

Massachusetts Department of Public Health

Division of Global Populations and Infectious Disease Prevention

Screening Infants and Children for Tuberculosis in Massachusetts

Executive Summary

In Massachusetts, tuberculosis (TB) remains an important public health problem, even as the incidence of TB disease has decreased in recent years. Persons born outside the United States are at particular risk for TB, and the largest number of TB cases occurs among young and middle-aged adults, the age groups that include most parents.

Children, especially those younger than 5 years of age, are at high risk for developing active TB disease if exposed and infected with *Mycobacterium tuberculosis*. Thus, although the number of cases of TB in children remains low, children in Massachusetts represent an important group at risk for TB infection progressing to TB disease. Eliminating TB in children requires identifying children at risk for TB, testing for TB infection, completing clinical evaluations and treating children with latent TB infection.

The Massachusetts Department of Public Health, in conjunction with the Medical Advisory Committee for the Elimination of Tuberculosis (MACET), recommends that medical providers:

- Assess children for risk of TB exposure by clinical history or TB risk questionnaire as an essential part of routine well-child care.
- Test, using a tuberculin skin test or interferon gamma release assay (IGRA), only those infants and children identified to be at risk of exposure to TB. Do not test infants and children at low risk for TB. Retest children who formerly were at risk only if risk recurs.
- IGRA is the preferred test for children 5 years of age and older with a history of BCG vaccination; use the Mantoux tuberculin skin test (5 TU PPD) for children of any age.
- Assure clinical evaluation of a child with a positive test for TB infection, which includes a history, physical examination, and a chest radiograph to exclude active TB and establish a diagnosis of latent TB infection once active TB is excluded.
- Treat all children diagnosed with latent TB infection. It is especially important to start treatment as soon as possible for those under the age of 5 years. Isoniazid (INH) with vitamin B6 (pyridoxine) for nine months generally is recommended.
- Arrange directly observed therapy (e.g., school-based treatment) for children who are unlikely to complete treatment. Therapy can be given two or three times per week. Consult [CDC Guidelines on Treatment of LTBI](#).
- [Report](#) newly diagnosed cases of latent TB infection and suspected or confirmed TB disease to the Massachusetts Department of Public Health.

Definitions

- 1) Latent tuberculosis infection, or LTBI, is the term for *Mycobacterium tuberculosis* infection that is asymptomatic and not contagious. The person has no physical or radiographic evidence of active disease. A positive test result from either a tuberculin skin test (TST) or an interferon-gamma release assay (IGRA) blood test may be the only evidence of TB infection. This stage (latent TB infection) may continue for the patient's entire lifetime or, over weeks to years, latent infection may progress to active TB disease. Treatment of latent TB infection aims to prevent the future development of active TB disease.
- 2) Tuberculosis disease is diagnosed on the basis of symptoms, physical findings and/or radiographic abnormalities and is confirmed by isolation of the organism by culture methods from involved sites. TB disease can affect the lung or other parts of the body (lymph nodes, central nervous system, bones and joints, other organs) and may be contagious to others. Tuberculosis in children, especially those under 5 years of age, rarely is infectious.
- 3) The Mantoux tuberculin skin test (TST) is the only acceptable skin test for the diagnosis of latent TB infection. The test requires intradermal injection of 5 TU of PPD, a complex mixture of *M. tuberculosis* proteins, followed by measurement of induration at the skin test site after 48-72 hours. The validity of the TST requires that the induration is measured by a trained health care worker (not a parent or relative). Often the TST is called a "PPD" test.
- 4) Interferon-gamma release assays (IGRA) are FDA-approved blood tests for the diagnosis of latent TB infection. Two tests are available, the QuantiFERON®-TB Gold In-Tube test and the T-SPOT.TB test. In many situations, IGRA tests may be used in place of the TST to diagnose TB infection in children 5 years of age or older. Since there are no good criteria for defining test conversion to positive, these tests should not be used where sequential or periodic testing is planned.

Introduction and Background

The incidence of tuberculosis (TB) disease in Massachusetts has decreased in recent years, with a case rate of 3.2 per 100,000 population reported in 2012. The rate of TB in children remains low, and children and adolescents account for fewer than 10% of active TB cases in Massachusetts.

