

# Chapter 3

## Diagnosis of Tuberculosis Disease

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# Introduction

## Purpose

Use this section to understand and follow national and Nevada guidelines for

- Classifying patients with tuberculosis (TB) disease and latent TB infection (LTBI)
- Detecting suspected cases of TB
- Understanding when to report suspected or confirmed cases of TB and
- Diagnosing TB disease.

It is important to understand when a person should be evaluated further for TB disease. Not recognizing TB symptoms promptly may lead to delays in initiating appropriate treatment thus extending the possible infectious time, transmitting more TB disease, and multiplying the number of contacts needing to be evaluated.

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 early and accurate detection, diagnosis, and reporting of TB cases, leading to initiation and completion of treatment.<sup>1</sup>

Improvement in the detection of TB cases is essential to progress toward the elimination of TB in the United States.<sup>2</sup> Case detection includes the processes that lead to the; presentation, evaluation, receipt of diagnosis, and reporting of persons with active TB.<sup>3</sup> Detecting and reporting suspected cases of TB are key steps in stopping transmission of *Mycobacterium tuberculosis* because it leads to prompt initiation of effective multiple-drug treatment, which rapidly reduces infectiousness.<sup>4</sup>

TB is commonly diagnosed when a person seeks medical attention for symptoms caused by the disease or a concomitant medical condition. Thus, healthcare providers, particularly those providing primary healthcare to populations at high risk, are key contributors to TB case detection.<sup>5</sup> The majority of pulmonary TB cases continue to be diagnosed at an advanced stage. Earlier diagnosis would result in less individual morbidity and death, greater success in treatment, less transmission to contacts, and fewer outbreaks of TB.<sup>6</sup>

A diagnosis of TB disease is usually based on positive cultures for *M. tuberculosis*. However, in the absence of a positive culture, TB may also be diagnosed on the basis of clinical signs and symptoms. Positive cultures for *M. tuberculosis* confirm the diagnosis of Tuberculosis and provide an organism for susceptibility testing as well as genotyping.



Contacts are mentioned within this section, but the contact investigation evaluation and follow-up are covered in more depth in Chapter 8, *Contact Investigation*. For information on treatment, refer to *Treatment of Tuberculosis Disease*, Chapter 4.

## High Risk Groups

Certain factors identify persons at high risk for tuberculosis (TB) infection and/or for progression to TB disease. In Nevada 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 an *M. tuberculosis* screening test.

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 Disease<sup>7</sup>**

For Tuberculosis Infection	For Progression to Tuberculosis Disease <sup>8</sup>
<ul style="list-style-type: none"> <li>▪ High-priority contacts such as housemates or coworkers or contacts of persons who have smear-positive pulmonary or laryngeal TB</li> <li>▪ Infants, children, and adolescents exposed to adults in high-risk categories</li> <li>▪ Recent immigrants (&lt;5 years) from countries with high incidence of TB (Asian, African, Latin American, and Eastern European countries have TB rates 5–30 times higher than U.S. rates, and an increasing percentage of TB cases here are occurring among immigrants from those countries)</li> <li>▪ Recent immigrants from Mexico</li> <li>▪ Migrant workers</li> <li>▪ Persons who have recently spent over 3 months in high-incidence countries (such as missionaries)</li> <li>▪ Native Americans</li> <li>▪ Persons with high rates of TB transmission:               <ul style="list-style-type: none"> <li>• Homeless persons</li> <li>• Injection drug users</li> <li>• Persons with human immunodeficiency virus (HIV) infection</li> <li>• Persons living or working in institutions with individuals at risk for TB such as:                   <ul style="list-style-type: none"> <li>▪ Hospitals, especially staff in nursing, emergency departments, and laboratories</li> <li>▪ Long-term care facilities</li> <li>▪ Homeless shelters</li> <li>▪ Residences for acquired immunodeficiency syndrome (AIDS) patients</li> <li>▪ Correctional facilities</li> </ul> </li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>▪ Persons with HIV infection</li> <li>▪ Infants and children aged &lt;5 years</li> <li>▪ Persons infected with <i>Mycobacterium tuberculosis</i> within the previous 2 years</li> <li>▪ Persons with a history of untreated or inadequately treated TB disease</li> <li>▪ Persons with radiographic findings consistent with previous TB disease</li> <li>▪ Persons who consume excessive alcohol or use illegal drugs (such as injection drugs or crack cocaine)</li> <li>▪ Persons with any of the following clinical conditions or other immunocompromising conditions:               <ul style="list-style-type: none"> <li>• Silicosis</li> <li>• Diabetes mellitus</li> <li>• End-stage renal disease (ESRD), chronic renal failure, hemodialysis</li> <li>• Some hematologic disorders (e.g., leukemias and lymphomas)</li> <li>• Other malignancies (e.g., carcinoma of head, neck, or lung)</li> <li>• Body weight ≥10% below ideal body weight</li> <li>• Prolonged corticosteroid use</li> <li>• Use of other immunosuppressive treatments (e.g., prednisone or tumor necrosis factor-alpha [TNF-α] antagonists)</li> <li>• Organ transplantation</li> <li>• Gastrectomy</li> <li>• Chronic Malabsorption Syndromes</li> <li>• Jejunioileal bypass</li> </ul> </li> </ul>

