should be given in renal failure. If side-effects occur, this is just the situation where therapeutic drug monitoring would be appropriate. Therapeutic drug monitoring is discussed in Chapter 15: *M. tuberculosis*, TB Medicines and Monitoring’, section 15.6.4.

Rifampicin

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

Ethambutol

Approximately two-thirds of the ingested dose of ethambutol is excreted unchanged in the urine. The frequency of dosage may be reduced according to the severity of renal impairment: 25 mg/kg three times per week with creatinine clearance of 50–100 ml/min, 25 mg/kg twice a week if creatinine clearance is 30–50 ml/min. Alternatively, the daily dosage adjustment can be based on the glomerular filtration rate (GFR) (see Table 17.1). However, the following should be noted:

- 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 (> 0.2–0.3 mmol/L, depending on muscle mass), then 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.

Doses used in conjunction with haemodialysis are discussed in section 17.3.3.
**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. For severe renal impairment, the recommendations listed in section 17.3.3 are appropriate. In severe renal impairment, taking into account its concentration-dependent mechanism of action (see Chapter 15, section 15.2.3), reduced frequency of administration is more appropriate than reduced dose.

**Quinolones**

The mode of excretion varies among the quinolone family, and drug management therefore varies in the presence of renal impairment. With:

- grepafloxacin and trovafloxacin, which have preferential hepatic metabolism, no dose adjustment is needed
- moxifloxacin, which is excreted both by renal (20–30%) and biliary pathways, no dose adjustment is needed; there are no pharmacokinetic data available for people on dialysis
- levofloxacin and ofloxacin, which are cleared entirely by renal excretion, dose adjustment is recommended if the creatinine clearance is less than 50 ml/min
- ciprofloxacin and sparflroxacin, ‘moderate adjustments’ are necessary.

**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, if possible. The role of aminoglycosides as anti-tuberculous agents is discussed in Chapter 15, section 15.2.2.

**Thiacetazone and p-aminosalisylic acid (PAS)**

These are partly excreted unchanged in the urine. Both are relatively weak anti-tuberculous drugs. The difference between the toxic and therapeutic dose of thiacetazone is small. PAS has the potential to exacerbate acidosis in patients with renal impairment. For all these reasons these agents should be avoided when significant renal impairment is present. (Note: thiocetazone is not available in New Zealand; it is used overseas.)
Table 17.1: Anti-tuberculous drug doses and renal impairment

<table>
<thead>
<tr>
<th>Drug</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>
</tbody>
</table>
| Ethambutol | GFR < 30 ml/min: 10-15 mg/kg/day.  
GFR < 10 ml/min: 5 mg/kg/day.  
OR: see text. | 15 mg/kg every 48 hours. | After dialysis:  
† 15-25 mg/kg with dialysis 3x/week  
† 45 mg/kg if 2x/week  
† 90 mg/kg if 1x/week |
| Pyrazinamide | Normal doses, unless GFR < 10 ml/min: then give less frequently. | 40 mg/kg 3x/week; or 60 mg/kg 2x/week. | 25-30 mg/kg 3x/week, after dialysis |
| Streptomycin | Avoid if possible; or, 500 mg as single dose and monitor serum levels. |                      |                |

* TB medicines are given after haemodialysis.

Note: In people who have a renal transplant:

† avoid the use of rifampicin with cyclosporin and tacrolimus

† avoid the use of streptomycin with cyclosporin therapy.

17.3.2 Peritoneal dialysis (CAPD)

Give the normal dose of rifampicin. Also give the normal dose of isoniazid, even in slow acetylators. Blood levels are not warranted. For other medications (level III evidence):

† pyrazinamide: thrice-weekly, using 40mg/kg; or twice-weekly, using 60 mg/kg
† ethambutol: 15 mg/kg every 48 hours (ethambutol is removed by peritoneal dialysis, and by haemodialysis to a lesser extent).

17.3.3 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 (300 mg) are safe and effective.

Ethambutol

Blood levels of ethambutol can vary from one patient to another in chronic renal failure due to variable absorption. This may be the result of pre-dialysis fluid overload. Better absorption may be achieved with post-dialysis dosing.

* See Introduction, Chapter 16, for an explanation of levels of evidence.
Recommended doses of ethambutol with haemodialysis are:

- 15–25 mg/kg given three times per week, after dialysis, when dialysis is given at that same frequency.

When the frequency of haemodialysis is not thrice-weekly, other authors have suggested:

- 45 mg/kg twice weekly for twice-weekly dialysis, and
- 90 mg/kg once each week for once-weekly dialysis.

Monitoring serum levels of ethambutol is highly desirable. *Regular ophthalmology tests are essential if ethambutol is used.*

**Pyrazinamide**

Pyrazinamide is significantly removed by haemodialysis. Doses of 25–30 mg/kg must be given after haemodialysis, three times/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/ethambutol (RHE) may be administered after haemodialysis, and this may facilitate directly observed therapy.

**Other TB drugs**

Ethionamide and PAS are not significantly dialysed. Cycloserine is significantly removed by dialysis and doses should be given after dialysis. Usual doses, given three times a week after dialysis, are recommended. Ethionamide is rapidly metabolised by the liver, and 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.
17.4 Pregnancy, lactation and oral contraceptive use

17.4.1 Pregnancy

TB is uncommon in pregnant women in New Zealand. Pregnancy does not increase the risk of developing TB, and there is no evidence that pregnancy alters the tuberculin response.

In a small, matched cohort study in Mexico City, obstetric morbidity and perinatal mortality were significantly higher in women with TB who started TB treatment late in pregnancy. Most authorities, however, believe that with appropriate treatment of TB, the prognosis for mother and baby should be excellent.

Congenital TB is discussed below in section 17.5.3.

Maternal TB treatment and the foetus

Many anti-tuberculous drugs (isoniazid, rifampicin and ethambutol) cross the placental barrier and are present in low concentrations in human foetal fluids and tissue. For instance, the ratio of foetal cord to maternal blood isoniazid concentrations is approximately 0.62–0.73, that for rifampicin is 0.12–0.33, and that for ethambutol is 0.75.

There is no evidence that these three drugs are teratogenic or carcinogenic in humans, and no evidence of an increased rate of spontaneous abortion, stillbirth or premature birth with these agents. In general these drugs are considered safe in pregnancy – certainly the very low potential risk of teratogenicity does not justify abortion on medical grounds (level II evidence).

Nevertheless the benefits of treatment during pregnancy should be balanced against the potential side-effects.

- If active disease is present (on clinical, radiological or bacteriological grounds) the benefits of treatment to the mother and baby certainly outweigh the risks of therapy.
- In pregnant women with no symptoms, negative bacteriology, lack of radiological change but evidence of past TB, initiation of therapy may be delayed until after the first trimester.

Isoniazid

Although isoniazid is not regarded as being teratogenic, its use for treatment of latent TB infection should generally be postponed until after delivery. Exceptions are women who have been recently infected, or those with medical conditions placing them at high risk of developing disease, such as HIV infection.

Pyridoxine should be used for all pregnant women receiving isoniazid in order to prevent neurotoxicity in the foetus.
**Pyrazinamide**

Its general use in pregnancy cannot be supported because of inadequate data on teratogenicity. In cases with severe drug resistance, the risk of taking pyrazinamide is less than the risk of not curing TB, and pyrazinamide use should be considered in this situation.

**Streptomycin, capreomycin and kanamycin**

These are potentially ototoxic to the foetus and should be avoided. This ototoxicity is independent of the ‘initial period’ early in embryogenesis, which is important in teratogenesis produced by other drugs.

**Ethionamide and prothionamide**

These are considered potentially teratogenic and should not be used during pregnancy. There is inadequate information on cycloserine, and this drug should also be avoided.

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**Practice point**

In pregnancy, initial anti-tuberculous therapy should consist of isoniazid, rifampicin and ethambutol (unless drug resistance is likely). The minimum duration of treatment with these agents is, of course, nine months, as explained in Chapter 16: ‘Treatment of Tuberculosis’, section 16.4.1.

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**17.4.2 Lactation**

Isoniazid is secreted in human milk but no detrimental effects on nursing infants have been demonstrated. Approximately 0.05% of a rifampicin dose is excreted into breast milk. Because small quantities of anti-tuberculous drugs in the breast milk generally do not produce toxicity in the breastfed newborn, breastfeeding is not contraindicated while taking standard TB treatment.

Conversely, anti-tuberculous drugs in breast milk should not be considered to serve as effective treatment for disease, or as preventive therapy for a breastfed infant.

Despite ethambutol levels in breast milk being the same as those in maternal serum, its use is still regarded as being compatible with breastfeeding.

Very low amounts of pyrazinamide are transferred in breast milk. Its slow metabolism by neonates adds a theoretical risk of accumulation in the newborn.
17.4.3 Hormonal contraceptives

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 people taking rifampicin or rifabutin, and contraceptive efficacy is lost. This applies to both combined oral contraceptives and progesterone-only pills. The induction of liver enzymes commences six days after the 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.

A method other than oral contraception should be used during rifampicin therapy and for one month after completing rifampicin, even if rifampicin treatment is taken for less than a week. The only effective administered contraceptive with rifamycins is the injectable progesterone, depot medroxyprogesterone acetate. A 12-weekly injection is the standard dosing interval.

The question arises as to whether the frequency of progesterone administration should be changed when rifampicin is being taken. The answer is not clear-cut. The prevailing recommendation to reduce the dosing interval to every 10 weeks (one source says every eight weeks) in females taking rifampicin, is only level III. We are not aware of any reported series of cases which document contraception failure with the standard dose interval and concurrent use of rifampicin. The UK product data sheet from the manufacturer does not advocate changing the dose interval.

In conclusion, it seems safer to reduce the dose interval of medroxyprogesterone from 12 to 10 weeks when rifampicin is also being taken. If medroxyprogesterone is not given, barrier-method contraceptive devices may be also be used (such as condoms), possibly in combination with a spermicidal agent.

* Rifabutin is a less potent enzyme inducer than rifampicin.
17.5 Tuberculosis in children*

17.5.1 Clinical differences from adult TB

The basic principles of TB and its treatment in children are essentially the same as those for adults. The three clinically important differences are as follows.

1 TB in children is usually an immediate complication of primary infection. A closed caseous lesion usually occurs which has relatively few mycobacteria. Open cavities are rare in children. Thus, infectious TB in a child is most unusual, and the prevalence of tuberculous infection in children is related to the number of smear-positive adults in the community.21

2 As the probability of acquiring drug resistance is proportional to the size of the bacillary population, children are considered to be at low risk of development of acquired drug resistance during treatment.

3 The risk of developing extra-pulmonary disease, particularly miliary or meningeal TB, is greater than in adults. TB in children aged under four years is more likely to disseminate and to be fatal. Therefore childhood TB requires prompt and vigorous treatment.22 23

17.5.2 Management in infants and children

Children should be managed in essentially the same way as adults, using appropriately adjusted doses of the drugs. The regimen for most forms of TB is the same as in adults, with six months’ minimum therapy. Primary intra-thoracic TB (parenchymal infiltrate, hilar adenopathy, or both) should be treated in the same way as pulmonary TB in adults. Longer durations are recommended for children with miliary, meningeal and bone and joint disease (9–12 months). Shorter duration may be adequate, but the data are currently inadequate to support this.

Limited data are available for intermittent regimens in children, but experience suggests they are equally efficacious in children and adults.

Due to multiple medications and limited preparations available, medication-taking can be difficult in children. This should be worked through carefully with close supervision from a public health nurse.