While the disease is becoming less common among the general population, TB is increasingly concentrated in specific subpopulations. Over the past several years, more than 75% of Massachusetts TB has occurred in foreign-born persons. At present, the largest number of TB cases appears in young and middle-aged adults, the age groups that include most parents. Tuberculosis is transmitted from person to person by inhalation of tiny droplets that are generated when a person with active, infectious TB of the lungs or airways coughs or sneezes. Often, this person has not yet been diagnosed with TB. Once infected, children, especially those younger than 5 years of age, are at high risk for developing active TB disease.

The major risk factors for TB infection in children in Massachusetts today are birth in a country with high rates of TB, household contact with foreign-born family members and visitors, and travel involving contact with the local population in countries with high rates of TB. For these reasons, risk-based testing for TB in children is recommended in Massachusetts (1) and this risk-based approach to screening for latent TB infection (LTBI) is the cornerstone to TB prevention (2).

TB testing options have increased. While the tuberculin skin test (TST) using purified protein derivative (PPD) applied by the Mantoux technique traditionally has been the primary screening method used to detect TB infection, newer blood tests for TB infection have been approved for children 5 years of age and older. Regardless of testing method, a risk-based testing strategy is essential; low risk children should not be tested.

These Massachusetts Department of Public Health recommendations for screening infants and children for TB have been developed in conjunction with the Medical Advisory Committee for the Elimination of Tuberculosis (MACET). They update the MACET guidance issued in 2001. (3)

Recommendations

1. Assessing Risk of Tuberculosis is an Essential Function of Primary Health Care for All Children

Risk of exposure to TB should be determined on entry into the health care system and at regular intervals thereafter. Depending on circumstances, a health care provider may decide to determine the risk of TB exposure through individual clinical history taking or by administering a simple TB risk questionnaire such as the one presented in Attachment 1, *Children Who Should be Tested for Tuberculosis*.

Birth in a country with a high prevalence of TB, visiting or traveling in a country with a high prevalence of TB, having household members or visitors from a high prevalence country, having contact with an adult with active TB, or a relative with a positive TST are risk factors for TB infection in children. These risk categories are based on data from a large validation study of a risk-assessment questionnaire, two case-control studies of young children with latent TB infection, and two studies specifically examining the risk of latent TB infection during travel to countries with a high prevalence of TB (4-8). A household contact with a positive TST, but without TB disease, is not the source of infection for a child, but his or her presence may indicate that a child is at increased risk of exposure to contagious TB from other sources. Testing is no longer recommended solely on the basis of exposure to adults who have AIDS or HIV infection, are homeless, use illicit drugs, or were recently incarcerated; however adolescents who themselves have HIV infection should be periodically tested. Similarly, adolescents who have been incarcerated in an institution with known high risk of tuberculosis exposure should also be tested as long as the risk persists.

The duration of foreign travel or residence associated with increased risk of acquiring TB infection is unknown. The American Academy of Pediatrics *Red Book* considers one week or more as potentially significant, although the type of living conditions, (e.g., living in a

household with local residents) and activity (e.g., health care work) while abroad is likely to be more important than the length of the stay.

Health care providers taking a clinical history or using a questionnaire to determine a child's risk of TB exposure should generally consider countries in the following regions to have a high prevalence of TB:

- Africa
- Asia and Pacific Islands (except Japan)
- Eastern Europe
- Mexico, Central America and South America
- The Caribbean
- The Middle East.

2. Only Infants and Children Who are at Risk of Exposure to Tuberculosis Should be Tested for TB Infection

Selective testing is a strategy that allows time, energy and resources to be focused on the populations at elevated risk of TB infection, the groups for whom treatment will have the greatest beneficial impact. In a population with a low prevalence of infection, some children with a "positive" TST or IGRA test result may be uninfected (i.e., have a false positive test) and may be treated unnecessarily. By not testing infants and children at low risk of infection, fewer children with a false positive test results will be treated and exposed to potential adverse side effects of treatment.