## Policy

In Nevada:

- Persons who show or report signs and symptoms of TB should be evaluated for TB disease as described in the “Diagnosis of Tuberculosis Disease” topic in this section and reported as suspected cases of TB as described in the “Reporting Tuberculosis” topic in the Surveillance section.
- Contacts should be evaluated as described in the Contact Investigation section, Chapter 8.



For roles and responsibilities, refer to the “Roles, Responsibilities, and Contact Information” topic in the *Introduction*, Chapter 1.

# Tuberculosis Classification System

The system for classifying tuberculosis (TB) is based on how the infection and disease develop in the body. Use this classification system to help track the status of TB in your patients and to allow comparison with other reporting areas.

**Table 2: TUBERCULOSIS CLASSIFICATION SYSTEM<sup>9</sup>**

Class	Type	Description
0	<ul style="list-style-type: none"> <li>▪ No tuberculosis (TB) exposure</li> <li>▪ Not infected</li> </ul>	<ul style="list-style-type: none"> <li>▪ No history of exposure</li> <li>▪ Negative reaction to the tuberculin skin test (TST) or interferon gamma release assay (IGRA)</li> </ul>
1	<ul style="list-style-type: none"> <li>▪ TB exposure</li> <li>▪ No evidence of infection</li> </ul>	<ul style="list-style-type: none"> <li>▪ History of exposure</li> <li>▪ Negative reaction to the TST or IGRA</li> </ul>
2	<ul style="list-style-type: none"> <li>▪ TB infection</li> <li>▪ No disease</li> </ul>	<ul style="list-style-type: none"> <li>▪ Positive reaction to the TST or IGRA</li> <li>▪ Negative bacteriologic studies (if done)</li> <li>▪ No clinical, bacteriologic, or radiographic evidence of TB disease</li> </ul>
3	<ul style="list-style-type: none"> <li>▪ TB disease</li> <li>▪ Clinically active</li> </ul>	<ul style="list-style-type: none"> <li>▪ <i>Mycobacterium tuberculosis</i> complex cultured (if this has been done)</li> <li>▪ Clinical, bacteriologic, or radiographic evidence of current disease</li> </ul>
4	<ul style="list-style-type: none"> <li>▪ TB disease</li> <li>▪ Not clinically active</li> </ul>	<ul style="list-style-type: none"> <li>▪ History of episode(s) of TB</li> </ul> <p style="text-align: center;"><b>Or</b></p> <ul style="list-style-type: none"> <li>▪ Abnormal but stable radiographic findings</li> <li>▪ Positive reaction to the TST or IGRA</li> <li>▪ Negative bacteriologic studies (if done)</li> </ul> <p style="text-align: center;"><b>And</b></p> <ul style="list-style-type: none"> <li>▪ No clinical or radiographic evidence of current disease</li> </ul>
5	<ul style="list-style-type: none"> <li>▪ TB suspected</li> </ul>	<ul style="list-style-type: none"> <li>▪ Diagnosis pending</li> <li>▪ May have positive AFB smear(s)</li> </ul>

Source: Adapted from: CDC. Classification system. In: Chapter 2: Transmission and Pathogenesis. *Core Curriculum on Tuberculosis (2000)* [Division of Tuberculosis Elimination Web site]. Updated November 2001. Available at: <https://www.cdc.gov/tb/education/corecurr/pdf/chapter2.pdf> . Accessed July 3, 2006.

