Guidelines for Tuberculosis Control in New Zealand 2010
Chapter 8: Diagnosis and Treatment of Latent Tuberculosis Infection
Acknowledgements

These guidelines have been updated with contributions by:
Dr Andrew Woodhouse
Mr Arthur Morris
Dr Cass Byrnes
Dr Cathy Pikholz
Dr Chris Lewis
Dr Don Bandaranyake
Ms Helen Heffernan
Dr Joshua Freeman
Dr Lesley Voss
Dr Margot McLean
Dr Mark Thomas
Dr Mitzi Nisbet
Dr Nigel Raymond
Dr Noel Karalus
Dr Peter Martin
Dr Sally Roberts
Ms Sharnita Singh
Contents

Summary 1

Introduction 2

1 Diagnosis 3
   1.1 Who should be tested for LTBI 3
   1.2 Risk factors for infection and developing TB disease 3
   1.3 Tests used to diagnose LTBI 6
   1.4 Which test to use 6
   1.5 Mantoux test 10
   1.6 Interferon-gamma release assays 18

2 Treatment 21
   2.1 Who should be offered treatment for LTBI 21
   2.2 LTBI treatment contraindications and precautions 26
   2.3 Who should prescribe treatment and follow up for LTBI 28
   2.4 LTBI treatment regimens 28
   2.5 Practical considerations in treating LTBI 33

References 37

List of Tables
   Table 1.1: Risk factors for infection 4
   Table 1.2: Risk factors for developing TB disease following infection 5
   Table 1.3: Definition of a positive Mantoux test in New Zealand (cutting points) 11
   Table 2.1: Recommended drug regimens for treatment of LTBI 29
Summary

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

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

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

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

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

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

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

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

LTBI is 'latent' because live, dormant (not reproducing) Mycobacterium tuberculosis organisms are sequestered in the tissues, although they are not clinically apparent. In LTBI the chest X-ray (CXR) is normal or shows trivial and stable evidence of past TB (eg, a small scar or patch of calcium). The number of TB organisms is low.

Worldwide about one-third of the population is thought to have LTBI. The prevalence of LTBI in New Zealand is not known. However the prevalence will vary in different subgroups within the New Zealand population, eg, in different age and ethnic groups.

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

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

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

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

1.1 Who should be tested for LTBI

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

Practice points

The following groups of people should be tested for LTBI:

- People likely to have been infected recently (see Table 1.1): primarily contacts of a patient with recent diagnosis of active infectious TB disease; refugees aged under 16 years.
- People who have an increased risk of developing active TB disease if they have LTBI, due to impaired immunity (see Table 1.2): eg, people living with HIV infection, chronic renal failure, solid organ transplantation, anti-tumour necrosis factor (TNF) alpha treatment and various other chronic conditions and treatments.
- Health care workers (HCWs), because they are at increased risk of exposure to people with active infectious TB disease (see Chapter 12).

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

1.2 Risk factors for infection and developing TB disease

1.2.1 Risk factors for infection

Risk factors for infection are summarised in Table 1.1. TB is almost always transmitted by active pulmonary or laryngeal TB in adults or adolescents. Almost without exception, transmission does not occur from people who only have extrapulmonary TB, such as lymph node, renal or bone disease.
Table 1.1: Risk factors for infection

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

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

1.2.2 Risk factors for developing TB disease following infection

People with LTBI have widely varying risks of progression to TB disease, depending on the factors listed in Table 1.2.

Other factors that are possible risk factors for LTBI progressing to TB disease, but for which there are variable amounts of evidence, include the following.

- **Socioeconomic status**: The relationship between socioeconomic status and TB is complex. The clear relationship between TB and poverty may be mediated through many factors, such as crowding, infectivity of source case, access to medical services, and attitudes and priority given to health. A study of paediatric TB in New Zealand from 1992 to 2001 found that poverty was strongly associated with TB. A recent ecological study using TB surveillance and census data showed that TB incidence in New Zealand is associated with household crowding at the census area unit (CAU) level.

- **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.
• No ethnic differences in TB risk have been documented in studies with appropriate control for confounders.8
• Twin and blood-group studies suggest some genetic predisposition.8
• Emotional or physical stress may increase risk.8

### Table 1.2: Risk factors for developing TB disease following infection

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time since infection</td>
<td><em>Inverse association:</em> 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 (eg, those who have lived or grown up in high TB-incidence countries but have resided in New Zealand for some years).</td>
</tr>
</tbody>
</table>
| Age                                   | *Inverse association:* Peaks in risk occur in the preschool years and adolescence and early adulthood. The lifetime risk of progressing from infection to active TB is:  
- 5–15% in adults  
- inversely proportional to age:  
  - 23–43% in infants under 1 year of age  
  - 11–24% in children aged 1–5 years  
  - 8–25% in children aged 6–10 years  
  - 16% in children aged 11–15 years. |
| Dose of infection                     | The risk is highest if the source case is smear-positive; less if smear-negative or culture-negative. |
| Size of tuberculin reaction           | 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. |
| Predisposing medical conditions       | HIV is the strongest risk factor (see Chapter 6). Other risk factors include diabetes, alcoholism and drug addiction, silicosis, gastrectomy, intestinal bypass and chronic malabsorption syndromes, and immuno-suppressive diseases (leukaemia, lymphoma and end-stage renal disease). Underlying illnesses such as diabetes mellitus, renal failure, chronic obstructive pulmonary disease, and HIV infection are also strong predictors of death from TB. |
| Immuno-suppressive treatment          | Current or recent oral steroid therapy (over 15 mg prednisone or equivalent per day for two to three weeks); anti-Tumour Necrosis Factor (TNF) alpha treatment; some cancer chemotherapy; immuno-suppressive drugs used in solid organ transplantation. |
| Immigrants who have recently arrived from a high-incidence country | Risk for migrants is highest in the first 1–2 years of being in New Zealand. |
| Body weight                           | Increased risk in underweight or malnourished individuals.8 |
| Smoking                               | Increased TB incidence in smokers (lowest risk in never smokers, intermediate in ex-smokers, highest in current smokers).21,22 |

Note: Numbers refer to references at the end of the chapter.
1.3 Tests used to diagnose LTBI

There is no gold standard test for the diagnosis of LTBI.

Tuberculin skin tests (TSTs) such as the Mantoux test have been used for many years. The Mantoux test is a TST using an intradermal injection of 5 tuberculin units (TU) of purified protein derivative (PPD), which is derived from cultures of \( M. \) \textit{tuberculosis}. In a person previously infected with \( M. \) \textit{tuberculosis} a hypersensitivity reaction occurs at the site of injection. The Mantoux test is the only TST currently used in New Zealand. See section 1.5 for further information regarding Mantoux testing.

IGRAs have been developed as an alternative to Mantoux tests for the diagnosis of LTBI. IGRAs work on the principle that if a person is infected with \( M. \) \textit{tuberculosis}, T-lymphocytes circulating in their blood will produce interferon-gamma (IFN-gamma) if re-exposed to TB antigens in vitro. See section 1.6 for further information regarding IGRAs, including a summary of some selected recent literature on the cost-effectiveness of IGRA, the use of IGRA in migrants, and a study on the prognostic value of IGRA for the progression from LTBI to TB disease.

1.4 Which test to use

While the Mantoux test has been used for many years, IGRAs are much newer tests and evidence for their use is still accumulating. In general, either test can be used to diagnose LTBI. However in certain circumstances one test may be preferable to the other, or both tests can be done, as outlined below. It is important to note that the limitations of both tests are similar, in particular that false negative results (and indeterminate results in the case of IGRAs) can occur, and are more likely to occur in immuno-compromised people.

Advantages of IGRAs compared with TST include that they have better specificity, require only one patient visit for the test, have the potential for more rapid availability of results, are not subject to inter- and intra-operator variability, are not subject to boosting and sensitisation, are not affected by previous BCG vaccination or by infection with most non-tuberculous mycobacteria (NTM) and have results that can be stored in the laboratory system. Disadvantages of IGRAs compared with TSTs are that they have higher upfront cost, require laboratory expertise and have a relative lack of evidence upon which to base decision-making, although research in this area is expanding.

The USA Centers for Disease Control and Prevention guidance recommends that QFT-G may be used in all circumstances in which TSTs are used. The UK National Institute for Health and Clinical Excellence (NICE) TB guidelines recommend that Mantoux testing should be done, and that in people with positive Mantoux tests, IGRAs should then be considered (if available).
1.4.1 Contact screening for LTBI

**Practice points**

Contacts aged seven years and under: use Mantoux test.

Contacts aged over seven years: use Mantoux test or IGRA or Mantoux test followed by IGRA (if Mantoux positive).

