

Diagnosis of Latent Tuberculosis Infection

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Introduction

Purpose

Use this section to understand and follow national, State of Michigan and MIACET guidelines to do the following:

- Classify patients with latent TB infection (LTBI).
- Diagnose LTBI.

In the 2005 guideline “Controlling Tuberculosis in the United States: Recommendations from the American Thoracic Society, Centers for Disease Control and Prevention, and the Infectious Diseases Society of America,” one of the recommended strategies to achieve the goal of reduction of TB morbidity and mortality is the identification of persons with LTBI at risk for progression to TB disease, and treatment of those persons with an effective drug regimen.¹



Contacts are mentioned within this section, but their evaluation and follow-up are covered in more depth in the Contact Investigation section. For information on treatment, refer to the Treatment of Latent Tuberculosis Infection section.

Policy

- In Michigan: Targeted testing for LTBI should be conducted only among persons in groups with identified risk factors for LTBI and/or progression to TB disease.
- Contacts should be evaluated as described in the Contact Investigation section.
- Health care professionals who administer and read tuberculin skin tests (TST), shall achieve certification through the TB skin test training course as identified by MDCH.



For roles and responsibilities, refer to the “Roles, Responsibilities, and Contact Information” topic in the Introduction.

High-Risk Groups

Certain factors identify persons at high risk for tuberculosis (TB) infection and/or for progression to TB disease. Persons in the high-risk groups listed in Table 1: **Persons at High Risk for Tuberculosis Infection and Progression to Tuberculosis Disease** are candidates for tuberculin skin testing in Michigan. Persons with risk factors from both columns may be at much higher risk than those with risk factors in only one column. For example, an individual born in a high-TB-prevalence country with HIV infection is at much higher risk of having active TB than a US-born individual with HIV infection.

TABLE 1: Persons at high risk for Tuberculosis Infection and Progression to Tuberculosis Disease²

For Tuberculosis Infection	For Progression to Tuberculosis Disease ³
<ul style="list-style-type: none"> ▪ High-priority or close contacts of persons who have smear-positive pulmonary or laryngeal TB (e.g. housemates or coworkers w/ frequent close contact to case) ▪ Infants, children, and adolescents exposed to adults in high-risk categories ▪ Recent immigrants (<5 years) from countries with high incidence of TB ▪ Recent immigrants from Mexico ▪ Migrant workers ▪ Persons who have recently spent over 3 months in high-incidence countries ▪ Social or ethnic minority groups (e.g. African-Americans, Hispanics, Asians or Pacific Islanders, Native Americans) ▪ Persons for whom risk for TB transmission is high: <ul style="list-style-type: none"> • Homeless persons • Injection drug users • Persons living or working in institutions with individuals at risk for active TB disease such as: <ul style="list-style-type: none"> ▪ Hospitals, especially staff in nursing, emergency departments, and laboratories ▪ Long-term care facilities ▪ Homeless shelters ▪ Residences for acquired immunodeficiency syndrome (AIDS) patients ▪ Correctional facilities 	<ul style="list-style-type: none"> ▪ Persons with HIV infection ▪ Infants and children aged <5 years ▪ Persons infected with <i>Mycobacterium tuberculosis</i> within the previous 2 years ▪ Persons with a history of untreated or inadequately treated TB disease ▪ Persons with radiographic findings consistent with previous TB disease ▪ Persons who abuse alcohol or use illegal drugs (such as injection drugs or crack cocaine) ▪ Persons with any of the following clinical conditions or other immunocompromising conditions: <ul style="list-style-type: none"> • Silicosis • Diabetes mellitus • End-state renal disease (ESRD)/chronic renal failure, hemodialysis • Some hematologic disorders (e.g., leukemias and lymphomas) • Other malignancies (e.g., carcinoma of head, neck, or lung) • Body weight $\geq 10\%$ below ideal body weight • Prolonged corticosteroid use • Use of other immunosuppressive treatments (e.g., prednisone or tumor necrosis factor-alpha [TNF-α] antagonists) • Organ transplantation • Gastrectomy • Chronic malabsorption syndromes • Jejunioileal bypass

Diagnosis of Latent Tuberculosis Infection

The diagnosis of latent tuberculosis infection (LTBI) has traditionally been based upon results of tuberculin skin testing. However, the QuantiFERON[®]-TB Gold (QFT-G) test and the QuantiFERON[®]-TB Gold in-tube (QFT[™]) test, which are whole-blood interferon gamma release assays (IGRAs), are now other options for detecting LTBI.