17.5.3 Management of neonates

Congenital TB is rare, with around 300 case reports in the literature. During pregnancy the spread of disease to the foetus is more likely to occur in women with disseminated disease than in women with pulmonary TB. Infants born to mothers with TB are not contagious and do not need isolation.

The stage of the mother’s TB at the time of delivery determines the appropriate management of the neonate.

* Most of section 17.5 was prepared by Dr Lesley Voss, Paediatrician, Starship Children’s Hospital, Auckland.
Mother with latent TB infection but no disease

There is no risk to the neonate and treatment or prophylaxis is not required. Household contacts should be evaluated for an infectious case.

Mother with active pulmonary TB

The newborn infant should be:
- assessed for congenital TB, and, if there is no evidence of this,
- started immediately on isoniazid prophylaxis, and
- carefully followed for the development of signs or symptoms of TB.

Separation from the mother is not required, although sleeping in the same room should be avoided. Breastfeeding can occur but precautions should be taken to guard against respiratory transmission. Separation of the infant from the mother should occur if multi-drug-resistant-TB is present.

A Mantoux skin test is placed after three months. BCG vaccination should be withheld until the infant is cleared of TB.

Mother with extra-pulmonary TB disease (excluding laryngeal disease)

The newborn is at no risk and does not need prophylaxis. Infants of mothers with disseminated TB during pregnancy should be evaluated for evidence of congenital TB.

17.5.4 Basic principles of treating TB in children

The basic principles of drug treatment of TB in children are essentially the same as those for adults. The two main differences are:
- due to different pharmacokinetics, children tolerate large doses of drugs/kg and are less likely to develop side-effects than adults
- lack of specific drug formulations for children can result in difficulties with administering medication\(^2\)\(^2\)\(^3\)

17.5.5 Drug preparations

TB medications are primarily formulated for adults, so crushed tablets and unstandardised suspensions may need to be used in children.

It is preferable to initiate treatment with crushed tablets and proprietary suspensions (rifampicin) before considering the use of non-proprietary suspensions. Tablets can be crushed and given mixed in small amounts of syrup or food as long as the child takes the entire amount. The majority of children will tolerate medication given this way.
Non-proprietary suspensions

These are prepared extemporaneously for multiple use, are based on non-validated formulae, and use non-funded excipients. They have a limited period before expiry, and the exact period will not be known.

These suspensions should rarely be needed. Occasionally they may need to be used in the very young or a child receiving medication via a naso-gastric tube. Rifampicin, isoniazid and pyrazinamide should never be put in a suspension together because the rifampicin becomes unstable.

Products containing vitamin C should be used with caution if added to any suspensions as it may reduce the concentration of the anti-tuberculous drug. Reduced serum levels have also been found when giving isoniazid suspension with apple sauce.

In the young child there can be considerable difficulties with the taking of multiple medications. Trained people experienced in this should be involved with the family early to resolve these issues. If it is not dealt with early and adequately, significant delays and interruptions in therapy can result which may effect the adequacy of treatment.

17.5.6 Pyridoxine

Most children do not require pyridoxine supplementation, as isoniazid peripheral neuritis is rare in children. Pyridoxine (25–50 mg/day) should be given to any:
- breastfeeding infant
- adolescent (rapidly growing)
- malnourished individual
- children with inadequate dietary intake (eg, meat- or milk-deficient diets)
- breastfed infants whose mother is taking isoniazid
- children who develop paraesthesiae.

17.5.7 Monitoring

Monitoring disease progression.

As sputum is generally not available in children or is smear-negative, bacteriology has little role in follow-up during treatment. Clinical and radiological follow-up are the mainstays of evaluating response to treatment. Radiological changes usually require longer than six months to resolve, and a normal CXR is not a necessary criterion for discontinuing anti-tuberculous medication. (This is also true for adults.)

Monitoring drug side-effects

Side-effects from anti-tuberculous medicines are uncommon in children. Transiently elevated liver transaminase levels occur in 3–10% of children but the risk of developing hepatotoxicity is very low (< 1%). Liver function tests can be considered at initiation of therapy, but routine biochemical monitoring is not required. Monitoring clinical symptoms and signs of hepatotoxicity is the only follow-up required.
In children there is no correlation between acetylation rate and either efficacy or adverse reactions with isoniazid.\textsuperscript{26} Ethambutol should be avoided in the young child due to difficulties in monitoring ocular toxicity. Ocular toxicity in children has not been reported with an ethambutol dose of 15 mg/kg/day.\textsuperscript{27}
References

Chapter 18: Tuberculosis and HIV Infection

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This chapter is endorsed by the Thoracic Society of Australia and New Zealand

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Summary

Epidemiology

- Human immunodeficiency virus (HIV) is the single greatest risk factor for the development of TB.
- TB is the commonest opportunistic infection of people infected with HIV.
- The UNAIDS/WHO estimates that there were 5 million new HIV infections in 2001, with 40 million people living with HIV worldwide. It is estimated that one-third of these are also infected with *M. tuberculosis*.
- HIV is spreading faster in the Asian region than in any other part of the world.
- New Zealand has relatively low rates of HIV infection. HIV-positive people here remain at high risk of TB if they are latently infected with *M. tuberculosis* or are contacts of infectious cases. Until the end of December 2001 there have been 1742 people in New Zealand found to be infected with the HIV virus.
- The proportion of HIV-infected people in New Zealand who have also been infected with *M. tuberculosis* is not known. A small but increasing number of people with HIV/TB co-infection has been documented in Auckland.
- Data on TB status of HIV-infected people are not routinely collected. The proportion of people with TB disease or latent TB infection who have HIV is also not known. Data collection methods that do not intrude on patient privacy are needed in New Zealand.

TB/HIV co-infection: immunopathology

- The CD4+ lymphocyte is a key component of host defence against TB. Stimulatory signals from CD4+ lymphocytes activate TB-infected macrophages to limit intra-cellular replication of *M. tuberculosis*.
- The CD4+ lymphocyte is also the target of the HIV virus, becoming infected and ultimately destroyed by the virus.
- With progression of HIV infection, CD4+ lymphocytes are depleted, which results in a weakened response to *M. tuberculosis*. 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. There is increased viral multiplication and an accelerated course of HIV infection in those with active TB.

HIV/TB co-infection: clinical aspects

**HIV testing in TB**

- TB is an important indicator illness for HIV infection, and each disease affects the clinical course of the other.
- An HIV test should be strongly considered for every patient with TB.

**Susceptibility**

- Reports of nosocomial outbreaks of TB among HIV-positive patients show that HIV infection leads to much greater susceptibility to TB infection progressing to disease.
Infection control processes must be rigorously applied in settings where HIV-infected people may come into contact with infectious TB cases.

Clinical presentation

- Maintain 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 immunosuppression.
- With normal or moderately reduced CD4+ counts the presentation is more typical, with pulmonary disease likely, including an upper lobe distribution and possibly also cavity formation. (The atypical TB features on CXR found in advanced HIV are shown in the full text.)
- With increasing immunosuppression, particularly when the CD4+ lymphocyte count falls below 200 cells/mm³, the clinical presentation becomes less typical. Pulmonary manifestations alter and extra-pulmonary TB becomes more common, either concurrently with pulmonary disease or in isolation.
- Tuberculin reactivity is lost as immunodeficiency progresses, due to the loss of an effective delayed-type hypersensitivity response to mycobacterial antigens. A negative Mantoux should not stop active investigation of patients for possible TB.
- TB should be considered in any HIV-infected person with respiratory tract symptoms.
- Abdominal TB can be particularly difficult to diagnose, and at low CD4+ counts it tends to manifest with visceral involvement and adenopathy rather than the peritoneal TB typically seen in HIV-negative patients.
- Every effort should be made to prove the diagnosis unequivocally: culture and susceptibility results are essential.

Infectivity

- Infectious patients should be appropriately isolated. The same guidelines apply as for HIV-negative infectious cases (see Chapter 9: ‘Infection Control’).
- There is no evidence that HIV-positive cases are more infectious to their contacts than HIV-negative cases.

Treatment of TB in HIV

Drug regimens

- The drug treatment of TB in the context of HIV infection applies the same basic approach as in HIV-negative individuals.
- Treatment regimens outlined in Chapter 16: ‘Treatment of Tuberculosis’ are applicable, but may need to be modified if concurrent anti-retroviral medication is taken (see below).

Duration of therapy

- Six-month regimens are appropriate for fully sensitive, non-extensive pulmonary disease.
Many authorities advocate giving consideration to longer treatment duration in HIV-positive patients, particularly if there is extensive disease or a slow response to treatment. This approach is recommended by the Ministry of Health’s Tuberculosis Working Group.

**Daily vs intermittent dosing / self-administration vs DOT**

- Intermittent dosing of TB drugs has been shown to be as effective as daily therapy in HIV-positive cases.
- The decision regarding directly observed therapy (DOT) versus self-administration should be based on an assessment of compliance and comprehension rather than HIV status.
- Consider DOT for any patient receiving complex anti-retroviral therapy regimens, to reduce the number of medications the patient must assume direct responsibility for administering. Avoiding missed doses of TB treatment is paramount.

**Anti-retroviral therapy and TB treatment**

- Highly active anti-retroviral therapy (HAART) consists of combination therapy with at least three anti-retroviral agents, usually with a ‘backbone’ of two nucleoside analogue viral reverse transcriptase inhibitor (NA) drugs combined with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). Some HAART combinations consist of three NA-class drugs.
- HAART aims to suppress HIV replication, with a subsequent recovery in CD4+ lymphocyte count. This form of therapy has dramatically altered the natural history of HIV infection, with a reduction in the frequency of opportunistic infections and a decline in rates of death from AIDS.
- The key issue with respect to TB is the occurrence of 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 > rifabutin).
- The net result of co-administration is a reduction in the serum level of the anti-viral agent. Allow two to three weeks after discontinuation of rifampicin before potentially interacting anti-virals are commenced, because of the risk of persisting enzyme induction.
- Protease inhibitors in turn lead to reduced metabolism of rifabutin, resulting in significantly increased serum rifabutin levels with a potential increase in toxicity (eg, uveitis).

**Ensuring adequate TB treatment and adequate anti-viral treatment in co-infection**

- Of paramount importance in the co-infected patient is appropriate, adequate treatment of TB. An algorithm that summarises current recommendations regarding the concurrent use of rifamycins, PI and NNRTI drugs in use in New Zealand is given in Figure 18.2.
- There are no significant drug–drug interactions between the nucleoside analogue agents and the rifamycins. This means that the three NA drug HAART combination of AZT/3TC/Abacavir is an attractive option to combine with a rifamycin-containing TB regimen when anti-viral treatment is indicated.
- Ritonavir and RTV/SQV combination are compatible with rifampicin use. Clinical experience with this combination is limited, and some caution is required.
Rifabutin levels are increased by all PIs and dose reduction is required as indicated in Figure 18.2 to avoid toxicity. Careful clinical monitoring of the patient is also mandatory.

The easiest combination when using rifamycins is the 3NA regimen mentioned above. Rifampicin and rifabutin may be used cautiously with PI and NNRTI agents. Careful follow-up is required, with attention given to both TB response and HIV suppression.

Due to the complexity and potential adverse effects of both HAART and anti-tuberculous treatment regimens it is recommended, where possible, to delay starting HAART during the intensive phase of TB treatment.

Paradoxical reactions during therapy and TB-related immune reconstitution syndrome

These are discussed in the full text.

Drug-resistant TB in HIV infection

Treatment of drug-resistant TB in HIV-infected patients applies the same principles as in non-HIV-infected people (see Chapter 16: ‘Treatment of Tuberculosis’).

