Policy 3.1 Diagnosis of Latent Tuberculosis Infection (Adults)

Title
Diagnosis of Latent Tuberculosis Infection

Reference Number
WA Tuberculosis Control Program Policy 3.1

Policy Statement
This document describes the indications and options for testing for latent tuberculosis infection (LTBI) in adults.

Areas Covered
Indications for testing for LTBI. High-risk populations. Diagnostic tests available for LTBI testing.

Policy sponsor
Medical Director, WA TB Control Program

Issued
02 March 2012

Review Date
02 March 2017

Related WA TB Control Program Policies

1.1 Diagnosis of tuberculosis – Laboratory
1.2 Diagnosis of tuberculosis – Clinical
2.1 Medical treatment of tuberculosis (adults)
2.2 Case management of tuberculosis
3.1 Diagnosis of latent tuberculosis infection
3.2 Treatment of latent tuberculosis infection
4.1 Tuberculosis (active and latent) in children
4.2 Management of tuberculosis in prisoners and immigration detainees
4.3 Tuberculosis (active and latent) in pregnant women
4.4 Tuberculosis and HIV
5.1 BCG Vaccination
6.1 Contact tracing for tuberculosis
6.2 Active surveillance for tuberculosis in recent migrants
6.3 Tuberculosis and health care workers
6.4 Active surveillance for tuberculosis prior to anti-TNF alpha treatment
7.1 Notification of tuberculosis and enhanced surveillance data
8.1 Diagnosis and management of Hansen’s disease
9.1 Management of confidential information for the WA Tuberculosis Control Program
9.2 Client record management policy for the WA Tuberculosis Control Program
9.3 Fees and charges associated with tuberculosis and leprosy treatment

Document Control

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<th>Effective Date</th>
<th>Author Comment</th>
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<td>22 September 2011</td>
<td>Initial Document</td>
</tr>
<tr>
<td>1.1</td>
<td>31 January 2012</td>
<td>Consultation and review</td>
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Acronyms

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<th>Description</th>
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<tr>
<td>BCG</td>
<td>bacille Calmette-Guérin</td>
</tr>
<tr>
<td>CFP-10</td>
<td>culture filtrate protein 10</td>
</tr>
<tr>
<td>ESAT-6</td>
<td>early secretory antigenic target-6</td>
</tr>
<tr>
<td>HIV</td>
<td>human immunodeficiency virus</td>
</tr>
<tr>
<td>IGRA</td>
<td>Interferon Gamma Release Assay</td>
</tr>
<tr>
<td>LTBI</td>
<td>Latent tuberculosis infection</td>
</tr>
<tr>
<td>NTAC</td>
<td>National TB Advisory Committee</td>
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<tr>
<td>PPD</td>
<td>purified protein derivative</td>
</tr>
<tr>
<td>QIFN</td>
<td>QuantiFERON-TB Gold In-Tube test</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>TST</td>
<td>Tuberculin skin test</td>
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1.0 Introduction

This policy describes the diagnosis of latent tuberculosis infection (LTBI) in adults. The medical management of LTBI and the management of special groups, including children and pregnant women, and active surveillance for tuberculosis (TB) is described in other WA TB Control Program policies detailed above.

1.1 TB infection versus disease

Following infection by mycobacteria, around 90% of non-HIV positive patients will develop no disease. While there may be some degree of lympho-haematogenous spread and the activation of cell mediated immunity, for most the mycobacteria are contained although viable bacteria may remain present in normal tissue. Following infection, the subsequent lifetime risk of active TB is generally estimated at 10% with half of these cases occurring within 2 to 5 years of infection (Northern Territory Centre for Disease Control, 2008).

Latent TB infection is that state in which inert viable bacteria remain contained in the body. Persons with LTBI do not display symptoms of active TB infection and are not infectious to the general population. However, LTBI has the potential of leading to active disease. Diagnosis of LTBI followed by preventive treatment will reduce the risk of developing active TB.

2.0 Rationale for testing for LTBI

An important strategy in TB control, especially in low prevalence countries is the identification of persons with LTBI at risk of progression to active TB disease and treatment of those persons with an effective drug regime (Communicable Diseases
Network Australia, 2002). This incorporates effective contact tracing of active TB cases, post-migration screening and treatment, and targeted screening of high-risk groups as detailed in other Western Australian TB Control Program polices.