Use the Mantoux tuberculin skin test (TST) or an IGRA to test for *Mycobacterium tuberculosis* infection. QFT-G or QFT[™] can be used in many circumstances in which the TST is used, but should not be used in addition to the TST.⁴



For information on testing methods available in Michigan, refer to the Laboratory Services section.



For a summary of the TB classification numbers, refer to the “Tuberculosis Classification System” topic in the Surveillance section.

Interferon Gamma Release Assays

Blood assay for *Mycobacterium tuberculosis* (BAMT) is a general term referring to recently developed in vitro diagnostic tests that assess for the presence of infection with *M. tuberculosis*. This term includes, but is not limited to, interferon gamma release assays (IGRAs). The IGRA currently approved by the Food and Drug Administration (FDA) and available in Michigan is the QuantiFERON[®]-TB Gold (QFT-G) test. The QFT-G test, as well as the newer QuantiFERON[®]-TB Gold in-tube (QFT[™]) test, usually can be used in place of the TST.⁵ Other cytokine-based immunoassays are under development and may also become useful in the diagnosis of *M. tuberculosis* infection. Future FDA-licensed products, in combination with Centers for Disease Control and Prevention (CDC)-issued recommendations, may provide additional diagnostic alternatives.⁶

The advantages of an IGRA, compared with the TST, are that results can be obtained after a single patient visit, and that, because it is a blood test performed in a qualified laboratory, the variability associated with skin test reading can be eliminated.⁷ In addition, the QFT-G and QFT[™] tests appear to be less affected by past BCG vaccination than the TST and may eliminate the unnecessary treatment of patients with BCG-related false-positive results.⁸ However, the QFT-G and QFT[™] tests have

practical limitations that include the need to draw blood and to ensure its receipt in a qualified laboratory in time for testing. For the QFT-G test, the blood must arrive at the laboratory less than 12 hours after collection to be incubated with the test antigens, while the lymphocytes are viable.⁹ For a QFT™ test, the blood specimens are collected directly into the three blood collection tubes, shaken vigorously, and then incubated at the collection site. After incubation, blood collection tubes should be stored no longer than three days prior to centrifugation and laboratory manipulation.

NOTE: A negative IGRA test performed on a TB patient following the initiation of anti-tuberculosis therapy should not be considered a basis for stopping antibiotic therapy.

Mantoux Tuberculin Skin Testing

The Mantoux method of tuberculin skin testing is also used to detect infection with *Mycobacterium tuberculosis*.

In general, it takes two to ten weeks after infection for a person to develop a delayed-type immune response to tuberculin measurable with the Mantoux tuberculin skin test (TST).¹⁰ During the test, tuberculin is injected into the skin. The immune system of most persons with tuberculosis (TB) infection will recognize the tuberculin, causing a reaction in the skin. Repeated TSTs do not produce hypersensitivity.

The size of the measured induration (a hard, dense, raised formation) and the patient's individual risk factors should determine whether TB infection is diagnosed.¹¹ Based on the sensitivity and specificity of the purified protein derivative (PPD) TST and the prevalence of TB in different groups, three cut-points have been recommended for defining a positive tuberculin reaction:

- Greater than or equal to 5 mm of induration
- Greater than or equal to 10 mm of induration
- Greater than or equal to 15 mm of induration¹²



For more information on cut-points for the TST, see the “Interpretation of the Tuberculin Skin Test” topic in this section.

Candidates for Mantoux Tuberculin Skin Testing

The Mantoux TST can be administered to all persons, including pregnant women¹³, persons who have previously been vaccinated with bacille Calmette-Guérin (BCG)¹⁴, and human immunodeficiency virus (HIV)-infected persons. However, persons with a documented prior positive TST do not need another TST, and the Mantoux TST should not be administered until four weeks after vaccination with live-virus vaccines.