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

**Rationale**

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

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

Studies indicate that IGRAs are more sensitive than Mantoux tests in people who are immuno-compromised.

**Interpretation of results in contacts**

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

If an IGRA is negative or indeterminate, or a Mantoux test is negative and:
- the person is asymptomatic and not immuno-compromised, no further action is required
- the person is symptomatic or immuno-compromised, the person should be referred for further investigation.

1.4.2 Health care worker screening for LTBI

**Practice point**

Use IGRAs to screen health care workers for LTBI.
Rationale
There are relatively high rates of BCG-vaccinated individuals and immigrants among healthcare workers in New Zealand.

Healthcare workers (HCWs) are at risk of occupational exposure to TB, so may need multiple tests to screen for LTBI during their working life. Use of IGRAs avoids the need for baseline two-step testing, as well as the occurrence of boosting and sensitisation that can be complications of serial Mantoux testing.

IGRA results will be stored in the laboratory system, which should facilitate the transfer of information between District Health Boards should HCWs move between regions.

Interpretation of results in health care workers
If an IGRA is positive, the HCW should be referred for further investigation and assessed on a case-by-case basis to determine their history of TB exposure, and therefore likelihood of progression to active TB disease, and to agree a management plan.

If an IGRA is negative or indeterminate and:
- the HCW is asymptomatic and not immuno-compromised, no further action is required
- the HCW is symptomatic or immuno-compromised, they should be referred for further investigation.

Note that care must be taken when interpreting the results of serial testing with IGRAs. Debate exists in the international literature about the most valid cut-off point for defining a true IGRA conversion in the context of serial testing. In line with guidelines from the Centers for Disease Control and Prevention, a change from a negative to positive result should be considered as a conversion and the person must be referred for further investigation. However, as more information becomes available this definition of an IGRA conversion may be amended.
1.4.3 Refugee screening for LTBI

Practice points
Refugee children aged seven years and under: use Mantoux test.
Refugee children aged 8–15 years: use Mantoux test or IGRA or Mantoux test followed by IGRA (if Mantoux positive).
An IGRA is particularly recommended:
• in BCG-vaccinated children
• in immuno-compromised children.
Refugees aged 16 years and older are not currently screened for LTBI in New Zealand. However if in future a policy decision is made to screen this group, either Mantoux test or IGRA should be used (as for refugee children aged 8–15 years).

Rationale
As for contact screening for LTBI (see above).

Interpretation of results in refugees
If an IGRA or a Mantoux test is positive, the person should be referred for further investigation and assessed on a case-by-case basis to determine their history of TB exposure, and therefore likelihood of progression to active TB disease, and to agree a management plan.

If an IGRA is negative or indeterminate, or a Mantoux test is negative and:
• the person is asymptomatic and not immuno-compromised, no further action is required
• the person is symptomatic or immuno-compromised, the person should be referred for further investigation.

1.4.4 Screening for LTBI in immuno-compromised people

Practice points
Use IGRAs to screen immunocompromised people where indicated eg, prior to starting anti-TNF alpha therapy or other immuno-suppressive therapies, in people with renal failure, prior to solid organ transplantation, etc.
In some situations, a clinician may elect to use both a Mantoux test and an IGRA to screen for LTBI in an immuno-compromised person.
Rationale

IGRAs have been shown to be more sensitive than Mantoux tests to screen for LTBI in immuno-compromised individuals, including people living with HIV and people with immune compromising conditions, including conditions requiring anti-TNF alpha therapy.30–32, 35

Interpretation of results in immuno-compromised people

If an IGRA or a Mantoux test is positive (ie, only one test was done), the immuno-compromised person should be treated for LTBI.

If IGRA and Mantoux test results are discordant in an immuno-compromised person (ie, both tests were done, and the Mantoux test is positive but the IGRA is negative or the IGRA is positive but the Mantoux test is negative), the clinician should consider treating the person for LTBI.

Even if an IGRA is negative or indeterminate or a Mantoux test is negative, the immuno-compromised person should be assessed on a case-by-case basis to determine their history of TB exposure, likelihood of having acquired LTBI and if so, of progression to active TB disease, and considered for treatment of LTBI accordingly.

1.5 Mantoux test

1.5.1 Administering and reading the Mantoux test

Those administering and reading the Mantoux test must be trained in the technique and should follow the technical guidance in the Ministry of Health’s Technical Guidelines for Mantoux Testing and BCG Vaccination.37 Medical officers of health should work with organisations offering Mantoux tests to facilitate the initial and ongoing training of those undertaking Mantoux tests.

Practice points

Read a Mantoux test as close as possible to 72 hours after placement.

The exception to this is the second step of a two-step Mantoux test, which should be read at 48 hours (see section below on the two-step Mantoux test).

A Mantoux test is read by measuring the presence or absence of induration (not redness). The result should be recorded in millimetres (mm).

If it is not possible to read a Mantoux test at 72 hours, a reading at 48 hours is acceptable.1,38 If this is not possible, readings may be done between 72 hours and seven days. However, as all the literature regarding the risk of developing TB is based on reading Mantoux tests at 48–72 hours, the interpretation of Mantoux tests that are read between 72 hours and seven days is uncertain.38
1.5.2 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 New Zealand data, so data collected in similar communities such as Canada\textsuperscript{38} must be used to establish appropriate points for New Zealand. Readings at the cutting points or higher are defined as positive. The cutting points are summarised in Table 1.3.

Children are at greater risk of severe and life-threatening TB disease than adults, so the cutting points shown in Table 1.3 are conservative.\textsuperscript{39–41}

Table 1.3 shows that previous BCG vaccination affects the cutting point in New Zealanders who have not resided in high-incidence countries. However, previous BCG vaccination does not affect the cutting point of a person who has resided in a high-incidence country.

Table 1.3: Definition of a positive Mantoux test in New Zealand (cutting points)

<table>
<thead>
<tr>
<th>Category</th>
<th>Adults (≥ 15 years)</th>
<th>Older children (5–14 years)</th>
<th>Younger children (&lt; 5 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Zealand born</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No BCG vaccination</td>
<td>≥ 10 mm</td>
<td>≥ 10 mm</td>
<td>≥ 5 mm</td>
</tr>
<tr>
<td>• Previous BCG vaccination</td>
<td>≥ 15 mm</td>
<td>≥ 10 mm</td>
<td>≥ 10 mm</td>
</tr>
<tr>
<td>Following residence in a high-incidence country*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• No BCG vaccination</td>
<td>≥ 10 mm</td>
<td>≥ 10 mm</td>
<td>≥ 5 mm</td>
</tr>
<tr>
<td>• Previous BCG vaccination</td>
<td>≥ 10 mm</td>
<td>≥ 10 mm</td>
<td>≥ 10 mm</td>
</tr>
<tr>
<td>With immuno-suppressive illness or taking immuno-suppressive drugs (with or without BCG vaccination)</td>
<td>5–10 mm\textsuperscript{†}</td>
<td>≥ 5 mm</td>
<td>≥ 5 mm</td>
</tr>
<tr>
<td>HIV/AIDS (with or without BCG vaccination)</td>
<td>≥ 5 mm</td>
<td>≥ 5 mm</td>
<td>≥ 5 mm</td>
</tr>
<tr>
<td>Close contacts of smear-positive cases (any origin) (with or without BCG vaccination)</td>
<td>≥ 10 mm</td>
<td>≥ 5 mm</td>
<td>≥ 5 mm</td>
</tr>
</tbody>
</table>

* As per the BCG chapter of the Ministry of Health’s \textit{Immunisation Handbook}.
† See the discussion following the table.

In adults with immuno-suppressive illness or taking immuno-suppressive drugs, the degree and duration of immune suppression should be documented and the appropriate cutting point selected as described here.

The 5 mm cutting point is appropriate with:

- immuno-suppressive treatment for organ transplantation
- aggressive immuno-suppressive cancer treatment
- cytotoxic immuno-suppressive agents such as cyclophosphamide or methotrexate
- systemic corticosteroid treatment that is prolonged (for example, for more than six weeks) and in a dose of prednisone of 15 mg or more per day (or equivalent with another steroid); the higher the dose, the greater the risk of reactivation of TB
• combinations of immunosuppressive conditions (for example, prednisone of less than 15 mg per day plus diabetes mellitus (on treatment), moderate or severely advanced malignancy, or malnutrition (this advice is empirical, not evidence-based)

• end-stage renal failure.

The 10 mm cutting point is appropriate with:
• doses of prednisone less than 15 mg per day long term
• diabetes mellitus (including insulin-dependent)
• alcoholism
• malnutrition
• disseminated malignancy.