Testing for latent TB infection should aim to identify those persons at high risk for progressing to active TB who would benefit from receiving treatment of LTBI especially those persons who are at increased risk for a poor clinical outcome (e.g. disseminated disease, meningitis) if active TB occurs. The latter group includes persons co-infected with HIV and children less than 2 years old (Marais, Schaaf, & Donald, 2009). In Western Australia a large proportion of TB disease is the result of reactivation of latent TB.

2.1 Risk factors for TB infection

Certain subgroups of the general population are more at risk of TB infection (Mazurek et al 2010). These are:

1. A contact of active TB,
2. Persons born, or who have lived for a prolonged period, in countries that have a high incidence of active TB defined as >50/100 000 per year (e.g. Africa, Asia). For country based tuberculosis incidence refer to the WHO website http://www.who.int/tb/country/data/profiles/en/index.html (World Health Organisation 2011)
3. Indigenous Australians
4. Certain occupational or residential settings (Table 1)

Table 1: Occupational or residential settings with increased risk of TB exposure

| • Hospitals and other health care facilities |
| • Nursing homes |
| • Other long-term health facilities |
| • Correctional facilities and detention centres |
| • Mycobacteriology laboratory personnel |

2.2 Risk factors for progression of LTBI to active TB

Once infected with \textit{M.tuberculosis} the majority of people do not develop active disease; however, there are certain subgroups of the population who are more at risk to progressing to active TB (Mazurek et al 2010; American Thoracic Society, 2000). They are:

1. Infants and children <2 years old (Marais, Schaaf, & Donald, 2009), especially if they are contacts of TB patients.
2. Persons recently infected with \textit{M.tuberculosis} (within 2 years).
3. Cigarette smokers
4. Persons with a history of untreated or inadequately treated active TB, including persons with fibrotic changes or upper lobe infiltrates on chest x-ray consistent with prior active TB.
5. Persons with associated medical conditions or treatments (Table 2).

Table 2: Co-morbid conditions which increase the risk of developing active TB

- HIV infection
- Immunosuppressive therapy such as anti-tumour necrosis factor alpha (TNFα), post organ transplantation immunosuppressant therapy and immunosuppressant therapy equivalent to prednisolone 15mg/day for 1 month
- Silicosis
- Diabetes mellitus
- Chronic renal failure/haemodialysis
- Leukemia or lymphoma
- Cancers of the head, neck or lung
- Persons who have had gastrectomy or jejunoileal bypass
- Malnutrition
- Medical conditions as a consequence of excessive alcohol use or illicit drug use

2.3 Indications for LTBI testing

Testing for LTBI is generally not indicated unless there is a risk for TB infection as detailed in section 2.1 above. Screening and testing for latent TB infection should be performed with the intention to offer treatment and targeted at persons with a high risk of developing TB (American Thoracic Society, 2000). This would include the following groups:

- Recent contact of a person with infectious TB,
- Chest x-ray changes consistent with past inactive untreated TB (e.g. fibronodular apical or upper lobe infiltrates),
- Screening of high-risk groups, including recent migrants or refugees from high prevalence countries and prisoners,
- High risk groups should only be screened if there is an intention to treat,
- As a baseline and ongoing surveillance in employees whose work may involve exposure to TB (Table 1). More detail regarding testing in health care workers is available in the WA TB Control Program policy 6.3 Tuberculosis and health care workers.

The presence (or in anticipation) of the high-risk medical conditions listed in Table 2 for progression of LTBI adds weight for the testing for LTBI in those groups.
3.0 Tests for Latent Tuberculosis Infection (LTBI)

The tests available for screening for LTBI in Western Australia are the:

1). Tuberculin skin test (TST), also called Mantoux test, and the
2). QuantiFERON-TB Gold In-Tube test (QIFN).

Both these tests are indirect tests that indicate a cellular immune response to previous sensitisation with mycobacterial antigens and cannot distinguish between individuals with latent TB infection, active TB infection or past TB infection.

A positive result in either the TST or QIFN test suggests tuberculosis infection. It does not however indicate the presence or absence of active tuberculosis disease. A positive TST or QIFN may not indicate active disease and a negative result does not rule out active disease. The result of either TST or QIFN must be interpreted with the patient’s history, clinical presentation and reason for testing. Active TB disease needs to be excluded before a diagnosis of LTBI is made on the basis of a positive screening test. If active TB disease is suspected then other additional testing is needed. (See WA TB Control Program policy 1.1 Diagnosis of tuberculosis (laboratory) and policy 1.2 Diagnosis of tuberculosis (clinical).