There is no compelling evidence that HIV infection is intrinsically a risk factor for drug-resistant disease. A higher than expected rate of rifampicin mono-resistance has been noted by some investigators in HIV-infected individuals.

With multi-drug-resistant TB in HIV, outcomes may be improved by HAART and immune reconstitution but there are no data available to confirm this.

Prevention of TB in HIV-infected patients

Screening for latent TB infection (LTBI) in HIV

HIV is the single greatest risk factor for the development of reactivation TB, so screening for LTBI should form part of the evaluation of all HIV-infected individuals.

A Mantoux test should be performed in all HIV-positive individuals.

Preventive treatment for LTBI should be given to HIV-positive patients with:
- Mantoux ≥ 5 mm
- previously documented positive Mantoux and no prior LTBI treatment
- minor/slight CXR abnormalities consistent with old TB (note: consider the need for full preventive treatment – see below)
- documented recent exposure to a smear-positive case.

Investigation of inactive pulmonary TB

All patients should have a CXR when HIV is diagnosed, unless a very recent film is available.

If the CXR shows change consistent with prior, inactive TB, investigations are needed to exclude active disease. These include induced sputum or bronchoscopy if the patient has little or no spontaneous sputum.

If microbiological tests show no evidence of active disease they should be considered for preventive treatment (see Chapter 16: ‘Treatment of Tuberculosis’).
Treatment of LTBI in HIV infection

- The efficacy of treatment of LTBI in HIV-infected people has been proven in a number of placebo-controlled trials.
- Current recommendations for drug regimens for LTBI with HIV are 9H or 2RZ:*
  - The 9H regimen has no relevant interactions and can be introduced after HAART is established if desired.
  - 2Rifabutin/Z is suggested as an alternative to 2RZ if PI or NNRTI anti-retrovirals are being used. There are no specific data on efficacy of this regimen.
- See Figure 18.2 for recommended dose adjustments when combining rifamycins with PI/NNRTI drugs, which also apply in this situation.
- The RZ combination must be carefully monitored in light of recent fatalities with this combination (see Chapter 3: ‘Latent Tuberculosis Infection’). If the 2RZ regimen is selected, anti-retroviral therapy can usually be safely delayed until LTBI therapy is completed, avoiding the HAART/rifamycin interaction issues described above.
- As mentioned above, allow two to three weeks after stopping rifampicin before potentially interacting anti-virals are commenced.

BCG vaccination in HIV infection

- In the absence of proven benefit, the Ministry of Health’s Tuberculosis Working Group considers that BCG cannot be recommended in any HIV-infected people.

Non-tuberculous mycobacterial infection

- Patients with HIV infection are susceptible to infection with a number of non-tuberculous mycobacteria.
- Disseminated *Mycobacterium avium intracellulare* complex (MAIC) infections occur late in the course of HIV infection when there is profound immunodeficiency, with CD4 counts below 100 cells/mm³ and more usually less than 50 cells/mm³.
- Typically MAIC presents as a febrile illness with high swinging fever and sweats. Anaemia and deranged liver enzyme tests are common and reflect the disseminated nature of the infection.
- Diagnosis of disseminated MAIC is confirmed by culturing the organism from blood or bone marrow. MAIC is also sometimes cultured from sputum and can be responsible for sputum acid-fast bacilli (AFB) smear-positivity in HIV-positive patients. Pulmonary MAIC in HIV may occur without dissemination, and culture-positivity commonly represents colonisation rather than overt disease requiring treatment.
- Smear-positive sputum should never be assumed to be due to MAIC. Appropriate isolation and anti-tuberculous therapy must be initiated until the organism is identified.

Future developments

- Measures should be promoted to increase the rate of testing for TB infection in HIV-infected people, and vice-versa.

* H = isoniazid; R = rifampicin; Z = pyrazinamide.
A project should be commissioned to examine the options for surveillance of co-infection.
Introduction

The management of HIV and TB co-infection is complex, and this chapter is designed to provide a broad overview of the field. The information contained elsewhere in these guidelines is largely applicable to the HIV-infected patient, but there are certain issues unique to this population which warrant special attention.

The chapter will provide 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 when anti-retroviral therapy is used concurrently with anti-tuberculous 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.

A number of review articles and guidelines have been published on this topic, and the reader’s attention is drawn to these for additional detail.1-5
18.1 Epidemiology

18.1.1 The world

Human immunodeficiency virus (HIV) is the single greatest risk factor for the development of TB. It is estimated that 40 million people in the world are infected with HIV, and the majority live in regions with high rates of TB.6–7

The HIV epidemic has compounded the worldwide problem of TB, which is the commonest opportunistic infection of people infected with HIV. In areas with access to contemporary anti-retroviral therapy, HIV/TB co-infection adds an additional level of complexity to the management of both conditions.

The HIV epidemic continues to expand, and despite some significant public health advances in some of the hardest-hit countries, new infections continue at an alarming rate. The UNAIDS/WHO estimates that there were 5 million new infections in 2001, with 40 million people living with HIV worldwide. It is estimated that one-third of these are also infected with *M. tuberculosis*.6–7

In the Asia–Pacific region there are thought to be some 7 million HIV-infected people, with over 1 million new infections in the region last year. Rates of new infection are particularly high in India and South East Asian countries such as Vietnam and Cambodia, with heterosexual sex being the commonest mode of transmission. Rates of TB are also high in these countries, and up to 2 million people may be co-infected. HIV is spreading faster in the Asian region than in any other in the world and the resulting potential for a public health disaster in these areas is obvious. The proximity of these regions to our own should not be forgotten.

18.1.2 New Zealand

New Zealand has relatively low rates of HIV infection compared to 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 when the HIV epidemic began until the end of December 2001 there have been 1742 people in New Zealand found to be infected with the HIV virus.8

The experience of the Auckland Hospital Infectious Diseases Unit, which sees around 45% of New Zealand HIV cases, illustrates that the number of people seen with co-infection is increasing (see Table 18.1).

Table 18.1: Number of patients with HIV and TB, Auckland Hospital Infectious Diseases Unit, 1985–2001

<table>
<thead>
<tr>
<th>Period</th>
<th>HIV/TB co-infection</th>
<th>HIV but not TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>1985–95</td>
<td>7</td>
<td>413</td>
</tr>
<tr>
<td>1996–2001</td>
<td>25</td>
<td>360</td>
</tr>
</tbody>
</table>

Note: odds ratio = 4.1 (95% CI 1.6–10.5). p = 0.0008.
In the six years since the original 11-year experience of that unit was published, an additional 385 patients have been cared for with a significant increase in the proportion diagnosed with TB. The majority of these individuals were born outside New Zealand, mostly in parts of the world with high rates of TB (Table 18.2).

Table 18.2: HIV/TB co-infection, by region of birth, Auckland Hospital Infectious Diseases Unit, 1996–2001

<table>
<thead>
<tr>
<th>Region of birth</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>9</td>
</tr>
<tr>
<td>Asia (South and South East)</td>
<td>8</td>
</tr>
<tr>
<td>New Zealand / Australia</td>
<td>6</td>
</tr>
<tr>
<td>South America</td>
<td>1</td>
</tr>
<tr>
<td>Europe</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>25</td>
</tr>
</tbody>
</table>

This trend of increasing numbers of co-infected patients is likely to continue, with ongoing inward migration to New Zealand from parts of the world with high rates of both TB and HIV infection.

18.1.3 Surveillance of TB/HIV co-infection

Surveillance of co-infection is important because of the significant interactions in pathology and treatment between the two infections. The rate of co-infection in New Zealand is unknown. The rate has increased in the UK, principally in London among white and black African people.10

**TB 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,9 the extent of dual testing is not known. Data on TB status of HIV-infected people are not routinely collected. Although the AIDS notification form collects data on opportunistic infections, it is likely to represent under-reporting of TB/HIV co-infection because Mantoux status is not specifically sought and TB disease may present after AIDS notification.

**HIV infection rates in people with TB**

The proportion of people with TB disease or latent TB infection who have HIV is not known because the TB Case Report Form does not collect information on HIV status.

**Options for surveillance of co-infection**

Since HIV-positive people are very concerned about breaches of their privacy, and HIV and AIDS surveillance is currently anonymised, adding HIV status to the TB Case Report Form is not feasible without discussion and consultation. Surveillance without resort to collection of named data would be preferable.
Co-infection surveillance could, perhaps, be achieved by adding TB status information to the HIV surveillance system which the AIDS epidemiology unit conducts with clinicians. The advantages of this would be to keep the number of doctors treating HIV low, and the testing (detection) rate for HIV high. Thus we would effectively have a co-infection register.

Data matching (with appropriate ethical review) between registers may be a feasible option. By matching codes in the AIDS epidemiology unit’s HIV database to those in the TB part of EpiSurv it may be possible to estimate co-infection rates. However, the result would be an underestimate, for a range of reasons. Matching of Florida AIDS and TB registries found that only 83% of co-infected people had been reported to the AIDS registry as having TB, and that 11.5% of co-infected patients on the AIDS registry had not been notified to the TB registry.\textsuperscript{11}

An alternative would be to ask public health offices to complete an HIV field in the TB case report form by resort to the clinical letters which the public health office receives from the TB clinician. However, that approach would be prone to procedural failure and therefore missing data. It would also be tantamount to creating a named HIV register (although it may be legal).

There are many issues to work through, and a project should be commissioned to examine the options for surveillance of co-infection.
18.2 TB/HIV co-infection: immunopathology

HIV infection results in progressive immunodeficiency in the majority of infected people. One of the components of host immunity critical to defence from TB is the CD4+ lymphocyte (see also Chapter 15: ‘M. tuberculosis, Medicines and Monitoring’ section 15.1). Antigen-specific type 1 CD4+ T helper lymphocytes provide stimulatory signals (eg, the cytokine gamma-interferon) which activate TB-infected macrophages to limit intra-cellular replication of M. tuberculosis. These cells are also the target of the HIV virus, becoming infected and 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 immunodeficiency in HIV-positive patients, and clinical features of TB in HIV infection correlate to a degree with CD4+ count12 (see below).

Conversely, the natural history of HIV infection is also altered by TB.113–15 In studies of TB/HIV co-infection in environments without effective anti-viral therapy, higher rates of death were seen in those with co-infection. This observation held not only during but also after successful treatment of TB. 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.1415

HIV viral load is observed to rise 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.16–18 The inflammatory cytokines tumour necrosis factor alpha (TNF-α) 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.1718 It is speculated that these pro-inflammatory cytokines lead to an increase in viral replication and a subsequent decline in CD4+ lymphocyte count.
18.3 HIV/TB co-infection: clinical aspects

18.3.1 HIV testing in TB

TB is an important indicator illness for HIV infection and an HIV test should be strongly considered for every patient with TB. The threshold for testing should be low because classical risk factors may not be identified. HIV testing is not being universally applied in TB, and a study in the US noted that around 5% of cases of TB/HIV co-infection were missed because heterosexual transmission was not considered a relevant risk factor for HIV infection.

Although New Zealand has relatively low rates of HIV infection, this should not lead to complacency and HIV testing should be done on all adult patients with active TB. (See also Chapter 14: ‘Clinical Investigation and Assessment of Tuberculosis’, section 14.1.9.)

18.3.2 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. 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.

These observations support the following recommendation.

<table>
<thead>
<tr>
<th>Practice point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection control processes must be rigorously applied in settings where HIV-infected people may come into contact with infectious TB cases.</td>
</tr>
</tbody>
</table>

18.3.3 Clinical presentation

*Maintain 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 immunosuppression (see Figure 18.1).