1.5.3 Situations in which people should not receive a Mantoux test

The following people should not receive a Mantoux test (incorporating guidance from the Canadian Tuberculosis Standards): 42

• those with documented active TB or a documented history of adequate treatment for LTBI or TB disease in the past (because the test is of no clinical utility and discomfort is likely)

• those with documented Mantoux reactions ≥ 15 mm or greater in the past (because no new diagnostic information will be gained and discomfort is likely)

• those with severe blistering Mantoux reactions in the past, or with extensive burns or eczema present over Mantoux testing sites (because of the greater likelihood of adverse reactions or severe reactions)

• those with major viral infections

• those who have received measles vaccination within the past four weeks (because this has been shown to increase the likelihood of false-negative Mantoux results; no data are available regarding the effect on Mantoux results of other live virus vaccinations – mumps, rubella, varicella and yellow fever – but it would seem prudent to follow the same guidance; however, if the opportunity to perform the Mantoux test might be missed, the test should not be delayed for live virus vaccines, as these are theoretical considerations; note that a Mantoux test may be administered before or on the same day as live virus vaccinations, but at a different site). 43

1.5.4 Situations in which people can receive a Mantoux test

The following people can receive a Mantoux test (incorporating guidance from the Canadian Tuberculosis Standards): 42

• those with a common cold

• those who are pregnant or are breastfeeding

• those immunised with any vaccine on the same day

• those immunised within the previous four weeks with inactivated vaccines

• those who give a history of a positive Mantoux reaction (other than blistering) that is not documented
• those taking low doses of systemic corticosteroids (< 15 mg prednisone (or equivalent) daily; it generally takes a steroid dose equivalent to ≥ 15 mg prednisone daily for 2–4 weeks to suppress Mantoux reactivity).

1.5.5 Serial Mantoux testing: boosting, conversion and reversion
Repeated Mantoux tests can result in larger reaction sizes, which can be due to non-specific variation, boosting or true Mantoux conversion. Non-specific increases occur because of differences in administration, reading and minor variation in the individual’s response. Increases due to non-specific variation are small, between 2 to 3 mm. Increases of 6 mm or more represent either boosting or conversion.

1.5.6 Boosting
The boosting phenomenon is seen when there has been sensitisation to mycobacteria (tuberculous or non-tuberculous) many years earlier, in which case an initial Mantoux test may produce a negative or a weakly positive response (below the positive cutting point). This is thought to occur because there are too few sensitised lymphocytes in circulation to produce a significant local response. If the test is repeated, a larger reading may be obtained due to the immune response being ‘recalled’ or ‘boosted’ by the first test.

The second boosted reading is the correct one (that is, the second result should be used for decision-making or future comparison). Boosting is maximal if the second test is placed one to five weeks after the initial test and it may continue to be observed for up to two years.

The boosting phenomenon is common, especially in older people and in populations with a high prevalence of BCG vaccination and/or exposure to non-tuberculous mycobacteria (NTM).

Two-step Mantoux test
In people who may need to have serial tests for LTBI (such as healthcare workers), IGRA are recommended, if available, as IGRA are not subject to boosting. However, if IGRA are not available, the two-step Mantoux test should be done as part of the initial testing, as it will help to distinguish boosting from conversion on subsequent testing.

The two-step Mantoux test utilises the boosting phenomenon and is performed when a true baseline Mantoux reaction needs to be established. Because boosting lasts up to two years, two-step testing is unnecessary in someone who has been tested in the preceding two years.

The second Mantoux test is needed only if the initial reading is negative. The two tests should not be given at the same site because this can result in increased reaction size.
In a two-step Mantoux test, the second test should be undertaken one week after the first test, and should be read at 48 hours, wherever possible, especially in subjects with previous BCG vaccination. In a small study of United Kingdom health service employees previously vaccinated with bacille Calmette-Guérin (BCG), boosting was maximal if the second test was read 48 hours after placement (injection) compared with after 72 hours and 96 hours.45

Two-step testing is not necessary for the initial Mantoux test in contacts exposed to TB. If contacts have had significant exposure to a person with infectious TB, they will have already been boosted by the time the first test is placed.

### Practice points

If IGRAs are not available, use the two-step Mantoux test to establish a true baseline Mantoux reaction in people who may need to have serial tests for LTBI, eg, healthcare workers, and travellers prior to travelling to high-incidence countries to live or work for more than six months (especially if they are likely to have contact with people with active TB disease in that country).

In a two-step Mantoux test, the first test should be placed and should be read 72 hours later. The second test should be placed, at a different site, one week after the first test was placed, and should be read 48 hours later.

### Example of the value of two-step testing

A 25-year-old nurse is new to a hospital. The nurse reports having had a BCG vaccination as a student at age 18. The nurse has a doubtful BCG scar. The nurse’s first Mantoux result is 3 mm. When the Mantoux test is repeated a week later, the result is 10 mm (that is, the correct, ‘boosted’, reading is 10 mm).

Six months later the nurse has unprotected exposure to a highly infectious case of pulmonary TB where diagnosis was delayed. The nurse provided care to the patient for several days. Eight weeks after exposure the nurse is again Mantoux tested and the reaction is 14 mm. There is no evidence of new TB infection, because the change from 10 mm to 14 mm is less than the 10 mm change required to demonstrate conversion.

Had the two-step test not been used when the nurse joined the hospital, an incorrect change in Mantoux from 3 mm to 14 mm would have been recorded and the nurse would have been managed as a Mantoux conversion.

### 1.5.7 Mantoux conversion

Mantoux conversion is the development of new or enhanced hypersensitivity due to infection with tuberculous or non-tuberculous mycobacteria, including BCG vaccination. By comparison, boosting is a recall of the hypersensitivity response in the absence of new infection.
Mantoux conversion is defined as an increase in the Mantoux reaction of 10 mm or more within a two-year period. Mantoux conversion has been associated with an annual incidence of TB disease of 4% in adolescents and 6% in contacts of smear-positive cases. People who have a Mantoux conversion should be investigated for TB disease (see Chapter 2). If the need for full treatment is excluded, they should be considered for treatment of LTBI.

Mantoux conversion occurs within eight weeks of infection. Therefore, when testing contacts of infectious TB cases for conversion, the first Mantoux test should be done as soon as possible and the second Mantoux test should be done eight weeks after the date of the last contact with the source case.

If a person has had a documented Mantoux test result within the past 12 months and is exposed to infectious TB, the documented pre-exposure result may be used as the baseline in testing for conversion. Therefore only one Mantoux test is necessary to detect conversion. This test should be done eight weeks after the date of last exposure. Positive reactions older than 12 months may wane, so cannot be relied on as a valid baseline.

**Increase in the Mantoux reading of less than 10 mm**

If the Mantoux test increases between tests by less than 10 mm, the second test is the correct reading. Depending on the applicable cutting point, sometimes the second test may be positive, but the change in diameter of induration does not meet the criterion for conversion. There is no evidence to guide a decision regarding whether or not to treat these cases (see section 2.1 for the Tuberculosis Working Group of the Ministry of Health’s recommendations in this situation).

1.5.8 Mantoux reversion

A Mantoux reversion is the change to a negative Mantoux result after a previous positive result. This phenomenon is uncommon in healthy individuals, occurring in less than 10% of people with a previously positive Mantoux.

Reversion is more common in older adults (estimated at 8% per year), when the initial Mantoux was less than 14 mm and in people whose initial positive Mantoux reaction was a boosted result (identified by two-step testing). There is no clinical or epidemiological information available to interpret the significance of a Mantoux reaction that reverts to negative and then becomes positive again.
1.5.9 Interpretation of the Mantoux test

**Practice point**
When interpreting a person’s Mantoux test, there are three dimensions to consider:
- positive predictive value
- the person’s risk of developing active TB disease (see Table 1.2)
- the size of the Mantoux reaction.

**Positive Mantoux result: predictive value for LTBI**
The positive predictive value of a Mantoux test represents the percentage of those with any given Mantoux reading who truly have TB infection. The predictive value varies with different clinical situations. Where the expected prevalence of true infection is low, as in screening situations in a low risk country, the influence of factors other than TB (such as BCG and non-tuberculous mycobacteria) is significant, so lower readings have a low positive predictive value. Where the expected prevalence of TB infection is high, as in contacts of smear-positive cases or immigrants from high-incidence countries, the positive predictive value of lower readings is higher. Therefore, in these situations the effects of factors such as BCG and non-tuberculous mycobacteria carry less weight.\(^38\)

In other words, where there is a low likelihood of TB disease, as in a screening situation, a positive Mantoux test is less likely to be due to TB and more likely to be caused by another factor. Where there is a higher likelihood of TB disease, as in a contact of a smear-positive case, a positive Mantoux is more likely to be due to TB.