Attachment 2 shows the American Academy of Pediatrics' recommendations on the frequency of TB testing. If a child has a negative test result using the TB skin test or an IGRA two or more months after a risk has resolved, then further TB tests are unnecessary. Repeat testing may be indicated in certain circumstances, however. For example, should the child travel to an area with risk of TB exposure, testing should be repeated afterward. (4,5) As noted above, if repeated or sequential testing is anticipated, IGRA should not be used.

3. Newly Diagnosed Cases of TB Infection in Infants and Children Should be Reported to the Department of Public Health

Since 2003, TB reporting requirements in Massachusetts have included latent TB infection, i.e. any positive TST or IGRA test. All providers who make a diagnosis of TB infection in a child or adolescent are required to [report](#) the diagnosis to the Massachusetts Department of Public Health.

4. Tuberculosis Skin Testing Should Follow Established Best Practices

All TST results (positive or negative) must be read and interpreted by qualified medical personnel. Mail-in or telephone responses of readings by parents are not acceptable.

Each office, health center and clinic administering the TST should design a work flow for reading test results that is fast and convenient for the patient and minimizes paperwork for the health care provider. Test documentation should be placed in a prominent, easily

visible part of the electronic or paper medical record. Staff need to be trained in proper intradermal administration of the test reagent (PPD), reading the test result in millimeters (mm) of induration (not erythema, or redness) measured at a right angle to the long axis of the arm (*i.e.*, measured across the arm) at 48-72 hours after placement, and risk-based interpretation of the test result. (See Attachment 3, *Definition of Positive Tuberculin Skin Test in Children and Adolescents*)

Many infants and children from countries with a high prevalence of TB have been vaccinated with bacille Calmette-Guerin (BCG). These children can receive a TST and results should be interpreted without regard to previous BCG vaccination. While effective in preventing serious disseminated forms of disease such as TB meningitis and miliary TB in young children, BCG vaccination does not prevent TB infection and immunity typically wanes within five years. Moreover, while BCG may induce a reaction to the TST, a positive TST in a child from a country with a high prevalence of TB who has received BCG vaccine may be due to latent TB infection, and the risk of failure to diagnose infection in a high risk child may be substantial.

5. IGRA Tests May be Used in Place of a TST to Diagnose TB Infection in Children 5 Years Of Age and Older

Two blood tests are approved in the United States for the diagnosis of TB infection in adults and children: QuantiFERON Gold-In Tube test and the T-SPOT.TB test. These tests are based on the ability of *M. tuberculosis* antigens to stimulate T cells from persons who have been infected with *M. tuberculosis*. The assays detect interferon-gamma produced by these activated cells *in vitro*, and are referred to as interferon-gamma release assays (IGRAs). These tests have two main advantages over TST. First, because IGRAs use antigens that are specific for *M. tuberculosis* but absent in BCG and most non-TB mycobacteria, a positive test should not result from cross-reactivity with BCG or other non-TB mycobacteria. This feature may be especially useful in BCG-vaccinated persons. Second, because IGRAs are performed in the laboratory using a blood sample, a single visit is required to complete the test (in contrast to the second visit required to read the TST result). Like a negative TST, a negative IGRA does not exclude the possibility of TB infection.

In studies comparing the TST with the IGRAs, the IGRAs have performed well enough to be recommended for the diagnosis of LTBI, and as an adjunct for the diagnosis of TB disease in adults and children. (9) In most studies assessing LTBI in contacts, the IGRAs are positive in a smaller proportion of patients than the TST. In many cases this difference has been interpreted as greater specificity of the IGRA tests because of the potential of the TST to be positive in some BCG-vaccinated persons or by prior exposure to non-TB mycobacteria.

Issues regarding the use of IGRA tests include, first, the meaning of discordant results (when either the TST or the IGRA result is positive and the other test result is negative) and, second, reproducibility of IGRA results. While some of the discordance may result from better specificity of the IGRA in BCG-vaccinated persons, the significance of a positive TST/negative IGRA, particularly in high-risk persons who have a strongly positive TST is not clear. In the United States, the CDC does not recommend that an IGRA be used as a confirmatory test for a TST result; however the American Academy of Pediatrics suggests that this may be useful in some circumstances. If a child has had both a TST and an IGRA, and the test results are discordant, a thorough risk assessment should be undertaken to

determine whether treatment should be recommended for the child. A child with discordant results and with a known risk factor for *M. tuberculosis* infection (e.g., recent exposure) or a medical condition that increases the risk for progression to TB disease (e.g., HIV infection) should be strongly considered for treatment of latent TB infection once TB disease is excluded.