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# Case Finding

## Identifying Suspected Tuberculosis Cases

The majority of tuberculosis (TB) cases are detected during the medical evaluation of symptomatic illnesses. Persons experiencing symptoms ultimately attributable to TB usually seek care not at a public health TB clinic, but rather from other medical practitioners in other healthcare settings.<sup>10</sup> Professionals in the primary healthcare sector, including hospital and emergency department clinicians, should be trained to recognize patients with symptoms consistent with TB.<sup>11</sup>

Be alert for cases of TB among persons who have not sought medical care during contact evaluations of patients with pulmonary TB and of other persons newly diagnosed as infected with Latent *Mycobacterium tuberculosis* Infection (LTBI). Perform screening for TB during evaluation of immigrants and refugees with Class B1, B2 or B3 TB notification status, during evaluations of persons involved in TB outbreaks, and occasionally in working with populations with a known high incidence of TB. Also, screen for TB disease when the risk for TB in the population is high and when the consequences of an undiagnosed case of TB are severe, such as in jails, prisons, and other facilities with congregate settings and or high-risk populations.<sup>12</sup>

Suspect pulmonary TB and initiate a diagnostic investigation when the historic features, signs, symptoms, and radiographic findings occur in adults. See these listed in Table 3, **When to Suspect Pulmonary Tuberculosis in Adults**, below. The clinical presentation of TB varies considerably as a result of the extent of the disease and the patient's response. TB should be suspected in any patient who has a persistent cough for more than two to three weeks or other compatible signs and symptoms.<sup>13</sup>

Note that these symptoms should suggest a diagnosis of TB, but are not required. TB should still be considered a diagnosis in asymptomatic patients who have risk factors for TB and chest radiographs compatible with TB.



All persons who have a chronic cough for more than two to three weeks<sup>14</sup> should be evaluated and be asked to use a mask or tissue to cover their mouth. Hemoptysis (coughing up blood) is a serious symptom, and patients who cough up blood should be evaluated as soon as possible. Be sure to have these patients wear a mask or use tissues to cover their cough.

**Table 3: WHEN TO SUSPECT PULMONARY TUBERCULOSIS IN ADULTS<sup>15</sup>**

<b>Historic Features</b>	<ul style="list-style-type: none"> <li>▪ Exposure to a person with infectious tuberculosis (TB)</li> <li>▪ Positive test result for <i>Mycobacterium tuberculosis</i> infection</li> <li>▪ Presence of risk factors, such as immigration from a high-prevalence area, human immunodeficiency virus (HIV) infection, homelessness, or previous incarceration*</li> <li>▪ Diagnosis of community-acquired pneumonia that has not improved after 7 days of treatment†.16</li> </ul>
<b>Signs and Symptoms Typical of TB</b>	<ul style="list-style-type: none"> <li>▪ Prolonged coughing (≥2–3 weeks) with or without production of sputum that might be bloody (hemoptysis)§.17</li> <li>▪ Chest pain<sup>18</sup></li> <li>▪ Chills<sup>19</sup></li> <li>▪ Fever</li> <li>▪ Night sweats</li> <li>▪ Loss of appetite<sup>20</sup></li> <li>▪ Weight loss</li> <li>▪ Weakness or easy fatigability<sup>21</sup></li> <li>▪ Malaise (a feeling of general discomfort or illness)<sup>22</sup></li> </ul>
<b>Chest Radiograph: Immunocompetent Patients</b>	<ul style="list-style-type: none"> <li>▪ Classic findings of TB are upper-lobe opacities, frequently with evidence of contraction fibrosis and cavitation¶</li> </ul>
<b>Chest Radiograph: Patients with Advanced HIV Infection</b>	<ul style="list-style-type: none"> <li>▪ Lower-lobe and multilobar opacities, hilar adenopathy, or interstitial opacities might indicate TB</li> </ul>
<p>* See Table 1: Persons at High Risk for Tuberculosis Infection and Progression to Tuberculosis Disease.</p> <p>† Patients treated with levofloxacin or moxifloxacin may have a clinical response when TB is the cause of the pneumonia.</p> <p>§ Do <b>not</b> wait until sputum is bloody to consider a productive cough a symptom of TB. Sputum produced by coughing does <b>not</b> need to be bloody to be a symptom of TB.</p> <p>¶ These features are not specific for TB, and, for every person in whom pulmonary TB is diagnosed, an estimated 10–100 persons are suspected on the basis of clinical criteria and must be evaluated.</p>	