**Whether size matters: significance of strongly positive Mantoux**
There is no correlation between size of reaction and likelihood of current active TB disease ie, the Mantoux test has a poor positive predictive value for current active TB disease.\(^15\) However, size of the Mantoux reaction is correlated with future risk of development of active TB disease.\(^16,17,48\)

A large retrospective population-based cohort study into the risk of TB development among over 26,000 untreated contacts with a 12-year follow-up found that TB rates were high for all tuberculin skin test (TST) sizes in household contacts, 0–10 year old contacts and immunosuppressed contacts. For all types of contacts (household contacts, close non-household contacts and casual contacts), the risk of developing TB disease increased with larger TST sizes.\(^49\)

Therefore, as the size of the Mantoux test result increases beyond the cutting point, the extent of increase should be taken into account as one of the risk factors for progression to disease. This is relevant when deciding whether to give treatment for LTBI.
False-positive Mantoux test results

False-positive Mantoux reactions can be caused by:
- previous BCG vaccination
- exposure to non-tuberculous mycobacteria
- factitious false positives, which may occur if the injection site is rubbed or scratched
- observer error
- recording error.

Post-BCG vaccination tuberculin reactions have been extensively studied, and the age at which BCG vaccination was performed affects subsequent Mantoux reactivity.\(^{50,51}\) Among people who received BCG in infancy, 3 to 5% have a subsequent positive Mantoux reaction, whereas 30 to 35% of people who received BCG at an older age may have a subsequent positive Mantoux reaction.\(^{38}\)

A Mantoux reaction larger than 15 mm induration should not be attributed to BCG vaccination. No relationship exists between the post-BCG vaccination Mantoux result and protection against TB disease. Therefore routine post-BCG vaccination Mantoux testing serves no purpose and should not be done.

Non-tuberculous mycobacteria (NTM) are found in soil and water in the environment, especially in warm and moist climates.\(^{38}\) Therefore, particularly in tropical and subtropical climates but also to a lesser extent in cold and temperate climates, people may have been exposed and sensitized to NTM antigens. This may result in a false positive Mantoux reaction due to cross-reactivity, as many of the antigens from NTM and \textit{M. tuberculosis} are similar.

IGRAs are not affected by previous BCG vaccination or by infection with most NTM.

False-negative Mantoux test results

A negative Mantoux test result usually signifies that the individual has never been exposed to \textit{M. tuberculosis}. However, some factors may cause a false-negative result or diminished ability to respond to tuberculin.\(^{1,46}\) Therefore a negative Mantoux does not absolutely exclude either LTBI or TB disease.

People with HIV infection may have a false-negative Mantoux or IGRA test.

A negative Mantoux reaction in an infant under 12 weeks of age may reflect the fact that very young infants may not mount an immune response. The test will need to be repeated if the child has been exposed to an infectious TB case.

IGRAs may have a place in investigating an unexpectedly negative Mantoux test.

Anergy testing is not recommended as a method to discover whether a negative Mantoux result is true or false in either HIV-positive subjects\(^{52}\) or HIV-negative subjects.\(^{53}\)
Causes of false-negative Mantoux test results are factors related to:

- the person being tested, including:
  - viral infections (especially HIV, but also measles, mumps and chickenpox)
  - severe and overwhelming TB
  - other bacterial infections (such as typhoid, brucellosis, typhus, leprosy or pertussis)
  - metabolic disorders (especially renal failure and diabetes)
  - disorders of lymphoid organs (sarcoidosis, lymphoma or leukaemia)
  - corticosteroids or other immuno-suppressive drugs (including commonly used agents such as prednisone at 15 mg or more per day, cyclophosphamide, methotrexate and azathioprine, together with many drugs used to treat cancer)
  - age (infants under 12 weeks of age, and older people, in whom sensitivity wanes)
  - stress (surgery, burns or severe illness of any type)
- technical factors, including the tuberculin solution used, method of administration and reading of results.

### 1.6 Interferon-gamma release assays

Interferon-gamma release assays (IGRAs) have been developed for the diagnosis of TB infection, as an alternative to tuberculin skin tests (TSTs) such as the Mantoux test.

One type of IGRA is the QuantiFERON-TB Gold In-tube assay (QFT-G IT), which has been available in New Zealand since 2006. Another type of IGRA is the T-SPOT TB test, which is available in Europe, but is not currently licensed for use in New Zealand.

#### 1.6.1 Underlying principle of IGRAs

IGRAs work on the principle that if a person is infected with *M. tuberculosis*, T-lymphocytes circulating in their blood will produce interferon-gamma (IFN-gamma) if re-exposed to TB antigens in vitro. In the QFT-G IT, the amount of IFN-gamma released is quantified using an enzyme-linked immuno-sorbent assay (ELISA).

#### 1.6.2 Administering the QFT-G IT test

The QFT-G IT is a blood test, and involves a small blood sample being collected into three specialised tubes (a ‘TB antigen tube’ that contain three synthetic TB antigens, a ‘nil control tube’ and a ‘positive control tube’ that contains mitogen).

#### 1.6.3 Interpretation of QFT-G IT results

When interpreting a person’s QFT-G IT result, the person’s risk of developing active TB disease (see Table 1.2) should be taken into account in addition to the test result itself.
**Practice points**

A QFT-G IT can be positive (which means that infection with *M. tuberculosis* is likely), negative (infection is unlikely) or indeterminate (the test cannot be interpreted).

If a QFT-G IT is positive, the person should be investigated further (as for a positive Mantoux test).

If a QFT-G IT is negative or indeterminate and:
- the person is asymptomatic and not immuno-compromised, no further action is required
- the person is symptomatic or immuno-compromised, the person should be investigated further (as for a positive Mantoux test).

An indeterminate QFT-G IT result means that the test cannot be interpreted (‘test failure’). Indeterminate results may be due to laboratory error, a low mitogen response or a high background response. If a person has an indeterminate result, it may be worthwhile repeating the QFT-G IT once, or a Mantoux test can be done. Indeterminate QFT-G IT results are more common in immuno-compromised people. See Chapter 11 for further technical details regarding the interpretation of QFT-G IT.

### 1.6.4 Selected literature on IGRA

#### Cost-effectiveness studies

A number of studies looking at the cost-effectiveness of IGRAs (mostly looking at QuantiFERON-TB Gold or QFT-G) have been published.\(^{54–58}\) One Canadian study concluded that, as long as screening was targeted at people at high risk of TB disease, QFT-G was cost-effective when used to test TST-positive persons,\(^{54}\) while another study concluded that implementation of QFT-G as a confirmatory test for TST-positive individuals could significantly reduce the number of people given LTBI treatment in a low-incidence country such as Canada.\(^{55}\) A third Canadian study concluded that the most cost-effective strategy was to use QFT-G in BCG-vaccinated contacts and to use TST for all others, although when the assumptions were altered to include a higher prevalence of recent infections and greater adherence to LTBI treatment, QFT-G became cost-effective in more subgroups.\(^{56}\) Studies from France and Germany concluded that the use of QFT-G alone was more effective in reducing the number of TB cases and more cost-effective than QFT-G followed by confirmatory TST.\(^{57,58}\)

#### Screening immigrants and asylum seekers

Several studies looked at IGRA use in screening immigrants and asylum seekers.\(^{59–61}\) Positive IGRA results in immigrants who were close contacts of smear-positive cases may have reflected TB exposure in their country of origin many years before, rather than infection due to recent exposure.\(^{59}\) A Norwegian study of asylum seekers found that 43% less asylum seekers needed referral for positive tests if QFT-G was used.\(^{60}\) A UK study in immigrants from high TB burden countries found that QFT-G testing followed by CXR was feasible, was cheaper than using the NICE guideline (which recommends IGRA following a positive Mantoux test) and identified more cases of LTBI.\(^{51}\)
Predicting the development of TB disease

A study of the prognostic value of IGRAs looked at whether the QuantiFERON-TB Gold In-tube assay (QFT-G IT) was better than the TST at predicting the development of active TB disease in 601 recently exposed close contacts of infectious TB cases over a two-year follow-up period. Of the contacts, 40.4% were TST positive at a 5 mm cut-off, while only 11% were QFT-G IT positive. QFT-G IT positivity, but not TST, was associated with exposure time ($p < 0.0001$). The progression rate to TB disease within the two-year follow-up period amongst untreated contacts was only 2.3% (five of 219 contacts) of those who were TST-positive. This was a significantly lower progression rate compared with the 14.6% (6 of 41 contacts) of those who were QFT-G IT positive who progressed to TB disease ($p < 0.003$). The conclusion was that QFT-G IT appears to be a more accurate indicator of the presence of LTBI that the TST and is at least as sensitive for detecting those who will progress to active TB disease.
2 Treatment

LTBI is treated to prevent the future development of TB disease. Effective treatment is available for LTBI.\textsuperscript{1,63,64}

2.1 Who should be offered treatment for LTBI

Treatment should be offered to those people with LTBI who are at high risk of developing TB disease. Refer to sections 1.1 and 1.2 above, and see practice points and text below.