With normal or moderately reduced CD4+ counts the presentation is more ‘typical’, with pulmonary disease likely and radiological findings including an upper lobe distribution and cavity formation. With increasing immunosuppression, particularly when the CD4+ lymphocyte count falls below 200 cells/mm³, the clinical presentation becomes less typical. Pulmonary manifestations alter and extra-pulmonary TB becomes more common, either concurrently with pulmonary disease or in isolation. The CXR may show lower zone infiltrates and unilateral or diffuse bilateral shadowing, and may even be normal despite culture-positive sputum.

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 the HIV-negative cases.

In summary, the range of CXR findings in TB that may be encountered in advanced HIV infection include:

- hilar and mediastinal adenopathy plus localised parenchymal shadowing
- diffuse shadowing, usually bilateral
- localised coarse nodular opacities
- miliary pattern
- pleural effusion
- normal CXR
- absence of cavities
- rapid progression if untreated
- radiological deterioration on treatment.

These types of presentation in the severely immuno-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 (DTH) response.

Tuberculin reactivity is lost as immunodeficiency progresses, once again due to the loss of an effective DTH response to mycobacterial antigens. A negative Mantoux should not stop active investigation of patients for possible TB, especially when the CD4+ lymphocyte count is low (see also section 18.5.2).
Figure 18.1: HIV/TB clinical features related to degree of immunosuppression

Features of HIV related TB infection with declining CD4+ lymphocyte count

<table>
<thead>
<tr>
<th>Pattern of disease</th>
<th>TST reactivity</th>
<th>Sputum</th>
<th>Smear</th>
<th>Chest X-ray</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary</td>
<td>+ve</td>
<td>+ve</td>
<td></td>
<td>Upper lobe infiltrates cavities</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pleural effusion</td>
</tr>
<tr>
<td>Higher infectivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Declining CD4+ count</td>
<td></td>
<td></td>
<td></td>
<td>Atypical infiltrates lymphadenopathy normal</td>
</tr>
<tr>
<td>Lower infectivity</td>
<td>-ve</td>
<td>-ve</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>- concurrent pulmonary</td>
<td>-ve</td>
<td>-ve</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- multifocal</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TB should be considered in any HIV-infected person with respiratory tract symptoms. Sputum smears should be examined for acid-fast bacilli (AFB) and sent for mycobacterial culture.

In the 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 particularly difficult to diagnose and at low CD4+ counts it tends to manifest with visceral involvement and adenopathy rather than the peritoneal TB typically seen in HIV-negative patients.27

As with all TB, every effort should be made to prove the diagnosis unequivocally. Culture of the organism should be the ultimate aim of investigations so that the identity can be confirmed and sensitivity testing undertaken.
18.3.4 Infectivity

Infectious patients should be appropriately isolated, and the same guidelines apply as for HIV-negative infectious cases (see Chapter 9: ‘Infection Control’).

A recent meta-analysis has concluded there is no evidence that HIV-positive cases are intrinsically more infectious to their contacts than HIV-negative cases. One recent case control study concluded that in fact the reverse was true, and it may be that transmission from infectious HIV-positive patients is reduced overall because bacillary loads tend to be lower and cavitary disease is less common.

These data do not mean that a lesser degree of infection control or contact tracing is required when dealing with HIV-infected smear-positive cases. At the individual level a smear-positive case represents a risk of transmission, which depends on number of bacilli, cough frequency, etc., rather than the case HIV status.
18.4 Treatment of TB in HIV

18.4.1 Drug treatment: general principles

Drug regimens

The drug treatment of TB in the context of HIV infection applies the same basic approach as in HIV-negative individuals, and the combination regimens outlined in Chapter 16: ‘Treatment of Tuberculosis’ are applicable. They may, however, need to be modified depending on concurrent anti-retroviral medication (see below for information on TB treatment while on highly active anti-retroviral therapy (HAART)).

Duration of therapy

The most recent CDC/ATS guidelines on the treatment of TB in HIV infection recommend that six-month regimens are appropriate for fully sensitive pulmonary disease and point out the absence of evidence to the contrary.\(^2\)

There remains some controversy as to whether short-course rifampicin-containing regimens are as suitable in HIV-infected people due to concerns about relapse.\(^30\) It is worth noting that the studies of six-month TB treatment in HIV infection have been with relatively small numbers of patients, and though not statistically significant there have been observed trends towards higher rates of relapse in the HIV-positive groups.\(^31\)

Many authorities advocate giving consideration to longer treatment duration in HIV-positive patients, particularly if there is extensive disease or a slow response to treatment. This seems a sensible approach,\(^1,5\) and is the one recommended by the Tuberculosis Working Group of the Ministry of Health.

Daily versus intermittent dosing, self-administration versus DOT

Intermittent dosing of TB drugs has been shown to be as effective as daily therapy in HIV-positive cases.\(^1,32\) Some authorities advocate directly observed therapy (DOT) for all cases of HIV-related TB, but this recommendation is heavily influenced by the population group being treated.\(^1\) In New Zealand the decision regarding intermittent or daily DOT versus self-administration should be based on an assessment of compliance and comprehension rather than HIV status (see Chapter 4: ‘Adherence to Treatment’, and Chapter 5: ‘Directly Observed Therapy’).

It is worth considering DOT for any patient receiving complex anti-retroviral therapy regimens in order to reduce the number of medications the patient must assume direct responsibility for administering. Study of HAART regimens has confirmed the relationship between pill burden and missed doses, and avoiding missed doses of anti-tuberculous drugs is paramount.
18.4.2 Anti-retroviral therapy and TB treatment

**Highly active anti-retroviral therapy (HAART)**

*Definition*

HAART consists of combination therapy with at least three anti-retroviral agents, usually with a ‘backbone’ of two nucleoside analogue viral reverse transcriptase inhibitor (NA) drugs combined with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). Some HAART combinations consist of three NA-class drugs.33

*Efficacy of HAART*

The development of HAART has dramatically altered the natural history of HIV infection, with a reduction in the frequency of opportunistic infections and a decline in rates of death from AIDS.34 35 Suppression of HIV replication with a subsequent recovery in CD4+ lymphocyte count is the aim of HAART, and is achieved, at least initially, in the majority of recipients of this treatment.

The natural history of HIV/TB co-infection in the HAART era has not been studied in the same detail as in untreated HIV infection, but early evidence suggests that effective viral suppression and immune reconstitution will impact favourably and reduce the incidence of reactivation disease and new infection.36–38

*Issues with HAART and TB treatment*

The key issue of HAART with respect to 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 potentially interacting anti-virals are commenced, because of the risk of persisting enzyme induction.

Protease inhibitors in turn lead to reduced metabolism of rifabutin, resulting in significantly increased serum rifabutin levels with a potential increase in toxicity (eg, uveitis).33 39
Ensuring adequate TB treatment and adequate anti-viral treatment in co-infection

Of paramount importance in the co-infected patient is appropriate, adequate treatment of TB. Decisions regarding anti-retroviral therapy must also be made, and Figure 18.2 presents an algorithm which addresses the issues that need to be considered.

Figure 18.2: TB treatment decisions in HIV co-infection

It is worth noting that there are no significant drug–drug interactions between the nucleoside analogue agents and the rifamycins. This means that the three NA-drug HAART combination of AZT/3TC/Abacavir is an attractive option to combine with a rifamycin-containing TB regimen when anti-viral treatment is indicated.

Table 18.3 summarises current recommendations regarding the concurrent use of rifamycins and PI and NNRTI drugs in use in New Zealand, but there are two points worth noting.

- The recommendation that ritonavir and RTV/SQV combination are compatible with rifampicin use is recent and revises the Centers for Disease Control guidelines from 1998. Clinical experience with this combination is limited and some caution is required.
There also remains debate in the literature and in practice regarding combining rifabutin with protease inhibitors. Some authors recommend monitoring serum trough PI levels when this combination is used, but this is not routinely available in New Zealand and the interpretation of such data is difficult. Rifabutin levels are increased by all PIs and dose reduction is required, as indicated in Table 18.3, to avoid toxicity. Careful clinical monitoring of the patient is also mandatory.

At a pragmatic level the easiest combination when using rifamycins is the 3NA regimen mentioned above. Rifampicin and rifabutin may be used cautiously with PI and NNRTI agents using the guidelines (as indicated below), but careful follow-up is required with attention to both TB response and HIV suppression.

Due to the complexity and potential adverse effects of both HAART and anti-tuberculous treatment regimens, it is recommended, where possible, to delay starting HAART during the intensive phase of TB treatment. Starting both treatments simultaneously is associated with high rates of HAART and TB treatment discontinuation due to adverse effects.

Table 18.3: Summary of recommendations for the use of PI and NNRTI anti-retrovirals with rifamycins

<table>
<thead>
<tr>
<th>Protease inhibitor</th>
<th>NNRTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indinavir (IDV)</td>
<td>Nelfinavir (NFV)</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampicin (R)</td>
<td>Usual dose = 600mg daily or 2 x weekly</td>
</tr>
<tr>
<td></td>
<td>✗ NR</td>
</tr>
<tr>
<td></td>
<td>IDV levels markedly reduced (p&lt;0.02)</td>
</tr>
<tr>
<td>Rifabutin (Rb)</td>
<td>Usual dose = 300 mg daily or 2x weekly</td>
</tr>
<tr>
<td></td>
<td>✗ Possible</td>
</tr>
<tr>
<td></td>
<td>Reduce Rb dose to 150 mg daily or 300 mg 2 x weekly</td>
</tr>
<tr>
<td></td>
<td>✗ Possible</td>
</tr>
<tr>
<td></td>
<td>Reduce Rb dose to 150 mg 2-3 x weekly</td>
</tr>
<tr>
<td></td>
<td>✗ Possible</td>
</tr>
<tr>
<td></td>
<td>Increase Rb dose to 450 mg daily</td>
</tr>
</tbody>
</table>

Notes: The table above applies to HAART regimens that consist of a 2NA ‘backbone’ plus one of the above. There are no relevant data pertaining to PI/NNRTI combinations.

✘ NR = not recommended
18.4.3 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-tuberculous chemotherapy.\(^1\)\(^5\)\(^3\)\(^4\) 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 (see also Chapter 15: ‘\textit{M. tuberculosis}, Medicines and Monitoring’, section 15.7.4). Estimates of frequency range between 7% and 36%, and the highest incidence has been seen in patients receiving anti-retroviral therapy.\(^4\)\(^4\) This is consistent with the proposed mechanism for the phenomenon, which is that paradoxical reactions are caused by an improved host response to mycobacterial antigens, a situation enhanced by CD4+ lymphocyte recovery and immune reconstitution.\(^4\)

Clinically, in HIV-positive patients, 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.\(^4\)\(^4\)\(^5\)

In general, paradoxical reactions are self-limited and last between 10 and 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.\(^3\)\(^4\)\(^4\)\(^5\)

18.4.4 TB-related immune reconstitution syndrome

Reconstitution syndromes are a group of disorders that can occur during HAART 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 \textit{Mycobacterium avium intracellulare} complex (MAIC) and cytomegalovirus, but can also occur with TB.\(^3\)\(^3\)

TB-related immune reconstitution syndrome may manifest as lymphadenitis or pneumonitis, typically with low bacillary numbers. The clinical approach remains to confirm the diagnosis and initiate anti-tuberculous treatment, applying the principles outlined above for the treatment of TB in patients receiving HAART. Anti-inflammatory agents or corticosteroids may be required to control troublesome inflammatory symptoms.\(^3\)\(^3\)

18.4.5 Drug-resistant TB in HIV infection

Treatment of drug-resistant TB in HIV-infected patients applies the same principles as in non-HIV-infected people (see Chapter 16: ‘Treatment of Tuberculosis’). Well-documented outbreaks of multi-drug-resistant disease among HIV-infected people have highlighted the difficulties of treating this group with drug-resistant isolates.\(^2\)\(^3\)
There is no compelling evidence that HIV infection is intrinsically a risk factor for drug-resistant disease, but 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 immunosuppression and non-compliance.\textsuperscript{46,47}

With multi-drug-resistant TB in HIV, outcomes may be improved by HAART and immune reconstitution, but there are no data available to confirm this as yet.
18.5  Prevention of TB in HIV-infected patients

18.5.1  Co-ordination of control measures

TB prevention should be a key component of the care of HIV-infected patients.\(^2\)\(^{,33}\) Identification of latent infection, treatment of LTBI and prevention of severe immunodeficiency by the appropriate use of HAART are all strategies that might be expected to reduce the mortality and morbidity of HIV-associated TB.\(^1\)

Reducing acquisition of new TB infection by HIV-positive patients will depend on the public health and hospital infection control measures outlined elsewhere in this publication. In districts where HIV and TB are managed by different services, close collaboration is required if these problems are to be managed in a consistent way.

