Queensland Health

Management of latent tuberculosis in children under 14 years of age

Guideline Version 2.0 May 2023

Queensland Government

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Please note: Updates after September 2023 are amended in the online Management of Latent Tuberculosis in Children under 14 years of age - Guideline Version 2.0 May 2023 **ONLY** – printed copies may not be current.

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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)[1], affects about one quarter of the world's population.[2]

Approximately 5–10% of people with LTB will develop active TB disease in their lifetime, with the majority developing it within the first 5 years after initial infection.[3]

Young children (under 2 years of age) are 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.[4] In Australia 65.6% of TB cases in migrant children occur within 2 years of arrival and 85% of cases within 5 years.[5]

Investigation for LTB is undertaken in children at risk for active TB and for whom preventive therapy is indicated. Active disease must be excluded. As most children diagnosed with active 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 14 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 (WHO) Guidelines on the management of LTB infection.[6]

3 Who to test for LTB

Testing for latent tuberculosis should be considered for:

a. Children at increased risk of acquiring TB infection 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.

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

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

- those who have acquired their infection recently, within 2 years e.g., household contact of an index case, recent migration from or prolonged travel to, a high TB burden country
- younger age – less than 5 years, particularly less than 2 years of age
- immunocompromised status including HIV infection, inherited immunodeficiency syndromes, and those on immunosuppressive agents such as immune modulators, chemotherapy, or post transplantation
- CXR abnormalities suggesting healed TB in children without previous full treatment:
  - discrete granulomas (especially if calcified) and pleural thickening
  - fibrotic scarring.

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 (QuantiFERON Gold Plus™ and TSpot test™). 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 considering the person's likelihood of exposure to TB.

Both tests are acceptable for the diagnosis of LTB but note the following:

- Both have imperfect sensitivity and can't be used to exclude LTB. False negatives may occur where testing has occurred very soon after infection.
- IGRA tests in children under 5 years of age are more likely to return indeterminate results than in older ages.[7]
- BCG vaccination does not cause false positive results with IGRA tests (as may be the case with TST).
- A positive TST reaction can occur as a result of environmental exposure to non-tuberculous mycobacteria; cross reaction with a small number of NTM is possible with IGRA tests e.g. *M. marinum*, *M. kansasii*.
- 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 (Table 1 and Table 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 excluded. 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.

TST prior to BCG vaccination

Local adverse reactions to BCG can occur in children who have had previous infection with/exposure to TB. Hence, TST used to be recommended prior to proceeding with BCG vaccination in children older than 6 months. However, recommendations have changed; currently a tuberculin skin test (TST, Mantoux) before BCG vaccination is only recommended in certain circumstances, based on risk factors for previous tuberculosis exposure (AIH, 2022)[1]:

- child was born in a tuberculosis-endemic country (> 40 cases per 100,000 population per year)
- child has lived in or travelled to a tuberculosis-endemic country or region (> 40 cases per 100,000 population per year)
- child has had exposure to a close contact with tuberculosis or who is under investigation for tuberculosis.

Children who develop an accelerated BCG reaction (defined as development of papule within 72 hours of vaccination) should be investigated for LTB with TST or IGRA.[15]

5 Clinical assessment following diagnosis of LTB

5.1 Rule out active TB disease

Active tuberculosis in children may be non-specific in symptomatology, and classical adult presentations of pulmonary TB are not typical until about the age of puberty.

Concerning symptoms include:

- fever
- night sweats
- unexplained weight loss/poor growth
- listlessness and fatigue
- enlarged cervical or axillary lymph nodes
- cough, for more than 2 weeks
- haemoptysis.

Physical examination with particular attention to

- presence of respiratory pathology
- significant lymphadenopathy
- hepatosplenomegaly
- 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. A careful assessment for mediastinal lymphadenopathy and pleural effusion should be made.

Assessment 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, 3 early morning gastric aspirates should be collected. An inpatient stay is usually required to collect gastric aspirates. In older children, 3 induced or spontaneous sputum specimens should be collected. All specimens should be tested for acid-fast bacillus (AFB) smear and culture +/- Xpert Ultra 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 cannot be safely performed, is nasopharyngeal aspirate acceptable. Ideally, 2 NP aspirates 4 hours apart are obtained.

Stool samples

- The use of Xpert Ultra to test stool samples from children suspected of having pulmonary TB is available from the Queensland Mycobacterium Reference Laboratory noting sputum and other respiratory tests are the preferred samples.
- Other imaging as required (e.g. CT) to assess lung fields, mediastinum or other organs.

5.2 Assessment and management of child contacts of TB cases

Children less than 5 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 and/or IGRA.
- If significant (TST)/positive (IGRA), exclude active TB as above.
- Irrespective of TST/IGRA result, all children less than 2 years old who have had close contact* with a case of active TB, should be recommended TPT.
- In children aged between 2–5 years, TPT should be given to those with significant/positive TST/IGRA result.
- For children with insignificant/negative TST/IGRA result, TPT should still be considered, particularly if contact with smear positive pulmonary TB or immune compromised.
- If TPT is given to a child who has not had TST/IGRA testing or has a TST < 5mm, TST should be performed at completion of treatment and if non-significant, the child should be offered BCG vaccination.