### Practice points

The following groups of people should be offered treatment for LTBI:

- People likely to have been infected recently (see Table 1.1)
- People who have an increased risk of developing active TB disease (see Table 1.2)
- Within the high risk groups in Tables 1.1 and 1.2, the following people with LTBI should be offered treatment as a priority:
  - Mantoux- or IGRA-positive people living with HIV
  - Children under five years of age who are close contacts of any pulmonary or laryngeal TB case (commence treatment irrespective of initial Mantoux reaction; reassess eight weeks after last exposure)
  - Mantoux- or IGRA-positive close contacts of pulmonary or laryngeal TB cases.

The Centers for Disease Control and Prevention’s *Targeted tuberculin testing and treatment of latent tuberculosis infection* is a useful reference document. It contains several useful tables, one showing the incidence of active TB in people with positive TST, by selected risk factors, and another showing relative risk for developing active TB, by selected clinical conditions, compared to a control population.\textsuperscript{1}

2.1.1 HIV infection

See Chapter 6. HIV infection is the greatest single risk factor for developing TB disease. About 30% of people with HIV who have untreated LTBI will develop active TB disease at some stage during their life. Treatment of LTBI reduces the risk of active TB in HIV-positive individuals, especially in those with a positive TST.\textsuperscript{64}

2.1.2 Children under five years of age

The risk of developing TB disease after infection is inversely associated with age. In children, the risk of developing TB disease after infection is as high as 40% in infants under one year of age,\textsuperscript{14} and disease can develop within weeks of infection.\textsuperscript{65,66}

Therefore all children under five years of age who are close contacts of pulmonary or laryngeal TB cases, regardless of the child’s initial Mantoux reaction and the TB case’s smear status, should be referred promptly to a paediatrician.
If the first Mantoux test is positive, a child under five should receive treatment for LTBI.

If a child under five is Mantoux-negative, preventive treatment for possible LTBI should be given for eight weeks, when a second Mantoux test should be done. If the Mantoux converts (an increase of 10 mm or more), a repeat CXR should be considered at that time (to exclude the possibility of active TB disease) and treatment should be continued until complete. If the Mantoux reaction increases between tests by less than 10 mm (ie, does not meet the criteria for conversion), the paediatrician should consider continuing treatment until complete (especially in children under two years of age). If the Mantoux test remains negative, treatment should be stopped and a BCG vaccination should be offered.

If, during the eight weeks between the first and second Mantoux tests, pulmonary specimens from the presumed source case are found to be culture-negative, treatment may be discontinued immediately. The second Mantoux test should still be performed, but it is extremely unlikely that it will convert if the case is culture-negative.

Children aged under five who are not close contacts (ie, are casual contacts) of pulmonary or laryngeal cases should be referred to a specialist only if their Mantoux test is positive on either the first or the second test.

2.1.4 Close contacts of infectious pulmonary or laryngeal TB cases

If they become infected, close contacts of infectious (smear-positive or culture-positive) pulmonary or laryngeal TB cases are at increased risk for developing TB disease, especially within the first one to two years following infection. Therefore Mantoux- or IGRA-positive close contacts should be offered treatment for LTBI. Investigation and follow up of contacts of TB cases is the responsibility of the local public health service.

2.1.5 Medical conditions and immuno-suppressive treatments

Various medical conditions and immuno-suppressive treatments increase the risk for developing TB disease following infection (see Table 1.2). Specialists who test their high risk patients for LTBI should do so with the intention to treat, and should have a clear plan for follow up, monitoring adherence and monitoring for side effects (see sections 2.3 and 2.5).

Renal failure

People who are on renal dialysis or are recipients of a renal transplant are at increased risk of developing TB disease (10–25 times greater risk than the general population). Treatment for TB disease in these patients is usually curative, but a higher risk of mortality has been noted for patients on dialysis compared with other TB patients.

In New Zealand many people with renal failure belong to ethnic communities that also have relatively high rates of TB disease, such as Pacific peoples, Māori, and Asian peoples. Therefore, these groups are at risk of LTBI and subsequent TB disease.
Isoniazid treatment of LTBI is well tolerated by renal transplant recipients, but encephalopathy resulting in temporary confusion and convulsions has been documented in uraemic patients.

All patients with chronic renal failure should be tested for LTBI, preferably with an IGRA, and if the test is positive should be considered for treatment of LTBI. Treatment for Mantoux- or IGRA-negative people with renal failure is not recommended, because there is no evidence to support this. However, if the CXR of a Mantoux-negative renal failure patient shows evidence of past, presumably inactive, TB disease, then their clinician should:

- compare with old CXRs, if possible
- investigate for possible active TB disease
- discuss the need for treatment of LTBI or inactive TB disease with a clinical TB expert.

Diabetes

People with diabetes have a 2–4 times greater risk of developing TB disease, compared with non-diabetics, and the risk is probably greater in those who have poorly controlled or insulin-dependent diabetes. A systematic review and meta-analysis of 13 observational studies showed that diabetes was associated with an increased risk of TB (RR = 3.11, 95% CI 2.27-4.26). A large Hong Kong study looking at diabetic control in elderly people found that diabetic subjects with a baseline haemoglobin A1c of < 7% were not at increased risk of TB, but that a three times greater risk of TB was observed in subjects with a baseline haemoglobin A1c of ≥ 7%.

Many people with diabetes in New Zealand are of Pacific, Māori, and Asian ethnicity. These communities also have relatively high rates of renal disease and TB disease. Therefore individuals from these groups may be at higher risk, due to an increased risk of exposure to TB cases, as well as multiple co-morbidities which increase their risk of subsequent TB disease.

Anti-TNF alpha treatment

Anti-tumour necrosis factor (anti-TNF) alpha treatment is used to treat various rheumatologic, skin and gastrointestinal conditions. People on these drugs are at around five times increased risk of developing TB disease. A higher incidence of TB disease has also been reported with other immunosuppressive and immunomodulatory treatments used in these diseases. Various guidelines are available, which all recommend screening for LTBI, and if an individual is Mantoux- or IGRA-positive, preferably starting treatment for LTBI at least one to two months prior to commencing anti-TNF alpha treatment, or completing LTBI treatment before commencing anti-TNF alpha treatment (although this is often not possible). People on anti-TNF alpha treatment, whether or not they are on LTBI treatment, should be monitored closely for development of TB disease.
Smoking

Several recent meta-analyses found that current smokers, compared with never smokers, have around a 1.8 times increased risk of infection (LTBI), and a 2.6 times increased risk of TB disease, while former smokers have around a 1.6 times increased risk of TB disease. Similar levels of increased risk were described for passive smoking, especially in studies of children and young adults in households of TB patients who smoke.

2.1.6 Situations where LTBI treatment may not be indicated

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

If the Mantoux reaction increases between tests by less than 10 mm, the change in diameter of induration does not meet the criterion for conversion. There is no evidence to guide a decision in such a situation, but the Tuberculosis Advisory Group of the Ministry of Health recommends that:

- a CXR be done
- treatment of LTBI should generally not be given unless there:
  - are risk factors for TB infection progressing to disease (ie, a child aged under five, immune-suppressive treatment, or medical conditions associated with immune-suppression (see Table 1.2)
  - has been close contact with a smear-positive pulmonary case.

Immigrants from high-incidence countries

See Chapter 10. Adult immigrants with a normal CXR and no known recent contact with an infectious TB case have probably been infected in the remote past, so are at lower risk of developing TB disease. However LTBI treatment may be considered if medical or other risk factors exist.

2.1.7 Management of previously treated people who are re-exposed

A person who has adhered to a course of treatment for LTBI or TB disease has a very low risk of later developing TB disease. Protection comes from the treatment and from innate and acquired resistance. However, it is possible to develop disease a second time following re-infection with TB. People who are re-infected cannot be distinguished by a Mantoux test or IGRA because these tests will be positive from their earlier episode of infection. Therefore repeat Mantoux or IGRA testing is not advised after re-exposure, and assessment must be with CXR. Re-treatment should be considered. Re-treatment is needed only for those who have been close contacts of a smear-positive case and have risk factors for progression to TB disease (see Table 1.2).