The preferred test of the WA Tuberculosis Control program for contact tracing is the tuberculin skin test (TST) with Interferon Gamma Release Assays (IGRAs), such as QIFN, used only as in certain circumstances (National Tuberculosis Advisory Committee Australia, 2009). Such circumstances would include the paediatric setting (see the WA TB Control Program policy 4.1 Tuberculosis (active and latent) in children, or when practical delivery of the TST is not convenient e.g. in remote Indigenous communities or where there is no trained staff to perform the TST.

3.1 Tuberculin Skin Test (TST)

The tuberculin skin test has been used in the management of tuberculosis since the 19th century. The form of tuberculin used in Western Australia is ‘Tubersol’, a Tuberculin Purified Protein Derivative, which is a protein derived from cultures of M.tuberculosis. It therefore contains no viable organisms and is safe to use in pregnancy, children and in the immunocompromised. When injected into the skin of a person previously infected with M.tuberculosis, a hypersensitivity reaction occurs at the injection site. It is this hypersensitivity reaction that is measured. A dose of 5 International Units of human PPD in 0.1ml is used.

Indication for TST

See section 2.3 ‘Indications for LTBI testing’.
Contraindications for TST

The TST is contraindicated in:
- Persons with a history of a severe skin reaction following a previous TST (vesiculation, ulceration, necrosis),
- Persons with a history of a severe immediate hypersensitivity reaction following a previous TST,
- Confirmed TB disease or infection,
- Persons previously treated for active TB disease, and
- Recent immunisation with MMR, varicella and yellow fever within the last month as the risk of a false negative result increases (Department of Health New South Wales, 2009)

Caution should be used in the following situations:
- Short-term immunosuppressant therapy (may cause a false negative reading).
- Documented prior positive reaction (reconsider the need for a repeat test).

Administration of the TST

All health professionals performing a TST should be appropriately trained and accredited to administer and interpret the TST. Informed consent should first be obtained from the patient. Recording and documentation of the TST should include as a minimum:

- Age
- Dates and result of any previous TST
- Previous adverse reactions
- Date of any previous BCG vaccination
- Reason for test

The form of tuberculin used in Western Australia is ‘Tubersol’, a Tuberculin Purified Protein Derivative and a dose of 5 International Units of human PPD in 0.1ml is used.

Reading of the TST

The reaction to the tuberculin skin test begins 5-6 hours after injection and produces maximum induration at 48-72 hours at which time it should be read. It is measured by the diameter of induration across the transverse axis of the forearm. Any surrounding erythema IS NOT included in the measurement.

Mantoux tests are recorded in millimeters (mm) along with the number of days following administration on which the test was read. Absence of induration should be recorded as 0 mm rather than as “negative” as this can cause confusion. Any blistering if present should be noted.
Adverse Reactions of the TST

Adverse reactions to the Mantoux test may include (Northern Territory Centre for Disease Control, 2008):

• Vaso-vagal reactions,
• Immediate flare with a local rash,
• Strong positive reactions of blistering, ulceration and necrosis at the site of injection. This can be alleviated with cold pack and topical corticosteroids. Such reactions may result in scarring.
• Lymphadenitis and regional adenitis,
• Anaphylaxis or life-threatening hypersensitivity reactions are rare but the TST should be done where access to adrenaline and resuscitation equipment are available.

Interpretation of the TST

The TST result should be interpreted in conjunction with the reason for testing, clinical features and medical history of the patient. The cutoffs listed below may be increased or reduced to improve specificity and sensitivity respectively. Cut off values may also change in specific circumstances e.g. mass screening exercises.

Table 3: TST diameter that is considered indicative of infection with *M. tuberculosis*.

<table>
<thead>
<tr>
<th>TST ≥ 5mm</th>
<th>TST ≥ 10mm</th>
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<tbody>
<tr>
<td>HIV positive patients (should be referred for medical assessment regardless of TST reading)</td>
<td>All others</td>
</tr>
<tr>
<td>Child &lt;5 years old <strong>AND</strong> significant TB risk e.g. contact of TB, abnormal chest x-ray, born or resident for &gt;3 months of a high prevalence TB country (defined as &gt;50 cases/100 000 population per year)</td>
<td></td>
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<tr>
<td>Significant immune suppression <strong>AND</strong> significant TB risk e.g. contact, abnormal chest x-ray, born or resident for &gt;3 months of a high prevalence TB country. Examples of immune suppression include:</td>
<td></td>
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<tr>
<td>o Persons with organ transplants,</td>
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<tr>
<td>o Persons on immunosuppressant therapy equivalent to prednisolone 15mg/day for 1 month,</td>
<td></td>
</tr>
<tr>
<td>o TNF alpha treatment, and</td>
<td></td>
</tr>
<tr>
<td>o Dialysis patients</td>
<td></td>
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</tbody>
</table>
Effect of BCG vaccination