Source: Adapted from: ATS, CDC, IDSA. Controlling tuberculosis in the United States: recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. *MMWR* 2005;54(No. RR-12):33.

## Extrapulmonary Tuberculosis

If a patient has a positive tuberculin skin test or interferon gamma release assay (IGRA) and pulmonary TB has been ruled out, consider signs and symptoms of extrapulmonary TB.

## Follow-up on Suspected Cases of Tuberculosis

When a person with signs and symptoms consistent with TB is identified, perform the following:



Refer to Table 4: **Guidelines for the Evaluation of Pulmonary Tuberculosis in Adults in Five Clinical Scenarios** in the “Diagnosis of Tuberculosis Disease” topic in this section. This table presents guidelines for the initial steps of TB case detection in five clinical scenarios encountered by providers of primary healthcare, including those serving in medical emergency departments.<sup>23</sup>



To formally report a suspected case of TB, see the “Reporting Tuberculosis” topic in the Surveillance section.



The patient should be masked and immediately excluded from the workplace or placed in airborne infection isolation (AII) until confirmed noninfectious. For more information, see the “Isolation” topic in the Infection Control section of this manual.



Laboratories are required to report positive smears or positives cultures, and primary healthcare providers are required to report suspected or confirmed cases of TB to the health department within 24 hours, as specified in the “Reporting Tuberculosis” topic in the Surveillance section. Prompt reporting allows the health department to organize treatment and case management services and to initiate a contact investigation as quickly as possible.<sup>24</sup>



Within 48 hours of suspect identification, administer a tuberculin skin test (TST) or perform an interferon gamma release assay (IGRA) and/or obtain a chest radiograph, if not already done. Evaluate the patient for TB disease as specified in the “Diagnosis of Tuberculosis Disease” topic in this section.

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# Diagnosis of Tuberculosis Disease

Consideration of tuberculosis (TB) disease as a possible diagnosis is the first step that must be taken before further evaluation, diagnosis, and management can occur. The diagnosis of TB disease is often overlooked because of the failure to consider it among possible diagnoses. While a definitive diagnosis may involve the addition of laboratory and radiographic findings, a high degree of suspicion can be based on epidemiology, medical history, and physical examination. In considering TB disease, it is also important to consider factors that may affect the typical presentation of TB, such as the patient's age, nutritional status, and coexisting diseases.

An individual who is suspected of having TB disease requires a complete medical evaluation, including the following:

- Medical history, including exposure, symptoms, previous treatment for TB, and risk factors
- Human Immunodeficiency Virus (HIV) screening
- Physical examination
- Tuberculin skin test or interferon gamma release assay
- Chest radiography
- Bacteriologic examination

When a suspected case of pulmonary TB is identified, refer to Table 4 for guidelines for the initial steps of TB case detection in five clinical scenarios encountered by providers of primary healthcare, including those serving in medical emergency departments.<sup>25</sup>