2.1.8 Deciding whether to treat LTBI

The decision to treat must be a joint one by the patient and the doctor (as well as the public health nurse, if the patient is a contact of a TB case).
Practice points
The decision to treat may be guided by the answers to the following four questions:
- How likely is the person to have been infected? (see Table 1.1)
- How likely is the person to progress to active TB disease? (see Table 1.2)
- What are the risks of an adverse reaction to treatment? (see section 2.2)
- How likely is the person to adhere to treatment? (see Chapter 4)

If the risks of infection and/or disease outweigh the risk of adverse reactions, and an appropriate TB drug is available for treatment (based on the sensitivity of index case’s isolate, if known), the patient should be offered treatment. In an immune-suppressed person who has been exposed recently to an infectious case and had a Mantoux conversion, the risks of infection and progression to disease are high and a directly observed nine-month or even 12-month course of isoniazid is appropriate. It is much less likely that treatment would benefit a Mantoux-positive, foreign-born migrant with a normal CXR who has been in New Zealand for many years or a healthcare worker with presumed LTBI discovered during routine pre-occupational Mantoux or IGRA screening. Prior BCG vaccination and its possible effect on Mantoux status should also be taken into account.

2.1.9 Chest X-ray prior to starting treatment
The diagnosis of LTBI depends on finding evidence of TB infection (positive Mantoux or IGRA) in an asymptomatic person in the absence of radiological or other signs of active or inactive TB disease. Therefore a CXR is essential as part of the diagnosis of LTBI, prior to starting LTBI treatment. In LTBI the CXR is normal or shows trivial and stable evidence of past TB (eg, a small scar or patch of calcium; see Table 4.1 in Chapter 2).

Practice points
In a person with LTBI, the CXR is normal, or shows trivial and stable evidence of past TB (eg, a small scar or patch of calcium; see Table 4.1 in Chapter 2).

People with radiological evidence of active or inactive TB disease should not be treated for LTBI, and require further investigations (see section 2.2, and Table 4.1 in Chapter 2).
2.2 LTBI treatment contraindications and precautions

In LTBI, treatment is being given to a well, asymptomatic person, so a lower level of risk is acceptable.

**Practice points**

People with clinical or radiological or laboratory evidence of active or inactive TB disease should *not* be treated for LTBI.

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

Caution is needed, and the risks versus the benefits of LTBI treatment need to be assessed carefully, when deciding whether or not to treat:

- a pregnant woman
- a person who has acute or chronic liver disease
- a person who is taking concurrent medications that can cause hepatotoxicity
- a person with a high alcohol intake or alcohol abuse, especially if they are not willing/able to stop or reduce their intake
- a person who is unlikely to adhere to treatment and/or to monitoring (clinical and/or laboratory)
- a person who has peripheral neuropathy, or risk factors for its development (eg, diabetes, chronic renal failure, alcohol abuse or malnutrition).

**2.2.1 Clinical, radiological or laboratory evidence of tuberculosis disease**

Treatment for LTBI is contraindicated if there is clinical, radiological or bacteriological evidence of active or inactive (old, healed) TB disease. Prompt investigation is needed to assess whether the disease is active or inactive (see Table 4.1 in Chapter 2 for radiological criteria for induced sputum testing or bronchoscopy), and if treatment is needed, full multi-drug treatment should be given.

**2.2.2 Close contacts of MDR-TB cases**

A 2006 Cochrane review (updated to 4 March 2009) of drugs for preventing TB in people at risk of MDR-TB found no randomised controlled trials (RCTs) that met the inclusion criteria. The conclusion was that the balance of benefits and harms associated with treatment of LTBI in people exposed to MDR-TB was far from clear. The World Health Organization (WHO) does not recommend the universal use of second-line drugs to treat LTBI in contacts of MDR-TB cases. One prospective cohort study found individualised tailored treatment to be effective in preventing active TB in children.

Outside the context of a well-designed RCT, drug treatments should only be offered to contacts of MDR-TB cases where they are informed of the current evidence on benefits and harms, along with the uncertainties.
It is important to note that those contacts of MDR-TB cases who have been assessed as requiring treatment with second-line drugs, as well as those contacts who are not treated but who are at high risk of progression to TB disease, should be managed by or co-case managed with a hospital specialist experienced in the treatment of MDR-TB cases and contacts of MDR-TB. Contacts started on drug treatment should be monitored very carefully for adverse effects, due to the toxicity of second-line TB drugs. All contacts should be educated about the need for lifelong awareness of the symptoms and signs of active TB disease, and should be monitored closely for at least two years.\textsuperscript{25,42}

2.2.3 Pregnancy and breastfeeding

Treatment of active TB disease is justified in pregnancy but treatment of LTBI is more controversial. Treatment of LTBI in pregnant women is usually delayed until after the birth of the baby, except in HIV-positive pregnant women or documented recent LTBI infection, where the risk of progression is high (eg, a documented conversion or Mantoux test of 15 mm or more after exposure to a smear- or culture-positive case).\textsuperscript{1} Isoniazid or rifampicin may be used for LTBI treatment in pregnant or breastfeeding women. Pregnant or breastfeeding women taking isoniazid should also receive pyridoxine (vitamin B6).

2.2.4 Acute and chronic liver disease

Treatment of LTBI is not contraindicated in hepatitis B surface antigen-positive carriers who have no evidence of active liver disease, or in people with hepatitis C. However, they may be more likely to develop hepatotoxicity, and hepatitis B e antigen positivity (HBeAg) represents an important risk factor for severe isoniazid hepatitis.\textsuperscript{5,97} Frequent monitoring of liver function is indicated (see Chapter 3).

Treatment of LTBI may need to be considered in a person who has acute liver disease and a high risk of TB infection progressing to disease after they have had close and prolonged contact with a highly infectious TB case; especially if the contact is receiving immuno-suppressive treatment.

2.2.5 Age

Isoniazid hepatotoxicity increases with age and underlying disease. However, United States and Canadian guidelines recommend no age limit for treatment of LTBI because the risk of severe or fatal hepatotoxicity is considered low, even in those aged over 35, and if testing and treatment are targeted at those at high risk, the risk-benefit ratio is acceptable.\textsuperscript{7,42} However, the elderly have fewer years left in which to benefit from treatment.\textsuperscript{38} The UK National Institute for Health and Clinical Excellence (NICE) TB guidelines do not recommend treatment for those aged over 35 years.\textsuperscript{25}

Rifampicin also carries a small risk of hepatotoxicity, but the risk does not appear to increase with age.\textsuperscript{99,100} See Chapter 3 for further details regarding adverse reactions associated with TB medications.
Age over 35 years should not be a contraindication to treatment for LTBI, if the clinical indications are strong, but closer monitoring of people over 35 years of age is probably advisable.\textsuperscript{1,42}

2.3 Who should prescribe treatment and follow up for LTBI

2.3.1 Prescribing

Treatment of LTBI is a specialised task. In New Zealand, TB medications may only be prescribed by specialist medical practitioners (e.g., respiratory physicians, infectious diseases physicians, renal physicians, paediatricians, occupational health physicians). Specialists who treat LTBI should have knowledge and experience in this area. General practitioners (GPs) should consult with an appropriate specialist if they have identified a patient who has LTBI, is at high risk of developing TB disease (see Table 1.2) and who would therefore benefit from LTBI treatment.

2.3.2 Follow-up

Careful follow-up of people on LTBI treatment is essential, and is the responsibility of the prescribing clinician. See section 2.5 on practical considerations in treating LTBI, including patient education, recommended baseline laboratory tests, and ongoing monitoring of adherence and for adverse effects.

Most public health units do not have the capacity to offer follow-up for high risk patients diagnosed with LTBI who are not contacts of active TB disease cases. Follow-up of non-contacts prescribed LTBI treatment is therefore the responsibility of the prescribing clinician. Investigation and follow up of contacts of TB cases notified to the medical officer of health is the responsibility of the local public health service’s medical and public health nursing staff.

2.4 LTBI treatment regimens

Note re abbreviations in this section: the commonly accepted abbreviations for TB drugs are used i.e., isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E). A number before a capital letter refers to the number of months of daily treatment in that regimen e.g., 3RH means three months of daily rifampicin and isoniazid. The terms used to describe study types and results include randomised controlled trial (RCT), relative risk (RR) and confidence interval (CI).

<table>
<thead>
<tr>
<th>Practice points</th>
</tr>
</thead>
<tbody>
<tr>
<td>The choice of drug regimen for treatment of LTBI in an individual depends on:</td>
</tr>
<tr>
<td>• the presence or absence of risk factors for progression to TB disease (Table 1.2)</td>
</tr>
<tr>
<td>• assessment of the individual’s likely level of adherence to treatment</td>
</tr>
<tr>
<td>• whether there are time constraints (i.e., need for a short course)</td>
</tr>
<tr>
<td>• the antibiotic susceptibility of the presumed source case (if known)</td>
</tr>
<tr>
<td>• whether the individual is likely to tolerate the drug(s).</td>
</tr>
</tbody>
</table>
Recommended drug regimens for treatment of LTBI are shown in Table 2.1.