If the person being tested is a contact, follow the procedures outlined in the Contact Investigation section.

Pregnancy

Tuberculin skin testing is entirely safe and reliable for pregnant women, and pregnant women at high risk for TB infection or disease should be tested. Screen pregnant women for TB infection if they have any of the following conditions:

- Symptoms suggestive of TB disease
- HIV infection
- Behavioral risk factors for HIV
- Medical conditions other than HIV infection that increase the risk for TB disease
- Close contact with a person who has pulmonary or laryngeal TB disease
- Immigration from an area of the world where incidence of TB is high

Bacille Calmette-Guérin Vaccine

BCG vaccines are live vaccines derived from a strain of *Mycobacterium bovis*. Because their effectiveness in preventing infectious forms of TB has never been demonstrated in the United States, they are not recommended as a TB control strategy in the United States, except under rare circumstances. They are, however, used commonly in other countries. A history of BCG vaccination is not a contraindication for tuberculin skin testing, nor does it influence the indications for a TST. Administer and measure TSTs in BCG-vaccinated persons in the same manner as in those with no previous BCG vaccination.

Diagnosis and treatment of LTBI should be considered for BCG-vaccinated persons with a TST reaction of equal to or greater than 10 mm induration, especially any of the following:

- Persons continually exposed to populations with a high prevalence of TB (e.g., some healthcare workers, employees and volunteers at homeless shelters, and workers at drug treatment centers)

- Persons who were born or have lived in a country with a high prevalence of TB
- Persons exposed to someone with infectious TB, particularly if that person has transmitted TB to others¹⁵

Evaluate these patients for symptoms of TB. If a patient has symptoms of TB disease, obtain chest radiography and (if the patient is coughing) collect sputum specimens.

Bacille Calmette-Guérin Talking Points

1. Tuberculin reactivity caused by BCG vaccination wanes with time but can be boosted with a TST.¹⁶
2. A diagnosis of *M. tuberculosis* infection should be considered for any BCG-vaccinated person who has TST reaction ≥ 10 mm of induration.¹⁷
3. Treatment for LTBI should be considered for a person who is TST positive and has previous BCG vaccination if the person is:
 - A contact of a person with infectious TB or
 - Vaccinated and born in (or resided in) a country of high prevalence of TB or
 - Exposed to persons at risk for TB¹⁸
4. BCG vaccination should be considered for infants and children who reside in high morbidity countries to prevent meningial TB.¹⁹
5. There is no scientific evidence of protective ability of BCG for preventing pulmonary TB in adolescents or adults.²⁰

Anergy Testing

Anergy testing is not routinely recommended in conjunction with TST for HIV-infected persons in the United States.²¹

Anergy testing is a diagnostic procedure used to obtain information about the competence of the cellular immune system. Conditions that cause an impaired cellular immune system include HIV infection, severe or febrile illness, measles or other viral infections, Hodgkin's disease, sarcoidosis, live-virus vaccination, and corticosteroid or immunosuppressive therapy. Persons with conditions such as these may have suppressed reactions to a TST even if infected with TB. However, there are no simple skin testing protocols that can reliably identify persons as either anergic or nonanergic and that have been proven to be feasible for application in public health TB screening programs.

Factors limiting the usefulness of anergy skin testing include the following:

- Problems with standardization and reproducibility
- Low risk for TB associated with a diagnosis of anergy
- Lack of apparent benefit of treatment for LTBI in groups of anergic HIV-infected persons

Documented Prior Positive Tuberculin Skin Test

Persons who have tested positive in the past and can provide documentation of their status should not have another TST. Instead, they should have a TB symptom assessment questionnaire administered to identify any symptoms of TB disease.²² Persons who are symptomatic should receive a chest radiograph.

Live-Virus Vaccines

The Mantoux TST can be administered in conjunction with all vaccines. However, the measles (MMR) vaccine—and possibly mumps, rubella, varicella, and live attenuated influenza vaccines—may transiently suppress the response to PPD.²³ Therefore, if a vaccine containing live virus (e.g., measles, smallpox) has already been given, the TST should be deferred until (or repeated) at least four weeks after the vaccine was administered.