**Table 4: GUIDELINES FOR THE EVALUATION OF PULMONARY TUBERCULOSIS IN ADULTS IN FIVE CLINICAL SCENARIOS<sup>26</sup>**

Patient and Setting	Recommended Evaluation
Any patient with a cough of $\geq 2$ –3 weeks duration	Chest radiograph: If suggestive of tuberculosis (TB)*, collect 3 sputum specimens for acid-fast bacilli (AFB) smear microscopy, culture, and nucleic acid amplification (NAA), if available <sup>27</sup>
Any patient at high risk for TB with an unexplained illness, including respiratory symptoms of $\geq 2$ –3 weeks duration <sup>†</sup>	Chest radiograph: If suggestive of TB, collect 3 sputum specimens for AFB smear microscopy, culture, and NAA, if available
Any patient with human immunodeficiency virus (HIV) infection and unexplained cough or fever	Chest radiograph, <u>and</u> collect 3 sputum specimens for AFB smear microscopy, culture, and NAA, if available
Any patient at high risk for TB with a diagnosis of community-acquired pneumonia who has not improved after 7 days of treatment <sup>†</sup>	Chest radiograph, <u>and</u> collect 3 sputum specimens for AFB smear microscopy, culture, and NAA, if available
Any patient at high risk for TB with incidental findings on chest radiograph suggestive of TB, even if symptoms are minimal or absent <sup>†§</sup>	Review of previous chest radiographs, if available, collect 3 sputum specimens for AFB smear microscopy, culture, and NAA, if available
<p>* Opacities with or without cavitation in the upper lobes or the superior segments of the lower lobes.<sup>28</sup></p> <p><sup>†</sup> See Table 1: Persons at High Risk for Tuberculosis Infection and Progression to Tuberculosis Disease.</p> <p><sup>§</sup> Chest radiograph performed for any reason, including targeted testing for latent TB infection and screening for TB disease.</p>	

Source: Adapted from: ATS, CDC, IDSA. Controlling tuberculosis in the United States: recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. *MMWR* 2005;54(No. RR-12):33.

## Medical History

The clinician should interview patients to document their medical histories. A written record of a patient’s medical history should include the following:

1. Exposure to infectious TB
2. Symptoms of TB disease (as listed in Table 3: **When to Suspect Pulmonary Tuberculosis in Adults**, page 3.7, Table 4: **Guidelines for the Evaluation of Pulmonary Tuberculosis in Adults in Five Clinical Scenarios**, page 3.10, and Table 5: **Symptoms of Tuberculosis Disease**, page 3.11)
3. Previous TB infection or disease
4. Risk factors (as listed in Table 1: **Persons at High Risk for Tuberculosis Infection and Progression to Tuberculosis Disease**, page 3.3)
5. Recent medical encounters (e.g., going to the emergency department for pneumonia)
6. Previous antibiotic therapy

## 1. Exposure to Infectious TB:

### Ask patients if they have spent time with someone with infectious TB.

Question patients about whether they know of any contact in the recent or distant past with persons diagnosed with pulmonary or laryngeal TB. It is important to note that patients often refer to latent TB infection (LTBI) as TB disease. Be aware that most persons become infected with *Mycobacterium tuberculosis* without knowing they were exposed. Clinicians should also consider demographic factors that may increase a patient's risk for exposure to TB disease and drug-resistant TB, such as country of origin, age, ethnic or racial group, occupation, and residence in congregate settings (such as a jail, homeless shelter, or refugee camp).

## 2. Symptoms of TB Disease:

### Ask patients about their symptoms.

Although TB disease does not always produce symptoms, most patients with TB disease have one or more symptoms that led them to seek medical care. When symptoms are present, they usually have developed gradually and been present for weeks or even months. Occasionally TB is discovered during a medical examination for an unrelated condition, such as ruling out a cancer diagnosis, or on a pre-op chest radiograph.

The symptoms in Table 5 below may be caused by other diseases, but they should prompt the clinician to suspect TB disease. For historic features and chest radiograph results that should raise suspicion of pulmonary TB disease, refer to Table 3: **When to Suspect Pulmonary Tuberculosis in Adults**, page 3.7.

