

# Management of Latent Tuberculosis in children up to 16 years

**Guideline**

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For more information contact: Communicable Diseases Branch Department of Health, GPO Box 48, Brisbane QLD 4001, email [NDPC@health.qld.gov.au](mailto:NDPC@health.qld.gov.au), phone 33289722.

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## 1. Background

Latent tuberculosis (LTB), defined as a state of persistent immune response to prior-acquired *Mycobacterium tuberculosis* antigens without evidence of clinically manifested active tuberculosis (TB)<sup>1</sup>, affects about one-third of the world's population<sup>2</sup>.

Approximately 10 per cent of people with LTB will develop active TB disease in their lifetime, with the majority developing it within the first five years after initial infection<sup>3</sup>.

Young children are particularly at risk of progressing to active disease with a high risk of disseminated tuberculosis (miliary TB and meningitis). The period of highest risk is within the first year following primary infection<sup>4</sup>. In Australia 65.6% of TB cases in migrant children occur within 2 years of arrival and 85% of cases within 5 years<sup>5</sup>.

Detection of LTB is undertaken in children at risk for active TB in whom active disease has been excluded and for whom preventive therapy is indicated. As most children who become infected with TB have been recently infected, prevention and early management of childhood TB transmission is an important part of a TB elimination strategy in a low incidence country such as Australia.

## 2. Target audience

This guideline documents recommendations of the Tuberculosis Expert Advisory Group for the diagnosis and management of latent tuberculosis in children up to the age of 16 years. It is intended as a resource to ensure consistent best practice by doctors and nurses who manage tuberculosis in children in Queensland. Medical practitioners who are inexperienced in TB medicine should adhere to this guideline but also discuss individual case management with a paediatrician or other medical officer experienced in TB diagnosis and care.

The recommendations are aligned with the World Health Organization [Guidelines on the management of LTB infection](#)<sup>6</sup>.

## 3. Who to test for LTB

Testing for latent tuberculosis should be directed at:

- a. Children at increased risk of acquiring TB infection and who have an increased risk of progressing from latent to active disease.
- b. Children where latent TB needs to be excluded as a prerequisite for administration of BCG vaccine prior to travel to a high burden TB country or where local epidemiology suggests increased community risk of TB acquisition.

Children at increased risk of acquiring TB are:

- Close household or other close contacts of an active case of tuberculosis with the highest risk occurring where the index case has smear positive pulmonary TB.
- Children from communities or countries with high TB burden.

- a. Certain Aboriginal and Torres Strait Islander communities.
- b. Migrants, including refugees from countries with a significant incidence of TB (generally defined as a WHO defined incidence of >40 per 100,000 population).

Children at increased risk of progression from latent to active tuberculosis are:

- Those who have acquired their infection recently, within 2 years eg household contact of an index case, recent migration from or prolonged travel to, a high TB burden country.
- Younger age – less than 5 years and especially less than 2 years of age.
- Immunocompromised status including HIV infection and inherited immunodeficiency syndromes.
- Medication risk—immune modulators, chemotherapy, post transplantation.
- CXR abnormalities suggesting healed TB in patients without previous full treatment:
  - o discrete granulomas (especially if calcified) and pleural thickening
  - o pulmonary fibrosis.

## 4. Diagnosis

LTB is diagnosed by detection of cell-mediated, delayed hypersensitivity to *Mycobacterium tuberculosis* via the Tuberculin Skin Test (TST) or by interferon gamma release assay (IGRA). The interpretation of the TST or IGRA reaction is based on the likelihood of the person being infected with TB as well as the likelihood of progression to disease if infected. The risk of true TB infection, rather than non-specific sensitisation with non-tuberculous mycobacteria or Bacille Calmette-Guerin (BCG) vaccination is assessed individually taking into account the person's likelihood of exposure to TB.

Both tests have imperfect sensitivity and can't be used to exclude LTB. False negatives may occur where testing has occurred very soon after infection. IGRA assays in children under five years of age are more likely to return indeterminate results than in older ages<sup>7</sup> - TST remains the recommended test for diagnosis of LTB in Queensland. IGRA tests (Quantiferon Gold in tube™ and TSpot test™) are acceptable alternatives. Unlike the TST, BCG vaccination does not cause false positive results with IGRA tests - IGRA tests may be the preferred test in children who have been BCG vaccinated, especially if vaccination has occurred after the first year of life.

The significance of a TST result depends on the age of the child as well as medical history and risk factors for exposure (Tables 1 and 2). The sensitivity of the TST (and IGRA) may be reduced in the very young and in immunocompromised children, particularly those with T cell immunodeficiency such as HIV. In immunocompromised children, consideration should be given to sequential TST and IGRA testing if the initial TST is negative. If either test is positive, then further assessment will be required.

Prior to a diagnosis of LTB and before treatment for LTB is commenced, active TB disease must always be ruled out. This will usually require the child to be asymptomatic with either a normal chest x-ray (CXR) or an abnormal CXR that is stable over time.