18.5.2  Screening for latent TB infection (LTBI) in HIV

HIV is the single greatest risk factor for the development of reactivation TB, so screening for LTBI should form part of the evaluation of all HIV-infected individuals. A Mantoux test should be performed in all HIV-positive individuals.

Induration of 5 mm or greater in response to a standard 5 TU purified protein derivative (PPD) test, irrespective of prior Bacillus Calmette-Guerin (BCG) vaccination status, should be regarded as positive in this population (see Chapter 2: ‘Mantoux Testing’), and in view of the high risk of developing disease, preventive treatment should be offered.\(^1\)\(^,2\)\(^,3\)\(^,33\)\(^,48\) A previously documented positive Mantoux with no record of preventive therapy is also an indication for treatment.

With increasing immunodeficiency the likelihood of a negative Mantoux increases due to impaired DTH response, but anergy testing is no longer recommended as an adjunct to Mantoux testing.\(^2\) 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.\(^2\)\(^,49\)

A CXR may show changes consistent with prior TB (see Chapter 14: ‘Clinical Investigation and Assessment of Tuberculosis’). Such individuals should be investigated to exclude active disease, including induced sputum or bronchoscopy if necessary. If there is no evidence of active disease they should be considered for preventive treatment irrespective of the Mantoux result. There are no systematic data evaluating either of these approaches.

Practice points

In summary, preventive treatment for LTBI should be given to HIV-positive patients with:

1. Mantoux ≥ 5 mm
2. previously documented positive Mantoux and no prior LTBI treatment
3. minor/slight CXR abnormalities consistent with old TB (note: you may need to consider full preventive treatment – see below)
4. documented recent exposure to a smear-positive case.
18.5.3 Investigation of inactive pulmonary TB

All patients should have a CXR when HIV is diagnosed, unless a very recent film is available. 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 14: ‘Clinical Investigation and Assessment of Tuberculosis’). Such individuals 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 (see Chapter 16: ‘Treatment of Tuberculosis’).

18.5.4 Treatment of LTBI in HIV infection

The efficacy of treatment of LTBI in HIV-infected people has been proven in a number of placebo-controlled trials. Regimens studied include 6H, 12H, 3RH and 3RHZ. In addition, the short-course regimen of 2RZ has been shown to be as effective as 12H. A recent systematic review has confirmed the benefit of treating LTBI in the context of HIV infection.

Current recommendations for drug regimens for LTBI with HIV are 9H or 2RZ, but the following should be noted.

- The 9H regimen has no relevant interactions and can be introduced after HAART is established if desired.
- 2Rifabutin/Z is suggested as an alternative to 2RZ if PI or NNRTI anti-retrovirals are being used.
- There are no specific data on efficacy of this regimen, but it is expected to be effective, extrapolating from treatment outcome data.
- The dose adjustments outlined in Table 18.3 when combining rifamycins with PI/NNRTI drugs also apply in this situation.
- The RZ combination must be carefully monitored in light of recent fatalities with this combination (see Chapter 3: ‘Latent Tuberculosis Infection’).

If the 2RZ regimen is selected, anti-retroviral therapy can usually be safely delayed until LTBI therapy is completed, avoiding the HAART–rifamycin interaction issues described above.

Persistence of enzyme induction after stopping rifamycins

As mentioned above in ‘Issues with HAART and TB treatment’ (see section 18.4.2), allow two to three weeks after stopping rifampicin before potentially interacting anti-virals are commenced.

* R = rifampicin; H = isoniazid; Z = pyrazinamide.
18.5.5 BCG vaccination in HIV infection

There are no systematic, prospectively collected data available that address the question of whether vaccination with the live attenuated (BCG) mycobacterium prevents the development of TB in HIV-infected people.\textsuperscript{1} There are multiple reports of adverse infectious complications from BCG in HIV-infected people, ranging from local effects (ulceration, regional lymphadenopathy) to dissemination.\textsuperscript{55} There are no prospective studies addressing the frequency of such adverse events.

The World Health Organization considers ‘BCG should not be given to children who are symptomatic for HIV infection’,\textsuperscript{56} but recommends it for asymptomatic infants in areas of the world with high rates of TB. However, in the absence of proven benefit, the Ministry of Health’s Tuberculosis Working Group considers that the use of BCG cannot be recommended in any HIV-infected people.
18.6 Non-tuberculous mycobacterial infection

Non-tuberculous mycobacteria are discussed in detail in Chapter 19. Patients with HIV infection are susceptible to infection from a number of non-tuberculous mycobacteria.

Disseminated *Mycobacterium avium intracellulare* complex (MAIC) infection occurs late in the course of HIV infection, when there is profound immunodeficiency with CD4 counts below 100 cells/mm$^3$ and more usually less than 50 cells/mm$^3$. Typically MAIC presents as a febrile illness with high swinging fever and sweats. Anaemia and deranged liver enzyme tests are common and reflect the disseminated nature of the infection.

Diagnosis of disseminated MAIC is confirmed by culturing the organism from blood or bone marrow (see Chapter 14: ‘Clinical Investigation and Assessment of Tuberculosis’, section 14.1.8). MAIC is also sometimes cultured from sputum and can be responsible for sputum AFB smear-positivity in HIV-positive patients.

Pulmonary MAIC in HIV may occur without dissemination, and culture-positivity commonly represents colonisation rather than overt disease requiring treatment. Smear-positive sputum should never be assumed to be due to MAIC, though, and appropriate isolation and anti-tuberculous therapy must be initiated until the organism is identified.
18.7 Future developments

The accumulation of data relating to outcomes of TB/HIV co-infection in the era of HAART will be of interest over the next few years.

Experience of the use of rifamycin drugs together with anti-retrovirals with potential interactions will continue to accumulate and may result in further modification of current recommendations.

Better access to anti-retroviral drugs in the developing world is desperately needed. All measures, including public health measures that contain the spread of the HIV epidemic, will have a favourable impact on TB infection.

Measures should be promoted to increase the rate of testing for TB infection in HIV-infected people and vice-versa.

A project should be commissioned to examine the options for surveillance of co-infection.
References


Chapter 18: Tuberculosis and HIV Infection


57 http://www.who.int/vaccines-diseases/diseases/HIV.shtml
Chapter 19: Non-Tuberculous Mycobacteria

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Respiratory Physician, Green Lane Hospital, Auckland

This chapter is endorsed by the Thoracic Society of Australia and New Zealand

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19.5.7 NTM that rarely cause human disease

19.5.8 Prognosis and referral

19.6 Future developments

References
Summary

Many species of mycobacteria other than *M. tuberculosis* complex are recognised human pathogens. The spectrum of disease caused by non-tuberculous mycobacteria (NTM) is wide and overlaps with that caused by *M. tuberculosis*. NTM and the sites where they cause disease are shown in Table 19.1.

Besides an overlap of disease spectrum with *M. tuberculosis*, infection with NTM may also give rise to positive acid-fast bacilli (AFB) smears and histopathology findings similar to those found in TB. However, the treatment and public health implications of NTM disease are very different from those of *M. tuberculosis*.

Epidemiology

Most NTM are isolated from water and soil, but some are isolated from other sources such as house dust.

Environmental sources, especially natural waters, are the reservoir for most human infections of *M. avium* complex (MAC). The aerosolisation of water may be an important means of transmission. Animal-to-human transmission is not important in human disease.

Rapidly growing mycobacteria such as *M. fortuitum*, *M. chelonae* and *M. abscessus* can be readily recovered from soil and natural water supplies. Investigations of some nosocomial outbreaks suggest that air, tap water and distilled water may be the sources for these mycobacteria.

For sources of *M. kansasii*, *M. marinum* and *M. xenopi*, see full text.

Human-to-human transmission is unlikely.

The predominant NTM species responsible for human disease varies between countries.

The reasons for the worldwide increase in incidence in both laboratory isolation and NTM disease remains uncertain.

Clinical disease caused by NTM

Pulmonary disease

Chronic pulmonary disease resembling TB is the most common clinical presentation of NTM infection. Patients are generally older adults – only rarely do children develop this type of NTM disease.

Signs and symptoms of NTM pulmonary disease are variable and non-specific. They include productive cough, dyspnoea, haemoptysis, malaise and fatigue. Fever, weight loss and night sweats occur less commonly than with TB.

Radiology findings in NTM lung disease: Type 1 and Type 2 patterns seen on CT scans are discussed in the full text.

Lymphadenitis

Infection of the sub-mandibular, sub-maxillary or cervical lymph nodes in children aged between one and five years is the most common presentation of NTM lymphadenitis.

In New Zealand and Australia approximately 80% of culture-positive cases of NTM lymphadenitis are due to *M. avium* complex.
Only about 5% of culture-proven mycobacterial cervical lymphadenitis in children in Western countries is due to M. tuberculosis.

More than 90% of culture-proven mycobacterial lymphadenitis at any site in adults is due to M. tuberculosis.

**Disseminated NTM disease in HIV/AIDS**

- *M. avium* is the most frequent bacterial opportunistic infection of AIDS.
- Average CD4 counts at the time of dissemination are < 50 cells/μl. Patients with < 100 CD4 cells/μl, not receiving prophylaxis, are at risk of developing disseminated disease at a rate of up to 20% per year.
- Fever, drenching night sweats and weight loss characterise disseminated disease. Widespread involvement of the reticuloendothelial system is common and results in hepatomegaly, splenomegaly and lymphadenopathy.

**Diagnosis of NTM infection**

- Correct species identification of NTM is one of the most complex tasks performed in a mycobacteriology laboratory.

**Skin-test antigen testing**

- It is unlikely that skin-test reagents will become available in the near future to aid in the diagnosis of NTM disease.

**Positive cultures: contamination, colonisation or disease?**

- A single positive sputum culture, especially with small numbers of organisms, does not suffice to diagnose NTM disease.
- Minimum evaluation should include three or more sputum specimens for AFB and efforts to exclude other confounding disorders such as TB and lung malignancy.

**Diagnosis of pulmonary infection**

- The clinical, radiological and bacteriological diagnostic criteria proposed by the American Thoracic Society should be used. To secure a diagnosis of pulmonary disease, all three criteria must be met.
- At least three respiratory samples should be evaluated from each patient.
- Other reasonable causes for the disease should be excluded.
- If the clinical situation is non-acute, and the diagnosis has not been established, repeating three sputum specimens a few months later is suggested if the person still has symptoms or worsening symptoms. Expert consultation should be sought when diagnostic difficulties are encountered.