Drug doses, pharmacological considerations and side effects are discussed in Chapter 3.

Table 2.1:  Recommended drug regimens for treatment of LTBI

<table>
<thead>
<tr>
<th>Clinical situation</th>
<th>Drug</th>
<th>Administration</th>
<th>Duration (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard regimen for adherent clients</td>
<td>H</td>
<td>Self, daily</td>
<td>6</td>
</tr>
<tr>
<td>Standard regimen for non-adherent clients</td>
<td>H</td>
<td>DOT, thrice weekly</td>
<td>6</td>
</tr>
<tr>
<td>Client HIV-positive (see Chapter 6)</td>
<td>H</td>
<td>Self, daily</td>
<td>9</td>
</tr>
<tr>
<td>Adherent clients with multiple risk factors (see Table 1.2)</td>
<td>H</td>
<td>Self, daily</td>
<td>9–12</td>
</tr>
<tr>
<td>Non-adherent clients with multiple risk factors (see Table 1.2)</td>
<td>H</td>
<td>DOT, thrice weekly</td>
<td>9–12</td>
</tr>
<tr>
<td>Short course regimen for adherent clients</td>
<td>RH</td>
<td>Self, daily</td>
<td>3</td>
</tr>
<tr>
<td>Short course regimen for non-adherent clients</td>
<td>RH</td>
<td>DOT, thrice weekly</td>
<td>4</td>
</tr>
<tr>
<td>Source case H-resistant or client cannot tolerate H or short course regimen preferred</td>
<td>R</td>
<td>Self, daily</td>
<td>4</td>
</tr>
<tr>
<td>Source case multi-drug-resistant* (see important note below)</td>
<td>Individually tailored (eg, ZE, or Z + quinolone)</td>
<td>Self, daily</td>
<td>6 (if immuno-competent) or alternatively no treatment 12 (if immuno-suppressed)</td>
</tr>
</tbody>
</table>

Notes: DOT = directly observed therapy; E = ethambutol; H = isoniazid; R = rifampicin; Z = pyrazinamide.
* Consultation and co-case management with a hospital specialist experienced in the treatment of MDR-TB/contacts of MDR-TB is essential. Most contacts of MDR-TB cases should not be treated but should be monitored closely for at least two years. Efficacy of these regimens is unproven. One prospective cohort study found individually tailored regimens to be effective in preventing active TB in children.

2.4.1 Efficacy of LTBI treatment regimens in HIV-negative people

Isoniazid

A Cochrane review of treatment of LTBI in HIV-negative people included 11 randomised trials (with a total of 73,375 participants) comparing isoniazid versus placebo. This review showed that in HIV-negative individuals, treatment of LTBI with isoniazid for six to 12 months prevents the development of TB disease (RR 0.40, 95% CI 0.31 to 0.52) and reduces deaths from TB disease, but does not reduce all-cause mortality. The number needed to treat (NNT) to prevent one case of TB disease was 100 overall. Efficacy and NNT vary, depending on an individual’s risk of progression to TB disease. In this review, durations of isoniazid of longer than six months (RR 0.38, 95% CI 0.28 to 0.50 for 12 months) had little additional benefit, compared with a duration of six months (RR 0.44, 95% CI 0.27 to 0.73).

The UK National Institute for Health and Clinical Excellence (NICE) TB guidelines recommend 6H (or 3RH) for HIV-negative adults and children.25

The recommended standard treatment regimen for LTBI in HIV-negative people in the USA and Canada is 9H.1,42
Contacts of isoniazid-resistant cases

For contacts of isoniazid-resistant TB cases, rifampicin is usually used to treat LTBI. However, evidence is sparse in this area.

In the USA and Canada, the recommended regimen for contacts of isoniazid-resistant TB cases is 4R. The NICE TB guidelines recommend 6R for contacts aged 35 years or younger of isoniazid-resistant TB cases.

A recent modelling study considered the rate of isoniazid resistance at which a rifampicin-containing regimen should be used for LTBI treatment in immigrant children originating from countries where isoniazid resistance is common. The study concluded that rifampicin should be considered for treatment of LTBI in children originating from countries which have > 11% isoniazid resistance.

Short course regimens

Overall, short course regimens using R or RH have better adherence, better completion rates, similar or fewer serious side effects, and are cost-effective.

However, large scale prospective studies of short course regimens are needed, with extended post-treatment follow up, to clarify the long-term rate of development of active TB disease following short course treatment of LTBI with R or RH, compared with standard isoniazid treatment.

The risk of development of acquired rifampicin resistance following LTBI treatment with rifampicin-containing regimens also requires study.

Rifampicin plus isoniazid regimens (3RH and 4RH)

The NICE TB guidelines recommend 3RH as an alternative to 6H for HIV-negative adults and children.

A meta-analysis of five trials comparing 3RH with H (for 6 to 12 months) included a total of 1926 adults with average duration of follow up between 13 to 37 months. The study concluded that 3RH and standard isoniazid regimens of 6 to 12 months duration were equivalent in terms of efficacy and safety.

A 1998 UK study conducted in one health district showed that no child notified with TB disease in the period 1987 to 1996 (the period during which shorter three and four month RH regimens were introduced) had received prior treatment for LTBI. No children needed to have treatment stopped due to adverse effects. A randomised controlled study of treatment of LTBI in children compared 9H with 4RH and also compared 3RH with 4RH. Follow-up was for a minimum of three years. The study concluded that 3RH and 4RH were as effective and safe as 9H, and were associated with much better adherence than 9H.
In tuberculin-positive people with silicosis in Hong Kong, treatment regimens 3RH, 3R and 6H were shown to have similar efficacy and were all effective compared with placebo.\textsuperscript{105}

**Rifampicin regimen (4R)**

In the USA and Canada, 4R is considered an acceptable alternative to isoniazid when a shorter regimen is needed, or for people who cannot tolerate isoniazid.\textsuperscript{1,42}

A recent meta-analysis of 4R versus 9H included four studies (including two RCTs and two non-randomised studies) with pooled data from a total of 3586 patients.\textsuperscript{106} Compared with 9H, treatment with 4R was associated with better compliance, showing a significant reduction in the risk of non-completion (RR 0.53, 95% CI 0.44 to 0.64). The 4R regimen was associated with significantly less hepatotoxicity than 9H (RR 0.12, 95% CI 0.05 to 0.30) and was more cost-effective. The authors noted that a large trial was needed to define the risks of TB disease among people who received 4R.

**Rifampicin plus pyrazinamide (2RZ) is no longer recommended**

The 2RZ regimen has been shown to be as effective as isoniazid in both HIV-negative and HIV-positive people,\textsuperscript{107} but is no longer generally recommended due to an unacceptably high rate of severe hepatotoxicity.\textsuperscript{108}

### 2.4.2 Efficacy of LTBI treatment regimens in HIV-positive people

**Isoniazid**

See the treatment of LTBI section in Chapter 6. A Cochrane review of LTBI treatment in HIV-infected people showed that treatment of LTBI with any regimen was associated with a reduced risk of developing active TB (RR 0.68, 95% CI 0.54 to 0.85).\textsuperscript{64} The benefit was more pronounced in Mantoux-positive individuals (RR 0.38, 95% CI 0.25 to 0.57). Efficacy was similar for all regimens, regardless of drug type, frequency or duration of treatment. However, compared to isoniazid monotherapy, short-course multi-drug regimens in HIV-positive people had more adverse effects requiring discontinuation of treatment. Isoniazid does not have any significant interactions with anti-retroviral therapy.