The main limitation of the use of IGRA tests in children involves the interpretation of discordant results, as noted above. In addition, because of the lower sensitivity of these tests in children under 5 years of age, use in these younger children is not recommended. In children 5 years of age and older the performance of IGRA tests appears to be comparable to their performance in adults. Below this age, there are fewer data and more uncertainty. It is important to note that an indeterminate (QuantiFERON) or equivocal/invalid (T-SPOT.TB) result should not be interpreted as negative and should not be taken as evidence of that a child does not have infection with *M. tuberculosis*.

The optimal way to test for TB infection in immunocompromised persons remains uncertain. In some studies the IGRAs function well in HIV-infected and other immunosuppressed persons, although their sensitivity falls with decreasing CD4 counts. Any negative test result for TB infection, therefore, should be interpreted with caution in an immunocompromised person who has risk factors for *M. tuberculosis* infection.

Based on these considerations, the Massachusetts Department of Public Health recommends that the IGRAs be used as follows:

- In healthy children 5 years of age and older, an IGRA test may be used in place of the TST for the diagnosis of latent TB infection or as an adjunct for the diagnosis of TB disease. A negative IGRA test, like a negative TST, does not exclude the possibility of *M. tuberculosis* infection.
- In children 5 years of age and older with a history of BCG vaccination, an IGRA test is preferred to the TST, although the TST is acceptable. Decisions regarding whether to initiate treatment of TB infection in this setting must be made on an individual basis after taking into account risk factors for *M. tuberculosis* infection and disease.
- IGRA tests should not be used in children under 5 years of age or in sequential or periodic testing scenarios.
- Indeterminate or borderline IGRA results do not exclude infection with *M. tuberculosis*, and the test should be repeated.

6. Evaluation of Tuberculosis Infection: Exclusion of Active TB and Diagnosis of Latent TB Infection

A diagnosis of latent TB infection in a child with any positive test for TB infection can be made only after active TB disease has been excluded by clinical evaluation. This evaluation includes: 1) a complete history, including a history of TB risk and co-morbidities that increase risk of TB disease, and a review for symptoms of TB, 2) a physical examination, and 3) a chest radiograph. (10) Children 11 years old and younger should have both PA and lateral views, while in children and adolescents over 11 years of age a single PA view usually is sufficient. . The radiologist who reads the radiograph must be informed of its indication, *i.e.*, to exclude active TB, in order to provide context for its interpretation.

Children with TB infection and no symptoms, signs, or findings of TB on examination and with a normal chest radiograph may be considered to have latent TB infection. These children are candidates for treatment of latent TB infection in order to prevent disease progression. Asymptomatic children who have a positive TST or IGRA may attend school pending chest x-ray results. Similarly, asymptomatic children deemed to be in a high risk category may also attend school pending results of TB testing.

Children under 5 years of age who are contacts to an individual with infectious TB, and TST-negative at the time of initial contact investigation screening, may be placed on isoniazid (INH) preventive therapy. This “window prophylaxis” is done to treat an early TB infection that is not yet detectable by TST and can prevent rapid progression to TB disease. Both TST and IGRA reactivity can take up to 12 weeks following exposure. If the TST remains negative at a second TST done 8-10 weeks after exposure has ended, the treatment can be stopped. Children on window prophylaxis may be prioritized for directly observed preventive therapy (DOPT) by a school nurse, local public health nurse or trained community health worker. Note that if the second TST is positive, indicating a new TB infection, completion of a full course of treatment (nine months of INH or another recommended regimen) is a high priority.

7. Completion of Treatment for TB Infection Should Be Given High Priority

The primary purpose of testing for TB infection in healthy infants and children is to identify those who have latent TB infection and whose future risk of TB disease can therefore be markedly reduced by treatment. Testing for TB infection should be linked with an intention to treat children identified as having latent TB infection. Treatment should be initiated as soon as possible once the diagnosis of latent TB infection is established and TB disease is excluded. This is especially so for children under 5 years of age in whom TB infection can progress rapidly to severe disease. By preventing TB disease, the potential for spread of TB to others in the community in the future also will be decreased.