**Diagnosis of extra-pulmonary NTM disease**

- Biopsies from any site of suspected NTM infection should be sent for both histopathology and microbiology testing.
Both laboratories must be alerted to the possibility of mycobacterial infection: media selection and temperature and duration of incubation depend on knowing that mycobacterial infection is suspected.

TB should not be forgotten as a possible diagnosis.

**Laboratory tests for disseminated NTM infection in HIV/AIDS**

- Mycobacteraemia is readily detected in appropriate blood culture media. These should be done routinely with unwell HIV patients under investigation.
- A single blood culture has a sensitivity of around 90%, and therefore no more than two blood culture sets are required.

**Susceptibility testing for NTM**

- Testing should only be performed by reference laboratories on isolates strongly suspected of causing disease.
- Single isolates from a series of smear-negative sputum specimens are unlikely to be clinically significant and do not require routine susceptibility testing.
- For advice about susceptibility testing for individual NTM species, see full text.

**Treatment of NTM disease**

**M. avium complex**

- Drug therapy for *M. avium* complex disease involves multiple drugs, and because of this the risk of drug toxicity is relatively high. Drug side-effects and drug interactions make treatment difficult for both the patient and the clinician.
- A rifamycin, ethambutol and clarithromycin are the agents for disease in immuno-competent patients.
- The treatment of *M. avium* complex disease is best undertaken by clinicians experienced in treating mycobacterial diseases.

**M. kansasii**

- The currently recommended treatment of *M. kansasii* pulmonary disease in adults is rifampicin with isoniazid and ethambutol. As isolates are normally susceptible to macrolides and these have been used as components of multi-drug treatment for this disease.

**NTM lymphadenitis**

- Excisional surgery without chemotherapy is the recommended treatment for children with NTM cervical lymphadenitis. The success rate with this procedure approaches 95%.
- If medical treatment is being considered, specialist advice is required.

**Infections due to rapidly growing mycobacteria**

- Pulmonary disease due to *M. abscessus* is particularly serious, with a fatality rate of 20% in one series.


**NTM in HIV/AIDS patients**

- Because of the difficult management decisions involved, drug toxicity concerns, as well as drug interactions and compliance issues, therapy for and prophylaxis against disseminated *M. avium* infection should only be undertaken by those with experience in this area.

**Prognosis and referral**

- Patients with NTM infection can be regarded as being non-infectious; notification is not required.
- The response to therapy depends on the NTM species and the site of infection. An expectation of gradual rather than rapid improvement should be given to patients.
- Specialist referral is advisable for:
  - all patients with pulmonary NTM infection – establishing the diagnosis is not simple and therapeutic regimens may be complex and potentially toxic
  - children with probable NTM lymphangitis
  - patients, particularly the immunosuppressed, with cutaneous infection
  - HIV/AIDS patients with systemic symptoms – the differential diagnosis is long and therapeutic decisions difficult.

**Future developments**

- Infection due to NTM is not a notifiable disease. There are few data on the number, type, and epidemiology of NTM infections in New Zealand.
- Therefore it would be helpful if the three New Zealand level III laboratories published their combined results each year for their NTM isolates along with any available demographic data.
- These could be published in the ESR report so that, over time, a picture of the common and clinically important NTM in New Zealand would develop.
Introduction

Many species of mycobacteria other than *M. tuberculosis* complex are recognised human pathogens. The spectrum of disease caused by non-tuberculous mycobacteria (NTM) is wide, and overlaps with that caused by *M. tuberculosis*. NTM and the sites they cause disease are shown in Table 19.1.1.

Besides an overlap of disease spectrum with *M. tuberculosis*, infection with NTM may also give rise to positive AFB smears and histopathology findings similar to those of TB. However, the treatment and public health implications of NTM disease are very different from those of *M. tuberculosis*. This chapter gives an overview of the epidemiology, diagnosis and treatment of this diverse group of organisms.

In 1959 Runyon separated the NTM into four groups based on their pigmentation, colony morphology and growth rate. However many NTM do not fit into any of the four groups of the Runyon scheme. Clinical laboratories have moved away from the Runyon scheme and favour the identification of NTM to species level. An overview of the geography and laboratory characteristics of NTM is given in Table 19.1.1.
19.1 Epidemiology

19.1.1 Sources of NTM infection

Most NTM are isolated from water and soil, but some are isolated from other sources such as house dust. It is now generally accepted that environmental sources, especially natural waters, are the reservoir for most human infections caused by *M. avium* complex (MAC). The aerosolisation of water may be an important means of transmission of infection, both in nature and domestically. Although *M. avium* is an important cause of disease in poultry and pigs, serological tests have shown that different strains affect animals and humans, and animal-to-human transmission is not important in human disease.

The aerosolisation of water may be an important means of transmission of infection, both in nature and domestically. Although *M. avium* is an important cause of disease in poultry and pigs, serological tests have shown that different strains affect animals and humans, and animal-to-human transmission is not important in human disease.

Water is also the likely source for *M. marinum*, which is commonly associated with fish tanks and swimming pools. In contrast, *M. kansasii* has yet to be recovered from soil or natural water supplies, but it has been isolated on numerous occasions from tap water.

The possibility of person-to-person transmission has been investigated. This was entertained for *M. malmoense*, but has been disproven by molecular epidemiology research. Familial cases of NTM lung disease are uncommon. Two Japanese families affected by *M. avium intracellulare* lung disease (MAILD) were studied, and mycobacterial DNA restriction fragments revealed that none of the MAC strains isolated from the patients was epidemiologically related to any of the others.

Rapidly growing mycobacteria such as *M. fortuitum, M. chelonae* and *M. abscessus* can be readily recovered from soil and natural water supplies. Investigations of some nosocomial outbreaks caused by these species have suggested that air, tap water and distilled water (used for dialysis or preparing surgical solutions) may serve as the sources for these organisms.

*M. xenopi* has been recovered almost exclusively from water, especially from hot water taps in hospitals, where it has been associated with cases of clinical disease.

Much remains to be understood about the pathogenesis of NTM infection and disease in humans. Epidemiological studies and skin-test surveys suggest that person-to-person transmission is not important in human disease. It is assumed that most persons become infected by environmental NTM. Of the likely sources of infection, airborne NTM may play an important role in respiratory NTM disease, whereas ingestion of NTM may be the source of infection for children with NTM cervical lymphadenitis and for patients with AIDS whose disseminated *M. avium* disease may begin with gastrointestinal infection. It is not known whether NTM disease develops soon after infection or, like TB, develops after a period of latent infection. Direct inoculation with NTM in water or other material is the likely source of infection for patients with soft-tissue infections.
## Table 19.1: Non-tuberculous mycobacteria recovered from humans

<table>
<thead>
<tr>
<th>Clinical disease</th>
<th>Common etiologic species</th>
<th>Features of the common species</th>
<th>Uncommon etiologic species</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Geography</td>
<td>Morphologic features*</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>1. <em>M. avium</em> complex</td>
<td>Worldwide</td>
<td>Usually not pigmented;</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>slow growth (&gt; 7d)</td>
</tr>
<tr>
<td></td>
<td>2. <em>M. kansasii</em></td>
<td>US, Europe</td>
<td>Pigmented; often large</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>and beaded on acid-fast</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>stain</td>
</tr>
<tr>
<td></td>
<td>3. <em>M. abscessus</em></td>
<td>Worldwide</td>
<td>Rapid growth (&lt; 7d); not</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pigmented</td>
</tr>
<tr>
<td></td>
<td>4. <em>M. xenopi</em></td>
<td>Europe, Canada</td>
<td>Slow growth; pigmented</td>
</tr>
<tr>
<td></td>
<td>5. <em>M. malmoense</em></td>
<td>UK, northern Europe</td>
<td>Slow growth; not</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pigmented</td>
</tr>
<tr>
<td>Lymphadenitis</td>
<td>1. <em>M. avium</em> complex</td>
<td>Worldwide</td>
<td>Usually not pigmented</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. <em>M. scrofulaceum</em></td>
<td>Worldwide</td>
<td>Pigmented</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>3. <em>M. malmonense</em></td>
<td>UK, northern Europe</td>
<td>Slow growth</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cutaneous disease</td>
<td>1. <em>M. marinum</em></td>
<td>Worldwide</td>
<td>Photochromogen; requires</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>low temperatures (28–30°C)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>for isolation</td>
</tr>
<tr>
<td></td>
<td>2. <em>M. fortuitum</em></td>
<td>Worldwide</td>
<td>Rapid growth; not</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pigmented</td>
</tr>
<tr>
<td></td>
<td>3. <em>M. chelonae</em></td>
<td>Worldwide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4. <em>M. abscessus</em></td>
<td>Worldwide</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5. <em>M. ulcerans</em></td>
<td>Australia, tropics, Africa, SE</td>
<td>Grows slowly; pigmented</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Asia</td>
<td></td>
</tr>
<tr>
<td>Disseminated disease</td>
<td>1. <em>M. avium</em> complex</td>
<td>Worldwide</td>
<td>Isolates from patients</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>with AIDS usually</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>pigmented (80%)</td>
</tr>
<tr>
<td></td>
<td>2. <em>M. kansasii</em></td>
<td>USA</td>
<td>Photochromogen</td>
</tr>
<tr>
<td></td>
<td>3. <em>M. chelonae</em></td>
<td>USA</td>
<td>Not pigmented</td>
</tr>
<tr>
<td></td>
<td>4. <em>M. haemophilum</em></td>
<td>USA, Australia</td>
<td>Not pigmented; requires</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>hemin, often low</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>temperatures, and CO₂ to</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>grow</td>
</tr>
</tbody>
</table>

*Photochromogen: isolate is buff-coloured in the dark but turns yellow after exposure to light.*
19.1.2 Geography and NTM species causing disease

There is variation in the NTM species responsible for human disease in different countries.\(^1\)

- *M. avium* is the most common NTM causing disease in the US, New Zealand, Australia and Hong Kong.\(^5\) This is true both for immunocompetent and immunosuppressed individuals.
- *M. malmoense* is a major pathogen in northern Europe, including Scotland and Norway.
- *M. kansasii* is common in the central states of the US.
- *M. xenopi* is common in Canada and Europe, but less so in the US.

19.1.3 Increasing incidence of NTM laboratory isolation and disease

An increase in incidence in laboratory isolation of NTM and of disease caused by them has been recognised worldwide.\(^1\) \(^5\) \(^6\) The reason for this remains uncertain. While increased awareness of disease caused by NTM will prompt increased testing for these organisms, other explanations are more likely, including:

- changes in living standards, such as the change to showering instead of bathing (this would increase exposure to aerosolised water)
- genetic transfer, leading to increased virulence of organisms (in contrast to *M. tuberculosis*, MAC is affected by plasmids)\(^1\)
- climatic changes
- more sensitive laboratory isolation techniques\(^7\)
- nosocomial acquisition (while there are many instances of different NTM infections being acquired in hospitals through contaminated tap water, distilled water, hot water systems, bronchoscopes, peritoneal dialysis fluid, injections and other sources, it is most unlikely that hospital sources account for more than a minority of all disease caused by NTM).

19.1.4 Ethnicity and NTM disease

The epidemiology of TB is well documented throughout most of the world (see Chapter 1 for the epidemiology of TB in New Zealand). The situation is the opposite for NTM, for which mandatory reporting and systematic data collection are not carried out. There is thus very little information about ethnicity and NTM disease.