Where BCG vaccination is being considered in the absence of known TB contact, no LTB test is required before the age of 6 months. After this age the TST rather than the IGRA should be used due to paucity of evidence to support IGRA testing in this setting. Non-specific TST reactions to environmental non-tuberculous mycobacteria may be relevant to predicting adverse reactions to BCG which would not be predicted by an IGRA test.

## 5. Clinical Assessment following diagnosis of LTB

### 5.1. Rule out active TB disease

Medical assessment and history. Concerning symptoms include:

- cough, for more than 2 weeks
- haemoptysis
- fever
- night sweats
- unexplained weight loss/poor growth listlessness and fatigue

Physical examination with particular attention to excluding respiratory pathology, significant lymphadenopathy, hepatosplenomegaly and skin/skeletal abnormalities.

Investigations:

- CXR

A CXR should be performed for all children with a significant TST or IGRA result (see Table 1), looking for changes suggestive of active TB. Look for changes of CXR abnormalities over time (if scarring present, ideally be able to demonstrate 12 months of stability of scarring) except where more expedient management is indicated ( see below)

- Sputum / gastric aspirates

If there is clinical or x-ray indication of current/previous TB infection, specimens should be collected. In infants and young children, three early morning gastric aspirates should be collected. An inpatient stay is usually required to collect gastric aspirates. In older children, three induced or spontaneous sputum specimens should be collected. All specimens should be tested for acid-fast bacillus (AFB) smear and culture +/- Xpert MTB/RIF for molecular detection of TB and the presence of rifampicin resistance.

Only in areas where inpatient facilities are not available and where sputum induction can not be safely performed, is nasopharyngeal aspirate acceptable. Ideally two NP aspirates 4 hours apart are obtained.

- Other imaging as required (eg CT imaging) to assess lung fields, mediastinum or other organs.

## 5.2. Assessment and management of child contacts of TB cases

### Children less than five years old

Following TB exposure, young children have a higher risk of developing primary TB infection, and of progressing to disseminated and/or central nervous system disease if infected.

- Perform TST
- If positive, exclude active TB as above.
- Irrespective of TST result, all children less than two years old who have had close contact\* with a case of active TB, should be recommended LTB treatment.
- In children aged between two and five years, LTB treatment should be given to children with positive TST, but should be considered also for children with negative TST result, particularly if contact with smear positive pulmonary TB. If LTB treatment is given to a child who has not had TST testing or has a TST < 5mm, TST should be performed at completion of treatment and if negative, the child should be offered BCG vaccination.

### Children five years or older

- Perform TST/IGRA.
- If positive, exclude active TB and recommend LTB treatment. If initial TST/IGRA is negative, and the test was performed sooner than 12 weeks after the last identified contact with active TB (“break of contact”), repeat testing should be undertaken after 12 weeks since break of contact; early infection may yield a false negative TST or IGRA result. If there is TST or IGRA conversion, then LTB treatment should be offered. If TST or IGRA remains negative, BCG vaccination should be considered on a case by case basis, taking into consideration likely future risk to the child.

### Immunocompromised children of any age

Close contacts of smear positive pulmonary TB should be offered LTB treatment. TST/IGRA testing is not required. BCG vaccination is contraindicated in the presence of immunocompromise. Sequential IGRA/TST may be of benefit where contact is casual or index case has extrapulmonary disease only.

\* Close contact is defined as household contact or eight hours cumulative contact in same room.

## 6. Treatment for LTB

Prior to initiating treatment for LTB, baseline liver function tests (LFTs) are not routinely indicated. However LFTs are indicated if other risk factors for hepatotoxicity are present. If baseline LFTs abnormal, perform hepatitis screen.

The risk of developing TB disease may be reduced by treatment for LTB. The preferred treatment is three months of isoniazid (10mg/kg, maximum 300mg daily) plus rifampicin (15mg/kg, range 10–20mg/kg, maximum 600mg daily) (3HR), although six months of isoniazid monotherapy can also be used. Three months of rifampicin and isoniazid (3RH) has been shown to be equivalent to isoniazid monotherapy in terms of effectiveness and safety<sup>8-11</sup>. In immunocompromised patients, isoniazid and rifampicin combination therapy should be extended to four months. Isoniazid monotherapy for 6 months duration is considered in children with chronic medical conditions where there may be potential drug interactions with rifampicin, for example, anti-retroviral therapy for HIV. Pyridoxine is added for breastfed babies, HIV infected or malnourished children to lower the risk of neuropathy. In contacts of a case with known isoniazid resistance or where isoniazid is not tolerated, four months of rifampicin should be used.

The main side effect of this treatment is hepatotoxicity though this risk is significantly lower in children. The important symptoms of drug toxicity must be explained to the parents prior to obtaining consent to commence treatment. Details of side effects, drug interactions and contraindications are complex and available from MIMS and other resources.