It should be noted that new shorter courses of treatment for latent TB infection in adults (2) have not been approved for use in children. Nine months of treatment with INH daily, supplemented with vitamin B6 (pyridoxine) and clinical monitoring for adherence and safety at least monthly is the preferred regimen currently recommended for infants, children and adolescents. Children with a positive IGRA or TST who were exposed to a person with known INH-resistant TB should be treated with six months of daily rifampin. For children with presumed infection by an organism that is multi-drug resistant (*i.e.*, resistance to at least INH and rifampin), expert consultation is recommended.

Treatment of latent TB infection may be managed by primary health care providers, with input as needed from the Massachusetts Department of Public Health or from pediatric infectious disease or pulmonary disease specialists. However, when the child with latent TB infection is not in a primary health care setting or when the primary health care provider does not feel that he or she is able to treat latent TB infection, the child should be referred for treatment to an [Massachusetts Department of Public Health-designated TB clinic](#), or to a physician with expertise in the management of latent TB infection in children.

Strategies to encourage completion of therapy in children might include directly observed therapy of each administered dose (DOT) by a school nurse or a trained health worker, or by provision of adherence support measures.

We urge each office, health center and clinic that performs screening and testing for latent TB infection to maintain its own statistics on the number of infants and children found to have latent TB infection and the proportion who complete a course of treatment whether on site or at a state TB clinic. These statistics can serve as the basis for continually monitoring and improving treatment completion rates as a quality improvement measure.

Citations

- (1) Screening infants and children for tuberculosis: Recommendations of the Medical Advisory Board of the Massachusetts Committee for the Elimination of Tuberculosis. 1996; Boston, MA.
- (2) Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *MMWR* 2000; 49 (No. RR-6):1-51.
- (3) The Medical Advisory Committee for the Elimination of Tuberculosis (MACET). Latent tuberculosis infection: A guide for Massachusetts providers. 2000; Boston, MA.
- (4) Froehlich H, Ackerson LM, Morozumi PA. Targeted testing of children for tuberculosis: Validation of a risk assessment questionnaire. *Pediatrics* 2001; 107: e54.
- (5) Saiman L, San Gabriel P, Schulte J et al. Risk factors for latent tuberculosis infection among children in New York City. *Pediatrics* 2001; 107: 999-1003.
- (6) Besser RB, Pakiz B, Schulte JM et al. Risk factors for positive Mantoux tuberculin skin tests in children in San Diego, California: Evidence for boosting and possible food-borne transmission. *Pediatrics* 2001; 108: 305-310.
- (7) Lobato MN, Hopewell PC. Mycobacterium tuberculosis infection after travel to or contact with visitors from countries with a high prevalence of tuberculosis. *Am J Respir Crit Care Med* 1998; 158: 1871-1875.
- (8) Cobelens FGJ, van Duetekom H, Draayer-Jansen IWE et al. Risk of infection with Mycobacterium tuberculosis in travelers to areas of high tuberculosis endemicity. *Lancet* 2000; 356: 461-465.
- (9) Lewinsohn DA, Lobato MN, Jereb JA. Interferon-gamma release assays: new diagnostic tests for Mycobacterium tuberculosis infection, and their use in children. *Curr Opin Pediatr* 2010; 22(1): 71-6.
- (10) Smuts, NA, Beyers, N, Gie, RP, et al. Value of the lateral chest radiograph in tuberculosis in children. *Pediatr Radiol*. 1994;24(7):478-80. PMID: 7885777.

Attachment 1

Risk Assessment to Identify Children Who Should Be Tested for Tuberculosis

A child who has been infected with tuberculosis (TB) may show no outward signs or symptoms. However, undetected and untreated infection can later lead to severe TB disease in children.