When giving the TST and the MMR, one of the following three sequences should be used:

- Apply the TST at same visit as the MMR.
- Delay the TST at least four weeks if the MMR is given first.
- Apply the TST first and then give the MMR when the TST is measured.²⁴

Multiple Puncture Tests

Multiple puncture tests (MPTs), such as the Tine test, should not be used. The MPTs are not reliable because the amount of tuberculin injected intradermally cannot be precisely controlled and there is no standard for interpretation.

Administration of the Tuberculin Skin Test

The TST should be placed by a healthcare worker who has received appropriate training and is following written protocols.

Table 2: BEFORE YOU BEGIN TO ADMINISTER A TUBERCULIN SKIN TEST

Before You Begin to Administer a Tuberculin Skin Test	
Review Information	<p>CDC. <i>Mantoux Tuberculin Skin Test Facilitator Guide</i>: http://www.cdc.gov/tb/pubs/Mantoux/guide.htm</p> <p>Infection control procedures (including hand washing before and after the procedure and the use of gloves and a sharps container) as described in CDC's Hospital Infection Control Practice Advisory Committee (HICPAC) report, available online at: http://www.cdc.gov/handhygiene.</p>
Gather Equipment	<ul style="list-style-type: none"> ▪ Gloves ▪ Alcohol pads or alternative skin cleanser ▪ Safety needle ▪ Tuberculin syringe (Do not pre-draw tuberculin into syringes prior to test.) ▪ Purified protein derivative (PPD) (Tubersol® or Aplisol®: See the warning in the text below in this table.) ▪ Sharps container <p>Note: Date PPD tuberculin vials when opened and discard them after 30 days. See the package insert for appropriate storage information.</p>



Read the PPD labels carefully before administering a TST. The packaging of tetanus toxoid-containing vaccines (TTCVs) is similar to Tubersol® and Aplisol®, and all are refrigerated. See the CDC's "Errors Involving Mix-up of Tuberculin Purified Protein Derivative and Vaccine Products" (*TB Notes Newsletter*. 2005;No. 1) at this hyperlink: http://www.tbchicago.org/tbguidecdc/newsletters/notes/TBN_1_05/Errors_mix_up.htm

How to Administer a Tuberculin Skin Test

1. Obtain the patient's written consent, if required by your health department.
2. Inject air into the vial air space (not into the solution). Injection of air into the air space in the vial prevents creation of negative pressure within the vial, allowing the antigen to be withdrawn easily. Injecting air into the solution creates bubbles and may interfere with withdrawing the correct amount of antigen.²⁵
3. The injection should be placed on the palm-side-up surface of the forearm, about two to four inches below the elbow. Your local institutional policy may specify the right or left forearm for the skin test. The area selected should be free of any barriers to placing and reading the skin test, such as muscle margins, heavy hair, veins, sores, tattoos, or scars.
4. After choosing the injection site, clean the area with an alcohol swab by circling from the center of the site outward. Allow the site to dry completely before the injection.
5. Using a disposable tuberculin safety needle and syringe, inject 0.1 ml of PPD tuberculin containing 5 tuberculin units (TU) intradermally with the needle bevel facing upward. Because some of the tuberculin solution can adhere to the inside of the plastic syringe, the skin test should be given as soon as possible after the syringe is filled.
6. The injection should produce a discrete, pale elevation of the skin (a wheal) 6 to 10 mm in diameter. **Note:** If a 6- to 10-mm wheal is not produced, repeat the test on the opposite arm or the same arm, 2 inches from the original site.
7. Record the date and time of TST administration, location of injection site, dose, name of the person who administered the test; the name and manufacturer of the tuberculin product used, its lot number, its expiration date; and the reason for testing.²⁶

Measurement of the Tuberculin Skin Test

A trained healthcare worker should read the TST 48 to 72 hours after the intradermal injection. Patients should never be allowed to read their own TSTs.²⁷

- A positive reaction can be measured anytime after 48 hours.
- If the results appear negative and more than 72 hours have passed, the test should be repeated. It can be repeated immediately, or after one week, if two-step testing is required.