The one exception is for NTM lymphadenitis. Caucasian ethnicity was a feature in children with NTM adenitis in both an Australian and two New Zealand studies of mycobacterial lymphadenitis.\(^8\)\(^-\)\(^10\) This contrasts with TB, where non-Caucasian ethnicity is a risk factor for TB because many non-Caucasians come from, visit or have contact with people who have lived in countries with a high incidence of TB.
## 19.2 Clinical disease caused by NTM

### 19.2.1 Pulmonary disease

Chronic pulmonary disease resembling TB is the most common clinical presentation associated with NTM. In the US *M. avium* complex and *M. kansasii* are the most common NTM species affecting the lungs. Other pathogens occasionally causing pulmonary disease include *M. chelonae, M. fortuitum, M. abscessus, M. xenopi* and *M. malmoense*. The proportion of pulmonary disease caused by different NTM varies in different regions of the world. Patients are generally older adults, and only rarely do children develop this type of NTM disease.

*Signs and symptoms of NTM pulmonary disease*

These are variable and non-specific. They include productive cough, dyspnoea, haemoptysis, malaise and fatigue. Fever and weight loss can occur but are less common and less severe than with *M. tuberculosis*. While differences occur in the radiological findings in pulmonary disease caused by NTM and those of *M. tuberculosis*, no radiological finding is pathognomonic or diagnostic of NTM. Evaluation is often complicated by symptoms caused by other pre-existing lung disease, which include previous mycobacterial disease, chronic obstructive airway disease, bronchiectasis and malignancy.

*Radiology findings in NTM lung disease*

NTM lung disease is divided into two main radiological types (type 1 and type 2), seen on chest CT scan. These have been mainly described with *M. avium intracellulare* lung disease (MAILD). The same patterns are seen with many other NTM, but there is no review of the frequency with which all types of NTM fit into these patterns.

The type 1 pattern is seen on a standard CXR. Features include:
- cavities (usually with thinner walls than in TB)
- macro-nodules (≥ 0.5 cm diameter)
- areas of consolidation.

Type 2 changes are only seen on chest CT (high-resolution films are preferable), and include:
- bronchiectasis
- micro-nodules (small) centri-lobular nodules (< 0.5 cm)
- geographical light and dark areas on expiratory scans – the dark areas are abnormal and are indicative of delayed emptying of lung lobules caused by small airway disease (see below).

Sometimes a mixture of types 1 and 2 changes occurs. The significance of these patterns becomes evident with the management of NTM lung disease.
19.2.2 Lymphadenitis

Infection of the sub-mandibular, sub-maxillary or cervical lymph nodes in children aged between one and five years is the most common presentation of NTM lymphadenitis. The disease occurs insidiously, with minimal symptoms. The involved lymph nodes are practically always unilateral and generally not tender. Normally there is no history of exposure to TB, and the chest radiograph is normal.

Approximately 80% of culture-positive cases of lymphadenitis are due to *M. avium* complex, with most of the remainder being due to *M. scrofulaceum*. Only about 5% of culture-proven mycobacterial cervical lymphadenitis in children is due to *M. tuberculosis*. In contrast, more than 90% of culture-proven mycobacterial lymphadenitis at any site in adults is due to *M. tuberculosis*.

19.2.3 Skin, soft-tissue and injection-site infections

The NTM species that most commonly cause infections of the skin and subcutaneous tissue are *M. fortuitum*, *M. chelonae* and *M. marinum*. However, virtually all species of NTM have been described as a cause of cutaneous disease.

Localised drainage or abscess formation at the site of puncture wounds, or after open traumatic injuries or fractures, is most often due to the rapidly growing mycobacterial species *M. fortuitum* or *M. chelonae*. Wound infection following augmentation mammoplasty and cardiac surgery is well recognised. An outbreak of infection caused by *M. abscessus* occurred in two US states as a result of a physician administering contaminated, non-FDA-approved ‘adrenal cortex extract’ by IM injection.11 Other NTM infections have resulted from IM injection.

*M. marinum* is the cause of ‘swimming pool granuloma’ or ‘fish tank granuloma’. The lesions usually appear as papules on an extremity, especially on the elbows, knees and dorsum of the feet and hands, progressing subsequently to shallow ulceration and scar formation. Clinical involvement of regional nodes is absent. The organisms may be introduced into the skin through abrasions in swimming pools and fish tanks, or by scratches or puncture wounds from fish, shrimp, fins, etc.

In Australia *M. ulcerans* is a well recognised cause of indolent necrotic lesions of the skin and underlying tissue.

19.2.4 Disseminated NTM disease in HIV/AIDS

*M. avium* is the most frequent bacterial opportunistic infection of AIDS. While many NTM species, including *M. kansasii*, *M. scrofulaceum* and *M. xenopi*, have caused disseminated NTM disease in HIV/AIDS, more than 95% of cases are due to *M. avium* complex isolates and most of these are *M. avium* rather than *M. intracellulare*. In the era before treatment with combination anti-HIV agents, autopsy series suggested that 30–50% of patients with AIDS had disseminated *M. avium* complex disease at the time of their death.
CD4 cell counts predict the incidence of *M. avium* complex bacteraemia, with the average CD4 count at the time of dissemination being < 50 cells/μl. Patients with < 100 CD4 cells/μl, not receiving prophylaxis, are at risk of developing disseminated disease at a rate of up to 20% per year. Fever, drenching night sweats and weight loss characterise disseminated disease. Widespread involvement of the reticuloendothelial system is common and results in hepatomegaly, splenomegaly and lymphadenopathy.
19.3 Diagnosis of NTM infection

A large number of potentially pathogenic NTM can be encountered in the clinical laboratory. Correct species identification of these organisms is one of the most complex tasks performed in a mycobacteriology laboratory. The appearance of NTM on microscopy is indistinguishable from *M. tuberculosis*, except that *M. kansasii* is often longer and has a more beaded appearance.

19.3.1 Skin-test antigen testing

‘Tuberculin-type’ antigens have been used in Australia but do not have widespread acceptance. Unfortunately, many antigens are shared by NTM and extensive cross-reactions are observed. It is unlikely that skin-test reagents will become available in the near future to aid in the diagnosis of NTM disease.

In the absence of specific diagnostic features in history and physical examination, CXR and differential skin testing, isolation of the NTM in a culture is usually required for diagnosis.

19.3.2 Positive cultures: contamination, colonisation or disease?

As NTM organisms are commonly found in nature, contamination of culture material or transient infection does occur. Thus, a single positive sputum culture, especially with small numbers of organisms, does not suffice to diagnose NTM disease. It has been suggested that the respiratory tract may be infected with the organism without disease, particularly in patients with chronic respiratory disease. This condition was often referred to as ‘colonisation’, and was described most often with *M. avium* complex. More recent studies with high-resolution CT scans have shown that these patients often have a combination of multi-focal bronchiectasis and nodular parenchymal disease, with the latter or both now felt to be due to mycobacterial disease. Colonisation in the true sense (ie, no tissue invasion) is probably rare.

Given these observations, the diagnosis of lung disease caused by NTM is usually not difficult if a combination of clinical, radiographical and bacteriological criteria (see below) are used. Minimum evaluation should include three or more sputum specimens for acid-fast bacilli (AFB) and efforts to exclude other confounding disorders such as TB and lung malignancy.

19.3.3 PCR and DNA probe testing

Molecular methods do not have a significant role to play in the diagnosis of NTM disease. Species-specific probes for MAC are used by level III laboratories in New Zealand. Their use significantly reduces the time needed to report the presence of MAC as opposed to the previous method of biochemical testing.
In some instances, however (eg, histopathology suggestive of mycobacterial infection but with negative cultures or no cultures performed), molecular methods may be worth considering (eg, PCR amplification and sequencing to try to prove the presence of mycobacterial DNA and the probable causative organism – see following section).

19.3.4 Organism identification by DNA sequencing

The traditional method of speciating NTM takes into account their pigmentation, growth rates and biochemical reactions. The latter may vary between strains of the same species, and confident identification can at times be difficult. As a result many studies have evaluated molecular methods for speciating NTM isolates. One method involves amplification of a region of the hsp65 gene, subjecting the amplicon to restriction enzymes and separating the different size sequences. The hsp65 gene codes for a 65-kDa heat-shock protein and this gene is present in all mycobacteria. The patterns produced allow for species identification. The method can also identify the presence of non-culturable mycobacteria (eg, M. leprae).

In addition the amplified heat-shock protein gene amplicon, or 16S ribosomal DNA sequences, can be sequenced and compared to known sequences stored in gene banks. The availability of gene bank data means that sequencing information is able to assist in establishing – and indeed confirm – the identity of an NTM isolate. Sequence data does, however, need to be quality controlled and must be evaluated alongside other information about the isolate if reliable identification is to be made. Sequencing methods are in use in Auckland, Waikato, Wellington and Christchurch Hospital laboratories. Isolates thought to require molecular identification must be discussed with the laboratory.

19.3.5 Diagnosis of pulmonary infection

Diagnosis of pulmonary NTM disease is not established by the mere isolation of a given isolate. The clinical, radiological and bacteriological diagnostic criteria proposed by the American Thoracic Society should be used to ensure, as far as possible, that a given isolate is responsible for disease. To secure a diagnosis of pulmonary disease all three criteria must be met.

Criteria for diagnosing pulmonary NTM

Clinical criteria are:

a. compatible signs/symptoms (cough, fatigue most common; fever; weight loss haemoptysis, dyspnoea may be present, particularly in advanced disease) with documented deterioration in clinical status if an underlying condition is present, and

b. reasonable exclusion of other disease (eg, TB, cancer) as alternative causes of the clinical condition, or adequate treatment of other condition which is causing increasing signs/symptoms.
Radiographical criteria are:

c. any of the following CXR abnormalities; if baseline films are more than one year old, there should be evidence of progression:
   - infiltrates with or without nodules (persistent two months, or progressive)
   - cavitation
   - nodules alone (multiple)

d. any of these high-resolution CT abnormalities:
   - multiple small nodules
   - multi-focal bronchiectasis with or without small lung nodules.

Bacteriological criteria are:

e. at least three sputum / induced sputum / bronchial wash samples within the previous 12 months:
   - three positive cultures with negative AFB smear results, or
   - two positive cultures and one positive AFB smear, or

f. single bronchial wash and inability to obtain sputum samples:
   - positive culture with an AFB smear with 1–9 AFB/10 fields; or
   - positive culture with 100 colonies on solid media.

g. If sputum / bronchial wash evaluations are non-diagnostic or another disease cannot be excluded, use:
   - transbronchial or lung biopsy yielding an NTM, or
   - biopsy showing mycobacterial histopathologic features (caseating granulomata with chronic inflammation and/or AFB) and one or more sputum specimens or bronchial washings are positive for an NTM even in low numbers, or
   - any growth from a usually sterile non-pulmonary site.

The above criteria fit best with *M. avium* complex, *M. abscessus* and *M. kansasii*. Too little is known of other NTM to be certain how applicable these criteria will be. At least three respiratory samples should be evaluated from each patient. Other reasonable causes for the disease should be excluded. If the clinical situation is non-acute, and the diagnosis has not been established, repeating three sputum specimens a few months later is suggested if the person still has symptoms or worsening symptoms. Expert consultation should be sought when diagnostic difficulties are encountered.