Most people vaccinated with bacille Calmette-Guérin (BCG) will develop a TST reaction within 2 months but this will wane with time (American Thoracic Society, 2000; Department of Health New South Wales, 2009). BCG vaccination given in infancy is unlikely to affect Mantoux test interpretation in adults. Where BCG has been given in the preceding 5 years, or, more than one BCG has been given, then the interpretation of the TST reading needs to be undertaken by a physician with experience in TB medicine. A QIFN test may be used for clarification. BCG vaccination is no longer considered when setting TST cut off points.

False negatives

Causes of a false negative TST i.e. negative test in the presence of *M.tuberculosis* infection are (Northern Territory Centre for Disease Control, 2008):

- PPD out of date or improperly handled,
- Subcutaneous injection or unrecognized leakage at the time of administration,
- Reading of the test <48 hours or >5 days after injection,
- Test performed too soon after TB infection. The TST may need to be repeated at 8-12 weeks following exposure,
- Acute viral or bacterial infections, including active TB,
- Impaired cellular immunity e.g. HIV, immunosuppression,
- Live virus vaccination within 4 weeks.

False positives

Causes of a false positive TST i.e. positive test in the absence of *M.tuberculosis* infection are (Northern Territory Centre for Disease Control, 2008):

- Rupture of a small venule at time of injection,
- Trauma to the site e.g. scratching,
- Failure to distinguish erythema from induration at time of Mantoux reading,
- Past BCG vaccination or exposure to non tuberculous mycobacteria,
- Sensitivity to preservative in PPD.

Booster reaction and Two step testing

The ability to mount an immune response to mycobacterial antigens may wane with time in some individuals with previous exposure and such an individual may not react when tested with the TST. However, the TST itself may boost immunological memory and a repeat TST shortly after the initial one may produce a much larger response (a boosted response). The initial test result should be considered a false negative result and the second result considered the true reading.

Two-step testing is performed when there is a need to establish a true baseline TST reaction. It is done to distinguish boosting from conversion in people who are having serial
TSTs. The second test is needed only if the initial reading is negative. The second TST of a two-step TST should be done 1-5 weeks after the initial negative TST with the second reading taken as the true result.

Two-step TST may be useful in pre-employment screening of health care workers who are likely to have subsequent testing following exposure to a TB case. In practice two-step testing might not be practicable as it requires four visits by the patient.

TST conversion

TST conversion is the change in reactivity of the TST with:
   i) A change from a negative to a positive reaction OR
   ii) An increase of 5mm in the TST diameter (Menzies, 1999).

TST conversion indicates the development of a hypersensitivity reaction to infection with tuberculous or non-tuberculous mycobacteria, including BCG vaccination. A TST used to document conversion following infection should be done at least 8 weeks after the last date of suspected exposure to TB.

3.2 Interferon gamma Release Immunoassays (IGRAs)

Interferon Gamma Release Immunoassays (IGRAs) are blood tests that detect cell mediated immune responses to TB specific antigens that are secreted by the *M. tuberculosis* organism. The QuantiFERON-TB Gold In-Tube test (QIFN) is used in Western Australia. In the QIFN test the antigens are i) early secretory antigenic target-6 (ESAT-6) ii) culture filtrate protein 10 (CFP-10) and iii) part of the sequence of TB 7.7 antigen. These proteins are present in all *M. tuberculosis* but are absent from BCG vaccine strains and most non-tuberculous mycobacteria with the exception of *M.kansasi, M.szulgai* and *M.marinum*.

The QuantiFERON-TB Gold In-Tube test should not replace the standard diagnostic investigations of active TB disease (See the WA TB Control Program policy 1.1 Diagnosis of tuberculosis – Laboratory). A positive QIFN may not indicate active disease and a negative result does not rule out active disease.