See the topic titled “Two-Step Tuberculin Skin Testing” in the Infection Control section.



Before you measure a TST, review information in the CDC’s *Mantoux Tuberculin Skin Test Facilitator Guide* at this hyperlink:

<http://www.cdc.gov/tb/pubs/Mantoux/guide.htm> .

How to Measure a Tuberculin Skin Test

1. Measure the TST site perpendicular to the axis of the forearm (from the thumb side of the arm to the little finger side of the arm or vice versa).
2. Induration is a hard, dense, raised formation. Measure only induration hardness and not swelling around the site of the injection. Do **not** measure erythema (redness). A TST with erythema, but no induration, is nonreactive.
3. Record the test result in mm, not as “positive” or “negative.” An exact reading in mm may be necessary to interpret whether conversions occur on a subsequent test. Record a TST with no induration as “0 mm.” Where there is induration, do not round off the reading, but record it exactly as read.
4. Report adverse reactions to a TST (e.g., blistering, ulcerations, necrosis) to the FDA’s MedWatch Program at 1-800-FDA-1088, or via the Internet at this hyperlink: <http://www.fda.gov/medwatch/>.

Interpretation of the Tuberculin Skin Test

TSTs should be interpreted by a trained healthcare worker. Use Table 3 below to interpret TSTs.



Call the MDCH TB Control Program at 517-335-8165 regarding TST reactions when interpretation and medical follow-up are unclear.



Before you interpret a TST, review information in the CDC's *Mantoux Tuberculin Skin Test Facilitator Guide* at this hyperlink: <http://www.cdc.gov/tb/pubs/Mantoux/guide.htm> .

How to Interpret a Tuberculin Skin Test

Use the table below to determine when a reaction is positive.

Table 3: POSITIVE TUBERCULIN SKIN TEST REACTIONS

Induration Size	Considered Positive For:
5 mm or more	<ul style="list-style-type: none"> ▪ Persons with human immunodeficiency virus (HIV) infection or acquired immunodeficiency syndrome (AIDS) ▪ Recent contacts to an infectious case of tuberculosis (TB) disease ▪ Persons with fibrotic lesions on chest radiograph consistent with healed TB ▪ Persons with organ transplants or other immunosuppressed persons (such as those receiving the equivalent of >15 mg/day of prednisone for >1 month) ▪ Persons receiving treatment with tumor necrosis factor-alpha (TNF-α) antagonists
10 mm or more	<ul style="list-style-type: none"> ▪ Foreign-born persons recently arrived (within 5 years) from countries with a high TB incidence or prevalence (e.g., most countries in Africa, Asia, Latin America, Eastern Europe, the former USSR, or from refugee camps) ▪ Injection drug or other substance abusers; alcoholics ▪ Residents and employees in high-risk, congregate settings (e.g., correctional institutions; long-term residential care facilities; hospitals and other healthcare facilities; homeless shelters; and refugee camps) ▪ Mycobacteriology laboratory personnel ▪ Persons with other medical conditions that increase the risk of TB disease ▪ Children younger than 5 years of age, or children and adolescents exposed to adults in high-risk categories
15 mm or more	<ul style="list-style-type: none"> ▪ Persons with no known risk factors for TB

When interpreting TST results, be aware of the following.

Skin test conversions: For persons previously skin tested, an increase in induration of 10 mm or more within a two-year period is classified as a conversion to positive.

False-negative reactions may be due to the following:

- Anergy



See “Anergy Testing” under “Candidates for Mantoux Tuberculin Skin Testing” in this section.

- Recent TB infection (within the past 10 weeks)
- Very young age (less than six months of age, because the immune system is not fully developed)
- Overwhelming TB disease
- Vaccination with live viruses (e.g. measles, mumps, rubella, varicella, oral polio or yellow fever)



TB skin testing should be done either on the same day as vaccination with live virus or at least four weeks after vaccination.



See “Live-Virus Vaccines” under “Candidates for Mantoux Tuberculin Skin Testing” in this section.