The recommended standard treatment regimen for LTBI in HIV-positive people in the USA and Canada is 9H.\textsuperscript{1,42}

The NICE TB guidelines\textsuperscript{25} recommend 6H (rather than 9H) for HIV-infected people of any age, based on the results of the Cochrane review.\textsuperscript{64}

**Contacts of isoniazid-resistant cases**

In the USA, for contacts of isoniazid-resistant TB cases (both HIV-positive and HIV-negative), the recommended regimen is 4R.\textsuperscript{1}

The NICE TB guidelines recommend 6R for contacts aged 35 years or younger of isoniazid-resistant TB cases.\textsuperscript{25}
Short course regimens

The 2RZ regimen has been shown to be effective in HIV-infected people,\textsuperscript{64,107,109} but as mentioned above, is no longer generally recommended due to an unacceptably high rate of severe hepatotoxicity.\textsuperscript{108}

Other short course regimens only appear to be recommended in HIV-positive people who are contacts of isoniazid-resistant TB cases (4R or 6R, see above).\textsuperscript{1,25}

2.4.3 Hepatotoxicity

The three TB drugs most likely to cause hepatotoxicity, which may result in drug-induced liver injury (DILI), are isoniazid, rifampicin and pyrazinamide.\textsuperscript{110,111}

Isoniazid hepatotoxicity is age related, occurring more frequently with increasing age.\textsuperscript{110,112} Elevated baseline transaminases and excessive alcohol consumption are other risk factors for hepatotoxicity.\textsuperscript{110,112} A literature review found limited data suggesting an association between chronic viral hepatitis infection (hepatitis B and hepatitis C) and isoniazid-associated hepatotoxicity during LTBI treatment (although there is substantial evidence suggesting an association in people treated for TB disease with isoniazid-containing multi-drug regimens).\textsuperscript{113}

The 2RZ regimen is no longer generally recommended due to an unacceptably high rate of severe hepatotoxicity.\textsuperscript{108}

Studies have found RH regimens to be as safe as isoniazid regimens in adults (3RH)\textsuperscript{102} and in children (3RH and 4RH).\textsuperscript{103,104}

A meta-analysis found that 4R was associated with significantly less hepatotoxicity than 9H.\textsuperscript{106}

2.4.4 Cost-effectiveness

The cost-effectiveness of treatment for LTBI, if treatment is targeted towards people at high risk of developing TB disease, compares favourably with that of other medical interventions.\textsuperscript{98}

Six months is probably the most cost-effective duration of treatment for isoniazid.\textsuperscript{1,114}

4R is more cost effective than 9H.\textsuperscript{106}

2.4.5 Impact of LTBI treatment on antibiotic susceptibility of tuberculosis

Concern that single drug treatment for LTBI might generate drug-resistant strains does not seem to have occurred, but this issue requires further study.\textsuperscript{98}

In New Zealand, isoniazid LTBI treatment regimens have been used for 30 years, but the rate of isoniazid resistance among New Zealand-born TB cases has not increased (see Chapter 1).
2.5 Practical considerations in treating LTBI

2.5.1 Baseline investigations including HIV status

All adults (and children who are considered at risk of HIV) should be tested for their HIV status when being considered for LTBI treatment, since HIV-positive people require a longer course of treatment (9H) and more treatment supervision than HIV-negative people.

Other recommended pre-treatment baseline tests in adults include haematology, creatinine, alanine amino-transferase (ALT) followed by full liver function tests (LFTs) if elevated, hepatitis B and hepatitis C serology. Children have a lower risk of hepatotoxicity from TB drugs than adults, therefore baseline tests may not always be needed.

2.5.2 Education

Patient education (using interpreters and written translations if needed) should include:

- the difference between TB disease and LTBI
- that LTBI is not infectious to others
- the possible adverse effects of treatment (including written information about the symptoms of hepatotoxicity and other adverse effects)
- timing for monitoring visits and blood tests
- the contact person/contact details if the patient needs further advice.

2.5.3 Alcohol and smoking

Patients should be advised that drinking alcohol is an important risk factor for hepatotoxicity, and that they should abstain from alcohol while taking drugs for LTBI.

Smokers should receive advice and be supported to stop smoking, as per the Ministry of Health’s New Zealand Smoking Cessation Guidelines.¹¹⁵

2.5.4 Communication with the patient’s usual doctor

When prescribing treatment for LTBI, the prescribing clinician should advise the patient’s doctor (usually the GP) in writing of the indications, drug(s), dosage and duration of treatment, and the management of adverse reactions and potential drug interactions, including the potential for hepatotoxicity. See Chapter 3 for further details regarding adverse reactions associated with TB medications.

2.5.5 Follow-up and monitoring for adverse effects and for adherence

Follow-up should be face to face, and at monthly intervals (or more frequently if necessary, for example if there are adverse effects). Monthly follow-up of contacts with LTBI being treated by public health services is usually done by public health nurses.
Follow up of non-contacts prescribed LTBI treatment is the responsibility of the prescribing clinician.

Prescriptions should be issued for one month at a time to ensure monthly face to face follow-up.

To prevent symptoms and signs of peripheral neuropathy in patients on isoniazid or isoniazid-containing LTBI regimens, 25 mg of pyridoxine daily should be prescribed for all adults, including pregnant women and mothers of fully breastfed infants. Breastfeeding infants who are on isoniazid should be prescribed pyridoxine, even if their mother is also taking it. The following groups of children may also need to take pyridoxine: older (ie, adult-sized) children and adolescents, those who develop paraesthesia, those with poor nutritional status and those with co-morbidities that may increase the risk of pyridoxine deficiency (seizure disorders, diabetes, uraemia, HIV).

At each follow-up visit patients should be asked about symptoms and signs of adverse effects and reminded to abstain from alcohol.

Patients should be reminded that it is essential to stop their LTBI drug(s) at the first symptom or sign of a possible adverse effect, and then to contact their prescribing clinician or GP immediately for further advice, as urgent LFTs are indicated. Severe liver injury may occur if LTBI treatment is continued in the presence of symptoms, and patients must not wait for signs such as jaundice to occur before stopping their drugs.

Symptoms and signs of possible hepatotoxicity for which patients should be alert include loss of appetite, nausea, vomiting, abdominal discomfort or pain, and unexplained fatigue or feeling generally unwell (symptoms), jaundice and dark urine (signs).

In people being treated for LTBI, monitoring of LFTs should generally be done at baseline, one month after starting treatment, and then every second month in people without risk factors for hepatotoxicity. In people with risk factors for hepatotoxicity, LFTs should be done monthly (or more frequently if necessary). See Chapter 3.

Efficacy of LTBI treatment is affected by both duration of treatment and adherence to the treatment regimen. Chapter 4 discusses how to improve adherence.

2.5.6 Threshold for stopping LTBI treatment due to hepatotoxicity

If AST or ALT reach three times the upper limit of normal consult with a clinical TB expert. If the patient has no symptoms, treatment can usually be continued, but the patient should be closely monitored. Re-check for symptoms and repeat LFTs three to four days later. In an asymptomatic person, with very close monitoring, AST or ALT may be allowed to rise up to five times the upper limit of normal.

If AST or ALT reach three times the upper limit of normal, and the patient has symptoms, treatment should be stopped. When LFTs have normalised, treatment with a different drug can be considered, with very close monitoring.
If ALP or GGT exceed twice the upper limit of normal, treatment should be stopped. When LFTs have normalised, treatment with a different drug can be considered, with very close monitoring.

2.5.7 Antibiotic susceptibility of source case

The antibiotic susceptibility of the presumed source case must be established (where possible). If the person with LTBI has been started on treatment before the antibiotic susceptibility of the source case is known, their regimen may need to be changed.

If the regimen needs to be changed, it should be started from scratch (i.e., the period during which the contact took the ineffective drug should not be counted).

The most common scenario necessitating a change in the LTBI regimen is a source case who is found to be isoniazid-resistant, in which case isoniazid should be stopped and 4RH should be started.

2.5.8 Search for a source case

When a child is diagnosed with LTBI, there must be an urgent search for the presumed source case, if they have not already been identified. The child’s immediate family or household should be assessed for symptoms and signs of active TB disease.

2.5.9 Changing regimens because of adverse effects

If a patient’s regimen is changed because of side effects or adverse effects from the first agent given, the whole period of treatment on the first agent counts toward the eradication of LTBI and a lesser period is needed on the second regimen.

2.5.10 Ending treatment

Treatment should be extended for the appropriate length of time to compensate for all missed doses/missed weeks on treatment.

For adults, an end-of-treatment CXR is needed only if the pre-treatment CXR was abnormal. Most children will need an end-of-treatment CXR because subtle radiological changes are more often seen in children and they are at higher risk of undetected progression to TB disease than adults.

The patient should be given a written record of their Mantoux test or IGRA result, the LTBI treatment they received, and a reminder of the need for lifelong awareness of the symptoms and signs of TB.

2.5.11 If treatment is not given

If treatment is contraindicated, declined or considered inappropriate (e.g., because of likely non-adherence), the patient and their GP should be alerted to the risk of future TB disease.

Routine CXR monitoring of people with LTBI who are not treated is not recommended.
Monitoring with CXRs over two years is recommended for some untreated IGRA- or Mantoux-positive people, including:

- children aged under five who are close contacts of smear- or culture-positive cases
- HIV-positive contacts
- contacts of MDR-TB source cases
- people with inactive fibrotic scars on the CXR.

### 2.5.12 Reporting LTBI under treatment to the medical officer of health

Although LTBI is not notifiable, if a clinical decision is made to offer treatment to a person with LTBI, the treating clinician should seek the person’s consent to report them as a case of ‘LTBI under treatment’ to the local medical officer of health. No public health action is required, but the case details are entered into the national surveillance database so that LTBI trends can be monitored.
References


29 Voss L. 2010. Personal communication.