Compared to the TST, IGRAs have been in use for a very short period of time. Further development of our understanding of IGRAs through research is required. The advantages and disadvantages of the two tests are summarised below:
### Table 4: Advantages and Disadvantages of TST versus QIFN

<table>
<thead>
<tr>
<th></th>
<th>Tuberculin Skin Test</th>
<th>QuantiFERON-TB Gold In-Tube test</th>
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<tbody>
<tr>
<td><strong>Advantages</strong></td>
<td>- Has been used for &gt;100 years and its use is better understood from experience and research, particularly longitudinal data.</td>
<td>- Convenience in administering.</td>
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<tr>
<td></td>
<td>- Improved specificity: the test is minimally affected by previous BCG or sensitisation to non-tuberculous mycobacteria (Pai &amp; O'Brien, 2008). This is especially useful in low incidence populations.</td>
<td>- Improved specificity: the test is minimally affected by previous BCG or sensitisation to non-tuberculous mycobacteria (Pai &amp; O'Brien, 2008).</td>
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<td></td>
<td>- Less inter-reader variability than with the TST.</td>
<td>- Less inter-reader variability than with the TST.</td>
</tr>
<tr>
<td></td>
<td>- No boosting effect from previous QIFN testing (Pai &amp; O'Brien, 2008).</td>
<td>- No boosting effect from previous QIFN testing (Pai &amp; O'Brien, 2008).</td>
</tr>
<tr>
<td></td>
<td>- Results are recorded and easily retrieved from a results database such as iSoft.</td>
<td>- Results are recorded and easily retrieved from a results database such as iSoft.</td>
</tr>
<tr>
<td><strong>Disadvantages</strong></td>
<td>- Requires 2 visits.</td>
<td>- Time limitations: blood samples need to be collected and processed within limited time frames. This can be a problem for samples collected outside the metropolitan area.</td>
</tr>
<tr>
<td></td>
<td>- Requires skilled practitioners to administer the test.</td>
<td>- There is limited data available on the use of IGRAs in immunocompromised patients, children and populations from TB endemic countries (Mazurek et al, 2010; Denkinger et al 2011).</td>
</tr>
<tr>
<td></td>
<td>- Reduced specificity: cross reactions may occur, giving false positive results in subjects who have had prior BCG vaccination or who have had exposure to environmental mycobacteria.</td>
<td>- Lack of evidence supporting its use for HCW screening and follow up.</td>
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<td></td>
<td>- Lack of longitudinal studies that inform us how the test performs over time, especially conversion from negative to positive (Mazurek et al, 2010).</td>
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<td></td>
<td>- The problem of indeterminate tests has yet to be resolved (Denkinger et al, 2011).</td>
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<td>- Uncertainty about the significance of threshold results (positive or negative results that are near the cutoff) and fluctuations in an individual's interferon gamma response over time (Mazurek et al, 2010).</td>
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3.3 Selection of LTBI test

Selection of which test(s) to use for the investigation of latent TB infection should take into account the reason for testing, the context of testing, the test availability and the logistics of administering the test.

The preferred test of the WA Tuberculosis Control Program is the TST. The possible exceptions to this, where QIFN is a preferred primary test or is used as a supplementary test, include:

- Low compliance rate of a second return visit for TST i.e. remote communities, transient populations
- Logistic considerations i.e. screening of newly arrived migrants from high prevalence countries
- BCG vaccination given within the previous 5 years
- Positive TST in an individual in which a false positive result due to cross reaction to NTM including BCG is considered likely e.g. low pre-test risk for LTBI
- Individuals in which TST is contraindicated (see above).

The QuantiFERON-TB Gold In-Tube test would not be suitable when specimens cannot reach the laboratory within an appropriate time i.e. rural and remote Western Australia (WA). In WA specimens need to reach the laboratory in Perth within 16 hours of collection.

4.0 Summary

Latent TB infection has the potential of leading to active tuberculosis infection. Diagnosis of LTBI followed by preventive treatment is an important strategy in TB control, especially in low prevalence countries.

This document describes those population groups who are at risk of i) acquiring TB infection and of ii) progression of latent infection to active disease. The two diagnostic tests available to detect latent TB infection are the TST and QIFN assay. The uses, advantages and disadvantages of both are described. The preferred test in WA is the TST, but there are circumstances in which QIFN is indicated.

A positive result in either the TST or QIFN test suggests tuberculosis infection. It does not however indicate the presence or absence of active tuberculosis disease. The result of either TST or QIFN must be interpreted with the patient’s history, clinical presentation and reason for testing. If active TB disease is suspected than other additional testing is needed.

Both the TST and QIFN test should be done with intent to offer preventive treatment for LTBI with the exception being baseline testing for health care workers. A positive result does not itself indicate preventive treatment but needs to be considered in the context of the pre-test risk for LTBI.
5.0 Works Cited


**Feedback or comments related to this policy should be addressed to the Medical Director, WA TB Control Program**  
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