Children 5 years or older

- Perform TST and/or IGRA.
- If significant/positive, exclude active TB and recommend TPT. If initial TST/IGRA is negative, and the test was performed sooner than 12 weeks after the last identified contact with active TB, repeat “Break of Contact” (BOC) testing should be undertaken after 12 weeks since contact as early infection may yield a false negative TST or IGRA result.
- If TST or IGRA remains negative at BOC, 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 immunocompromised contacts of smear positive pulmonary TB should be offered TPT. 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 the index case has extrapulmonary disease only.

** Close contact is defined as household contact or 8 hours cumulative contact in the same room (Australian Government Department of Health and Aged Care, 2020)*

6 Tuberculosis Preventative Treatment (TPT)

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

The risk of developing TB disease is reduced by TPT. The preferred treatment is 3 months of isoniazid (10mg/kg, maximum 300mg daily) plus rifampicin (15mg/kg, range 10–20mg/kg, maximum 600mg daily) (3HR).[8-11]Child friendly fixed dose combination tablets are not registered in Australia but are available through the Special Access Scheme. The following alternative regimens are also acceptable:

- six months of isoniazid monotherapy (6H), especially where there may be potential drug interactions with rifampicin, for example, anti-retroviral therapy for HIV
- four months of rifampicin monotherapy (4R), especially where there is known isoniazid resistance in an index case or where isoniazid is not tolerated
- three months of rifapentine and isoniazid weekly (3HP) (rifapentine is not registered in Australia but is available through the Special Access Scheme).

In immunocompromised patients, isoniazid and rifampicin combination therapy should be extended to 4 months (4HR).

Where isoniazid is used, pyridoxine (vitamin B6) supplementation is recommended for breast-fed babies, HIV infected or malnourished children to lower the risk of neuropathy.

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.

Published product information should always be consulted to ensure a complete list of adverse events, drug interactions and contraindications for any of the agents recommended in this guideline.

6.1 Monitoring during TPT

Children on TPT should be reviewed by a doctor (or TB nurse where a doctor is not available) 4–6 weeks after commencement and at the end of treatment, to confirm compliance and completion. Phone reviews are acceptable in selected cases. 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 3 times the upper limit of normal. If the child is asymptomatic; therapy should be ceased if aminotransferases exceed 5 times the upper limit of normal. Rifampicin can be cautiously reintroduced when hepatotoxicity has abated. A 4-month regimen of rifampicin monotherapy would be appropriate if isoniazid was felt to be the cause of hepatotoxicity.

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

7 Surveillance

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

If parents or caregivers decline the recommended TPT for their children, they need to be educated regarding symptoms of TB disease. For children at risk, 6 monthly clinical reviews are recommended for 2 years. Investigations such as CXR are only indicated if there are clinical concerns.

8 Re-exposure following TPT

If a child who has previously received TPT is 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% protection against development of disease following re-exposure,[12] irrespective of previous LTB therapy. Therefore, a second course of TPT is generally not recommended, even if the exposure was close/intense.[13] However, if the child is under 5 years of age or has HIV infection and there may not be any effective immunity conferred by prior TB infection, then it is recommended to repeat the full course of TPT. If parents or caregivers have previously

declined TPT, and the child is re-exposed, TPT should be offered again in keeping with earlier age specific recommendations.

9 Serial TST testing and conversions

Serial testing occurs to identify a new TB infection after a recent exposure in the context of a contact investigation

A TST conversion is indicated when the initial TST reaction is insignificant and the repeat TST reaction is significant (see Table 1 below). When change in TST diameter is incorporated into the overall assessment, a change of at least 6mm is considered significant. Anyone with a TST > 10mm has a higher likelihood of TB infection.[17-18]

As IGRA testing is more specific for TB infection it may be a useful supplementary test.

10 Classification of significant TST reactions

Table 1 Interpretation of TST cut-offs for adults and children 5 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/
Immunosuppressed #	Travel to a high incidence country for a period of > 3 months^	
	Those at increased risk of TB exposure or greater host susceptibility+	

(National Tuberculosis Advisory Committee (NTAC), 2017)

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/

+ 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.

"**as Qld/Aus is low incidence that there is no wide screening program for low risk individuals as such, an incidental significant result should be followed up to assess risk or potential LTB.

Table 2 Interpretation of TST cut-offs for children under 5 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+ regardless of BCG	

(National Tuberculosis Advisory Committee (NTAC), 2017)

This group may not be at significant enough risk for LTB to warrant further assessment and treatment. Consider IGRA 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 3 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.

, 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.

11 Supporting and related documents

World Health Organization

Guidelines on the management of latent tuberculosis infection

Communicable Diseases Network

CDNA National Guidelines for the Public Health Management of TB

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