### 19.3.6 Diagnosis of extra-pulmonary NTM disease

Biopsies from any site of suspected NTM infection should be sent for both histopathology and microbiology testing. Both laboratories should be alerted to the possibility of mycobacterial infection. This is essential information for the microbiology laboratory because media selection as well as temperature and duration of incubation depend on knowing that mycobacterial infection is suspected.
19.3.7 Diagnosis of NTM lymphadenitis

The presumptive diagnosis of NTM lymphadenitis is based on the histopathological appearance of the lymph node showing caseating granulomata with or without AFB, and a negative tuberculin skin test. Failure of the node to yield *M. tuberculosis* provides strong presumptive evidence for the diagnosis of NTM lymphadenitis. Recovery of an NTM, most commonly MAC, from lymph node tissue or aspirate is diagnostic.

19.3.8 Skin and soft-tissue infection

All skin and soft-tissue samples should be incubated at two temperatures: 35°C and 28–32°C. A number of common pathogens (eg, *M. haemophilum*, *M. ulcerans*, *M. marinum* and *M. chelonei*) may only grow at the lower temperature.

Inoculated media should be supplemented with hemin or ferric ammonium citrate to allow the growth of *M. haemophilum*. *M. genavense* may only grow from the blood in BACTEC13A medium or comparable broth culture. It requires incubation for at least eight weeks. Some have found better growth in the slightly acidic (pH 6) pyrazinamide test medium.

The presence of an AFB smear-positive sample with no growth on solid media should suggest the possibility of *M. haemophilum*, *M. conspicuum* or *M. genavense*.

19.3.9 Laboratory tests for disseminated NTM infection in HIV/AIDS

Mycobacteraemia is readily detected by blood cultures, and these should be routine tests with unwell HIV patients under investigation. A single blood culture has a sensitivity of around 90%, and therefore no more than two blood culture sets are required. Two negative sets practically exclude mycobacteraemia.

The blood culture request form needs to specify culture for mycobacteria because special blood culture bottles need to be inoculated. Routine blood culture bottles are designed to recover bacteria and yeasts, not mycobacteria. Culture of tissue from various sites may be indicated in individual patients, but is seldom required.
19.4 Susceptibility testing for NTM

While there is clear agreement on how to perform susceptibility testing and what antimicrobial agents to test for *M. tuberculosis*, the same cannot be said for NTM.\(^1\)\(^{21}\)\(^{22}\) Testing should only be performed by reference laboratories on isolates strongly suspected of causing disease. The testing methods used should follow published standards.\(^21\)\(^{22}\)

Single isolates from a series of smear-negative sputum specimens are unlikely to be clinically significant and do not require routine susceptibility testing. Ideally the laboratory should communicate with the person looking after the patient before deciding what antibiotic agents to test.

19.4.1 *M. avium* complex

Susceptibility testing against rifabutin and the anti-tuberculous drugs is not recommended.\(^1\)\(^\) Correlation between *in vitro* susceptibility test results for MAC isolates and clinical response has only been demonstrated in a clinical trial using a macrolide. Strains from patients who have not been treated with macrolides are highly unlikely to be resistant to them. Routine testing against clarithromycin should not be performed. Clarithromycin testing should be reserved for isolates from patients who have failed previous macrolide treatment or prophylaxis. An MIC of 32 \(\mu\)g/ml is recommended as the resistance breakpoint.\(^1\)

19.4.2 *M. kansasii*

Routine testing should be restricted to rifampicin. Methods or breakpoints for other drugs have not been established.\(^1\)\(^\) Isolates resistant to rifampicin should be tested against other agents in an experienced reference laboratory.\(^{22}\)

19.4.3 *M. marinum*

Routine testing is not recommended because the species is consistently susceptible to agents used for treatment and the risk of acquired mutational resistance to one or more of these agents is minimal.\(^{22}\)

19.4.4 Rapidly growing mycobacteria

Testing should not be performed with the anti-tuberculosis agents.\(^1\)\(^\) The clinically significant species *M. fortuitum, M. chelonae* and *M. abscessus* should be tested against doxycycline, the fluorinated quinolones, a sulphonamide, cefoxitin and clarithromycin. Imipenem may be reported for *M. fortuitum*. Amikacin should be tested against *M. fortuitum* and *M. abscessus*. Tobramycin is the most effective aminoglycoside for infections caused by *M. chelonae* and should be the one tested with this species. Because of the variable drug susceptibility among these species, *susceptibility testing of all clinically significant isolates is essential for optimal patient management*.\(^1\)
19.5 Treatment of NTM disease

19.5.1 *M. avium* complex

The early experience with medical treatment of MAC disease was disappointing, and the best outcomes were in those patients subjected to resectional surgery. No controlled clinical trials in this disease have been conducted, and treatment recommendations have been based largely on empirical data. Surgical resection can be contemplated only with localised MALT. Hence, this will only be appropriate for people with type 1 disease. This pattern was described earlier (see section 19.2.1).

For most patients, especially those with non-cavitary disease, a period of observation of at least several months may be needed to assess the contribution of MAC disease to the overall clinical picture. During this time patients should receive therapy for underlying pulmonary disease, if present (e.g., daily home-based chest physiotherapy for those with bronchiectasis, bronchodilators, broad-spectrum antibiotics and stopping smoking). If the disease remains undiagnosed, sputum AFB cultures may be needed on a regular basis (e.g., every month for two months).

Drug therapy for *M. avium* complex disease involves multiple drugs, and because of this the risk of drug toxicity is relatively high. Drug side-effects and drug interactions make treatment difficult for both the patient and the clinician. Standard medical treatment involves the use of a rifamycin, a macrolide (clarithromycin or azithromycin) and ethambutol. The treatment of *M. avium* complex disease is best undertaken by clinicians experienced in treating pulmonary or mycobacterial diseases.

19.5.2 *M. kansasii*

Untreated strains of *M. kansasii* are susceptible to rifampicin, isoniazid, ethambutol, ethionamide, clarithromycin and streptomycin at concentrations readily achievable in the serum with usual therapeutic doses.\(^1^{,2,3}\) *M. kansasii* is also susceptible *in vitro* to sulphamethoxazole, amikacin and rifabutin, although there is limited information on the clinical usefulness of these drugs.\(^1\)

There have been no randomised controlled trials of treatment for disease caused by *M. kansasii*, comparing one drug regimen with another or with no drug treatment at all. Early reports of treatment with anti-mycobacterial drugs in the pre-rifampicin period were disappointing. With rifampicin-containing therapy, the long-term relapse rate is very low. Surgery, therefore, is now considered to have no role in the management of routine cases of *M. kansasii* pulmonary disease. Although the currently recommended treatment of *M. kansasii* pulmonary disease in adults is rifampicin with isoniazid and ethambutol,\(^1\) isolates are normally susceptible to clarithromycin,\(^2,3\) and macrolides have been used as components of multi-drug treatment for this disease.\(^2,4\) If macrolides are being considered as part of a treatment regimen, the patient should be asked if they have received a macrolide previously, because this has been associated with resistance and treatment failure.\(^2,5\)
19.5.3 Lymphadenitis

Excisional surgery without chemotherapy is the recommended treatment for children with NTM cervical lymphadenitis. The success rate with this procedure approaches 95%. For children with recurrent disease, a second surgical procedure is usually performed. A clarithromycin-containing multiple drug regimen such as that used for pulmonary disease should be considered for recurrent disease or for children in whom surgical risk is high (e.g., risk of facial nerve damage). If medical treatment is being considered, specialist advice is required.

19.5.4 Infections due to rapidly growing mycobacteria

The majority of clinical disease (more than 90%) is due to *M. fortuitum*, *M. abscessus* or *M. chelonae*. *M. fortuitum* and *M. chelonae* are resistant to the first-line anti-TB agents, but they are susceptible (especially *M. fortuitum*) to a number of traditional anti-bacterial agents. Isolates of *M. fortuitum* are susceptible to amikacin (100%), ciprofloxacin (100%), sulphonamides (100%) and imipenem (100%); most are susceptible to clarithromycin (80%) and cefoxitin (80%); and 50% are susceptible to doxycycline. Isolates of *M. abscessus* are susceptible to clarithromycin (100%), imipenem/cilastatin (50%), amikacin (90%) and cefoxitin (70%). Isolates of *M. chelonae* are susceptible to amikacin (80%), tobramycin (100%), imipenem (60%), ciprofloxacin (20%), clarithromycin (100%) and doxycycline (25%).

Treatment for serious disease requires a period of intravenous combination treatment determined by susceptibility results. Treatment may be possible with oral agents, depending on the response to intravenous treatment and susceptibility results. A period of four to six months’ treatment is usually required.

Surgery is often needed in extensive disease, abscess formation, or where drug treatment is difficult. Removal of foreign bodies such as breast implants, percutaneous catheters, etc. is probably essential for recovery.

Pulmonary disease due to *M. abscessus* is a particularly serious condition. The disease course ranges from a slowly progressive disorder to fulminant rapidly progressive infection. Relapses are common and for some patients suppressive treatment to control the infection may be all that is possible. In one series the fatality rate of those with pulmonary *M. abscessus* infection was 20%.

19.5.5 *M. marinum*

A number of treatment modalities have been used for cutaneous disease caused by *M. marinum*. These include simple observation for minor lesions, surgical excision, the use of anti-TB therapy, and the use of single antimicrobial agents. Acceptable treatment regimens include minocycline or doxycycline, trimethoprim-sulphamethoxazole, or rifampicin and ethambutol.
The rate of clinical response is variable, and a minimum of three weeks of therapy should be given before considering that a patient may not be responding. Recommendations for the duration of therapy vary. If infection is superficial and the response is prompt, treatment may only need to be continued for four to six weeks following resolution. Deeper infections and those slow to respond require prolonged therapy. Surgical debridement may also be important, especially for disease involving the closed spaces of the hand or for disease that responds poorly to drug therapy.1

19.5.6 NTM in HIV/AIDS patients

Many studies have documented that some individual drugs or multiple drug combinations reduce or eliminate mycobacteraemia.1 Because of the difficult management decisions involved, drug toxicity concerns, as well as drug interactions and compliance issues, therapy for and prophylaxis against disseminated _M. avium_ infection should only be undertaken by those with experience in this area.1

19.5.7 NTM that rarely cause human disease

Although almost any species can cause disease, especially in a severely immuno-compromised patient, some species can be regarded as essentially non-pathogenic. These include _M. gordonae, M. scrofulaceum_ (other than from a cervical node in a child), _M. terrae, M. nonchromogenicum_ and _M. triviale_. Before any of these species are taken as being the cause of disease, the entire clinical history as well as any radiological and histopathology results must be considered.

19.5.8 Prognosis and referral

Patients with NTM infection can be regarded as being non-infectious and should be advised accordingly. The response to therapy depends on the NTM species and the site of infection, but may be slow, especially for pulmonary infections. The expectation of gradual rather than rapid improvement should be conveyed to patients.

Specialist referral is advisable for:

- all patients with pulmonary NTM infection – establishing the diagnosis is not simple, and therapeutic regimens may be complex and potentially toxic
- children with probable NTM lymphangitis
- patients, particularly the immunosuppressed, with cutaneous infection
- HIV/AIDS patients with systemic symptoms – the differential diagnosis is long and therapeutic decisions difficult.
19.6 Future developments

Infection due to NTM is not a notifiable disease. There are few data on the number, type and epidemiology of NTM infections in New Zealand.

It would be helpful if the three New Zealand level III laboratories combined their results each year for their NTM isolates. It would be useful if these laboratories also recorded the number of isolates from each patient, the smear results and whether the isolates were treated.

Ideally, a yearly summary of NTM isolates could be published in the ESR report, so that over time a picture of the common and clinically important NTM in New Zealand could be developed.
References