**Table 5: SYMPTOMS OF TUBERCULOSIS DISEASE<sup>29</sup>**

Pulmonary	General: Pulmonary and Extrapulmonary	Extrapulmonary
<ul style="list-style-type: none"><li>▪ Coughing</li><li>▪ Coughing up sputum or blood</li><li>▪ Pain in the chest when breathing or coughing</li></ul>	<ul style="list-style-type: none"><li>▪ Chills<sup>30</sup></li><li>▪ Fever</li><li>▪ Night sweats</li><li>▪ Loss of appetite<sup>31</sup></li><li>▪ Weight loss</li><li>▪ Weakness or easy fatigability<sup>32</sup></li><li>▪ Malaise (a feeling of general discomfort or illness)<sup>33</sup></li></ul>	<p>The symptoms depend on part of body affected by tuberculosis (TB) disease:</p> <ul style="list-style-type: none"><li>▪ TB of the spine may cause pain in the back.</li><li>▪ TB of the kidney may cause blood in the urine.</li><li>▪ Meningeal TB may cause headaches or psychiatric symptoms.</li><li>▪ Lymphatic TB may cause swollen and tender lymph nodes, often at the base of the neck.</li></ul>

Source: Adapted from: ATS, CDC, IDSA. Controlling tuberculosis in the United States: recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. *MMWR* 2005;54(No. RR-12):33

### **3. Previous Latent TB Infection or TB Disease:**

**Ask patients whether they have ever been diagnosed with or treated for TB infection or disease**

**Patients who have had LTBI or TB disease before** should be asked when they were diagnosed and what treatment they received. If documentation of treatment is not available ask how many pills were taken per day (to determine what treatment regimen was used and whether they received injections) as well as the duration of the regimen. Ask if they experienced any adverse reactions to the medications, if they completed the regimen and if they didn't complete the reason for discontinuing treatment.

If the regimen prescribed was inadequate or if the patient did not follow the recommended treatment, TB may recur, and it may be resistant to one or more of the standard four drugs used.

**Patients known to have a positive skin test reaction** may have TB infection. If they were infected within the past two years, they are at high risk for TB disease if certain immunosuppressive conditions exist or if immunosuppressive therapies are being taken. (See Table 1: **Persons at High Risk for Tuberculosis Infection and Progression to Tuberculosis Disease.**)<sup>34</sup> For persons previously skin tested, an increase in induration of 10 mm within a two-year period is classified as a conversion to positive.

### **4. Risk Factors for Developing TB Disease:**

**Determine whether the patient has any conditions or behaviors that are risk factors for developing TB disease.**

For a list of behaviors and conditions that increase the risk that TB infection will progress to disease, see Table 1: **Persons at High Risk for Tuberculosis Infection and Progression to Tuberculosis Disease.**

### **5. Recent Medical Encounters:**

**Determine what medical services patients have received for this condition.**

Has the patient been diagnosed with pneumonia or another bacterial infection in the recent past?

### **6. Previous Antibiotic Therapy:**

**Newly diagnosed TB patients might have fluoroquinolone resistance as the result of the wide use of fluoroquinolones for bacterial infections**<sup>35</sup>.

Moxifloxacin is in the family of fluoroquinolones and is sometimes used to treat TB. If the patient has developed a resistance to fluoroquinolones, moxifloxacin will not be an effective medication to use to treat their TB.

## **Physical Examination**

A physical examination is an essential part of the evaluation of any patient. It cannot be used to confirm or rule out TB, but it can provide valuable information about the patient's overall condition; other factors, such as human immunodeficiency virus (HIV) infection, which may affect how TB is manifested; and the presence of extrapulmonary TB.<sup>36</sup>

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# Laboratory Tests

## Human Immunodeficiency Virus Screening

Voluntary counseling and testing for human immunodeficiency virus (HIV) is recommended for all patients with TB. HIV counseling and testing has also been recommended for contacts of persons with TB.<sup>37</sup>

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 any patient's known risks for HIV infection
- Annual HIV screening of patients known to be at high risk<sup>38</sup>

## Tuberculin Skin Test and Interferon Gamma Release Assays

Use the Mantoux TST or an interferon gamma release assay (IGRA) to test for *M. tuberculosis* infection. Note that for patients with a previous documented positive TST reaction, a TST is not necessary. However, an IGRA can be done if there is suspicion that the TST result was a false positive.