A risk-based approach to screening for latent TB infection (LTBI) is the cornerstone to TB prevention in children. To determine whether a child may need testing, the following questions will provide a health care provider with information the child's risk for TB. If a child is identified to be at risk of exposure to TB, testing is indicated. Use an approved interferon-gamma release assay (IGRA) for children ages 5 and older or the Mantoux tuberculin skin test (5 TU PPD) for children of any age. IGRA is the preferred test for children ages 5 and older with a history of BCG vaccination.



Children with any of the following risk factors are candidates for TB testing, unless there is written documentation of a previous positive TB test (TST or IGRA).

TB Risk Assessment	Yes	No
Was the child born in Africa, Asia and Pacific Islands (except Japan), Central America, South America, Mexico, Eastern Europe, the Caribbean or the Middle East? In what country was the child born?	<input type="checkbox"/>	<input type="checkbox"/>
Has the child lived or traveled in Africa, Asia and Pacific Islands (except Japan), Central America, South America, Mexico, Eastern Europe, the Caribbean or the Middle East for more than one month?	<input type="checkbox"/>	<input type="checkbox"/>
Has the child lived with or spent time with someone who has been sick with TB in the last 2 years?	<input type="checkbox"/>	<input type="checkbox"/>
Have any members of the child's household come to the United States from another country?	<input type="checkbox"/>	<input type="checkbox"/>
Does the child have any history of immunosuppressive disease or take medications that might cause immunosuppression?	<input type="checkbox"/>	<input type="checkbox"/>

Attachment 2

Recommendations for TB Testing

Test Promptly

- Contacts of persons with confirmed or suspected infectious tuberculosis (contact investigation)
- Children with radiographic or clinical findings suggesting tuberculosis disease
- Children who have immigrated from countries where TB infection is endemic
- Children with travel to countries where TB infection is endemic or significant contact with persons from such countries

Test Annually

- Children infected with HIV, if there is continued risk of TB exposure
- Incarcerated adolescents, only if the facility is high risk

Test Promptly and Periodically

Children with potential exposure to tuberculosis and who have increased risk for progression to severe tuberculosis including those with:

- Diabetes mellitus
- Chronic renal failure
- Malnutrition
- Congenital or acquired immunodeficiencies

Test Before Initiating Immunosuppressive Therapy

Children with underlying conditions that necessitate immunosuppressive therapy should have an initial tuberculin skin test before initiation of immunosuppressive therapy.

* Modified from American Academy of Pediatrics. Report of the Committee on Infectious Diseases. Red Book 2012:740.

† The American Academy of Pediatrics does not specify a time interval.

Attachment 3
**Definitions of Positive Tuberculin Skin Test¹ (TST) Results
in Infants, Children and Adolescents²**

A TST reaction of ≥ 5 mm induration is considered positive for

- Children in close contact with known or suspected infectious individuals with tuberculosis disease
- Children suspected to have tuberculosis disease
 - Chest radiograph consistent with active or previously active tuberculosis
 - Clinical evidence of tuberculosis
- Children receiving immunosuppressive therapy³ or with immunosuppressive conditions, including HIV infection

A TST reaction of ≥ 10 mm induration is considered positive for

- Children at increased risk of disseminated tuberculosis disease:
 - Children younger than 4 years of age
 - Other medical conditions, including Hodgkin disease, lymphoma, diabetes mellitus, chronic renal failure, or malnutrition
- Children with increased exposure to tuberculosis disease
 - Children born, or whose parents or other household members were born, in high-prevalence regions of the world
 - Children who travel and exposure to high-prevalence regions of the world
 - Children frequently exposed to adults who are HIV infected, homeless, users of illicit drugs, residents of nursing homes, incarcerated or institutionalized

A TST reaction of ≥ 15 mm induration is considered positive for

Children 4 years of age or older without any risk factors

Note: These definitions apply regardless of previous bacille Calmette-Guerin (BCG) immunization.

¹ 5 Tuberculin Units of Purified Protein Derivative administered via Mantoux method; induration measured at 48-72 hours after placement by qualified medical personnel.

² Modified from American Academy of Pediatrics. Tuberculosis. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2012 Report of the Committee on Infectious Diseases*. Elk Grove Village, IL: American Academy of Pediatrics; 2012:737.

³ Including immunosuppressive doses of corticosteroids.