If the index case of a close child contact has MDR TB, there is no national or international consensus on whether to treat or what agents to use. In those children at greatest risk for disease progression, preventative treatment should be considered with reference to the document [Management of contacts of multidrug-resistant tuberculosis](#).

All nursing and medical consultations, as well as tests and treatment, are provided free of charge in Queensland.

### 6.1. Monitoring during treatment for LTB

Children on treatment for LTB should be reviewed by a doctor (or TB nurse where doctor is not available) six weeks after commencement and at the end of treatment, to confirm compliance and completion. Parents should be educated on the potential side effects of treatment, including signs and symptoms of hepatotoxicity and peripheral neuropathy.

At each outpatient clinic:

- assess adherence
- evaluate for signs and symptoms of active TB disease and drug reactions
- remind parents and child (if age-appropriate) of signs and symptoms of hepatotoxicity and peripheral neuropathy
- perform LFTs if there is clinical concern for hepatotoxicity.

Note: If a child is symptomatic, isoniazid and rifampicin should be discontinued if aminotransferase values are **three times** the upper limit of normal. If the child is



asymptomatic, therapy should be ceased if aminotransferases exceed five times the upper limit of normal. Rifampicin can be cautiously reintroduced when hepatotoxicity has abated. A four month regimen of rifampicin monotherapy would be appropriate.

In the event of treatment interruption, extend treatment by the time missed to compensate. If more than one month is missed, restart whole course.

## 7. Surveillance

Children who have completed a satisfactory course of treatment for LTB do not require ongoing surveillance. Parents and caregivers should be educated regarding symptoms of TB disease.

If parents or caregivers decline the recommended LTB treatment for their children, they need to be educated regarding symptoms of TB disease. For children at risk, six monthly clinical reviews are recommended for two years. Investigations such as CXR only indicated if clinical concerns.

## 8. Re-exposure following LTB treatment

If patients are re-exposed through contact with a case of active TB, there is no value in repeating the tests for LTB. In immune-competent adults, there is evidence that a first episode of TB infection (not disease) provides approximately 80 per cent protection against development of disease following re-exposure<sup>12</sup>, irrespective of previous LTB therapy. Therefore a second course of LTB treatment is generally not recommended, even if the exposure was close/intense<sup>13</sup>. However, if the child is under five years of age or has HIV infection (there may not be any effective immunity conferred by prior TB infection), then it is recommended to repeat the full course of LTB therapy.

## 9. Classification of significant TST reactions

**Table 1 Interpretation of TST cut-offs for adults and children five years of age or older**

≥5 mm	≥10 mm*	≥15 mm
HIV infected	Close contact of active TB case regardless of BCG	No TB risk factors/normal host/regardless of BCG
Immunosuppressed #	Travel to a high incidence country for a period of >3 months^	
	Those at increased risk of TB exposure or greater host susceptibility <sup>†</sup>	

# Receiving immunomodulators, chemotherapy, ≥ 15mg prednisone/day for more than one month, or organ transplantation.

\*In those who are BCG naive, or are at increased risk for TB exposure or infection, and parents are reluctant for LTB treatment, consider IGRA as a supplementary test.

^Travel—someone who has travelled to a high incidence country, or countries, for a period of more than three months (>40/100,000). For country profiles see:

[http://www.who.int/tb/publications/global\\_report/en/](http://www.who.int/tb/publications/global_report/en/)

+ Increased likelihood of infection due to immigration from high incidence country (>40/100,000), or host factors, such as, diabetes, chronic renal failure, neoplastic disease and malnutrition.

**Table 2 Interpretation of TST cut-offs for children under five years of age**

≥5 mm	≥10 mm
Close contact of active TB or XPTB case regardless of BCG	History of BCG; no risk factors
No history of BCG; no risk factors#	
Those at increased risk of TB exposure or greater host susceptibility <sup>†</sup> regardless of BCG	

# This group may not be at significant enough risk for LTB to warrant further assessment and treatment. Consider quantiferon testing in this group and if positive, recommend LTB treatment.

+ Increased likelihood of infection due to birth in, or residence for a period of more than three months in, a high incidence country (>40/100,000), close contact of Sputum Smear negative pulmonary TB/extra-pulmonary TB or host factors, such as, HIV, immunosuppression, diabetes, chronic renal failure, malignancy and malnutrition.

*Children with TST > 5mm should not receive BCG in case of severe local reaction.*

However if TST = 5mm, if prior TB infection is unlikely and if child is at moderate to high risk of acquiring TB (e.g. will spend > 3 months in a high TB burden country), consider giving BCG after discussion of risk with parents.

## 10. Supporting and related documents

### World Health Organisation

- [Guidelines on the management of latent tuberculosis infection](#)

### Communicable Diseases Network

[CDNA National Guidelines for the Public Health Management of TB](#)

## Revision history

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## Document custodian

Director, Communicable Diseases Branch

## Approving group

Tuberculosis Expert Advisory Group

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