- Some viral infections (measles, mumps, chickenpox, or HIV)
- Corticosteroids or other immunosuppressive agents given for two or more weeks

False-positive reactions may be due to the following:²⁸

- Nontuberculous mycobacteria (NTM) or mycobacterium other than tuberculosis (MOTT)
- BCG vaccination



See “Bacille Calmette-Guérin Vaccine” under “Candidates for Mantoux Tuberculin Skin Testing” in this section.

Human Immunodeficiency Virus Screening

The Centers for Disease Control and Prevention (CDC) recommends the following:

- Routine HIV screening for all patients ages 13–64 seeking health care for any reason, without regard to patient’s known risks for HIV infection
- Annual HIV screening of patients known to be at high risk²⁹

Follow-Up Activities

After testing, complete the following tasks:



If the person has signs or symptoms of TB, evaluate for TB disease as described in the “Diagnosis of Tuberculosis Disease” topic in the Diagnosis of Tuberculosis Disease section. Refer to Table 1: **When to Suspect Pulmonary Tuberculosis in Adults**.



If the person is a contact, follow the procedures for testing and evaluation in the Contact Investigation section.



If the person is a participant in two-step screening, see the topic titled “Two-Step Tuberculin Skin Testing” in the Infection Control section.



If the TST result is positive, a chest radiograph should be obtained for the patient, as specified in the “Chest Radiography” topic in this section.

Chest Radiography

All individuals being considered for LTBI treatment should undergo a chest radiograph to rule out pulmonary TB disease. For information on how to classify TB, see the “Tuberculosis Classification System” topic at the beginning of this section. Refer to Table 4 below to determine when to obtain a chest radiograph and what follow-up is required for chest radiograph results.

A posterior-anterior radiograph of the chest is the standard view used for the detection and description of chest abnormalities in adults. In some instances, other views (e.g., lateral, lordotic) or additional studies (e.g., computed tomography [CT] scans) may be necessary.



Children younger than five years of age should receive posterior-anterior and lateral radiographs.³⁰



For more information on chest radiography, refer to the Francis J. Curry National Tuberculosis Center's *Radiographic Manifestations of Tuberculosis: A Primer for Clinicians* (Francis J. Curry National Tuberculosis Center Web site; 2006) at this hyperlink:

http://www.nationaltbcenter.ucsf.edu/products/product_details.cfm?productID=EDP-04.



For persons recently exposed to TB, follow the procedures for testing and evaluation in the Contact Investigation section.

Table 4: TARGETED TESTING FOR LATENT TUBERCULOSIS INFECTION: WHEN CHEST RADIOGRAPHS ARE REQUIRED AND HOW TO FOLLOW UP ON RADIOGRAPHY RESULTS

Signs or Symptoms of TB Disease?	TST or IGRA Result?	Recent Exposure to Infectious TB?	Chest Radiograph: Required and Results?	Follow-up Action
Yes	Positive or negative	Yes or no	CXR Required: Yes Results: normal or abnormal	<ul style="list-style-type: none"> Classify as Class 5. Evaluate for TB disease. Refer to the Diagnosis of Tuberculosis Disease section.
No	Negative	No	CXR not recommended unless the patient has HIV infection or other forms of immunosuppression are present	<ul style="list-style-type: none"> Classify as Class 0.
No	Positive	No	CXR Required: Yes Results: normal	<ul style="list-style-type: none"> Classify as Class 2. Consider treatment for LTBI. Refer to the Treatment of Latent Tuberculosis Infection section.
			CXR Required: Yes Results: abnormal noncalcified fibrotic lesions suggestive of old, healed TB; comparison film available and stable	<ul style="list-style-type: none"> Classify as Class 4 or 5. Consider evaluating for TB disease. Refer to the Diagnosis of Tuberculosis Disease section.
			CXR Required: Yes Results: abnormal consistent with TB disease; no comparison film	<ul style="list-style-type: none"> Classify as Class 3 or 5. Evaluate for TB disease. Refer to the Diagnosis of Tuberculosis Disease section.
Definitions of abbreviations: CXR = chest radiograph; HIV = human immunodeficiency virus; IGRA = interferon gamma release assay; LTBI = latent tuberculosis infection; TB = tuberculosis; TST = tuberculin skin test.				

Resources and References

Resources

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