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*. The term commonly used to discuss these tests is IGRAs (Interferon-Gamma Release Assays) which describes the mode of action these tests utilize. The IGRAs currently approved by the Food and Drug Administration (FDA) and available on the market are QuantiFERON<sup>®</sup>-TB Gold In-Tube (GIT), QuantiFERON<sup>®</sup>-TB Gold Plus In-Tube (GPIT), and the T-SPOT<sup>®</sup>.TB test, all of which can be used in all circumstances where the TST is used. Additional cytokine-based immunoassays may be developed 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.<sup>39</sup>

The advantages of IGRA tests, 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 placement and reading can be eliminated.<sup>40</sup> In addition, the Blood Assay for *Mycobacterium tuberculosis* (BAMT) are not affected by past Bacille of Calmette-Guérin (BCG) vaccination and may eliminate the unnecessary treatment of patients with BCG-related false-positive results.<sup>41</sup> However, the IGRA tests have practical limitations that include the need to draw blood and ensure its receipt in a qualified laboratory in time for testing. Refer to [www.quantiferon.com](http://www.quantiferon.com) for available test sites. Refer to the Qiagen web-site <http://quantiferoncellestis.com/us> for additional information regarding QuantiFERON<sup>®</sup>-TB Gold In-Tube (IT) and visit <http://www.oxfordimmunotec.com/> for information regarding the T-SPOT<sup>®</sup>.TB test which is the most recent test to have been approved by the FDA.

For both the TST and IGRA, additional tests, such as chest radiography and bacteriologic examination, are required to confirm TB disease.<sup>42</sup>

Persons with a positive QFT-GIT result or a positive TST result, regardless of symptoms and signs, must be evaluated for TB disease before LTBI is diagnosed. At minimum, a chest radiograph is required to assess for abnormalities consistent with TB disease.<sup>43</sup>

A negative TST does not rule out TB disease<sup>44</sup>—as many as 20% of patients with TB disease have a negative TST reaction.<sup>45</sup> A negative TST result or a negative QFT-G result should not be used alone to exclude *M. tuberculosis* infection in persons with symptoms or signs suggestive of TB disease. Medical evaluation of such persons should include a history and physical examination, chest radiograph, bacteriologic studies, serology for human immunodeficiency virus (HIV), and, when indicated, other tests or studies.<sup>46</sup>



For more information on the Mantoux TST, see the Diagnosis of Latent Tuberculosis Infection section, Chapter 5. For more information on IGRAs and the QuantiFERON®-TB Gold/Gold Plus In Tube (QFT-GIT/GPIT) Test, see the CDC's "Updated Guidelines for Interferon Gamma Release Assays to Detecting *Mycobacterium tuberculosis* Infection, United States, 2010" (*MMWR* 2010:59(RR-5) at <https://www.cdc.gov/mmwr/PDF/rr/rr5905.pdf>

## Chest Radiography

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 5 years of age should receive posterior-anterior and lateral radiographs.<sup>47</sup>

Certain abnormalities on chest radiographs are suggestive, but are not diagnostic, of TB. In pulmonary TB, radiographic abnormalities are often seen in the apical and posterior segments of the upper lobe or in the superior segments of the lower lobe. However, lesions may appear anywhere in the lungs and may differ in size, shape, density, and presence or absence of cavitation, especially in HIV-infected and other immunosuppressed persons.

In HIV-infected persons, pulmonary TB may present atypically on the chest radiograph. For example, TB may cause opacities without cavities in any lung zone, or it may cause mediastinal or hilar lymphadenopathy with or without accompanying opacities and/or cavities. In HIV-infected persons, almost any abnormality on a chest radiograph may

indicate TB. In fact, the radiograph of an HIV-infected person with TB disease may even appear entirely normal.<sup>48</sup>



For more information on chest radiography, see the Francis J. Curry National Tuberculosis Center's *Radiographic Manifestations of Tuberculosis: A Primer for Clinicians* (2011) at

<http://www.currytbcenter.ucsf.edu/products/radiographic-manifestations-tuberculosis-primer-clinicians-second-edition> .

<http://www.currytbcenter.ucsf.edu/products/radiographic-manifestations-tuberculosis-primer-clinicians-second-edition>

## Bacteriologic Examination

Refer to Table 6 below to determine the types of specimens needed to assist in the diagnosis of TB.

**Table 6: SPECIMENS FOR DIAGNOSING TUBERCULOSIS DISEASE**

Suspected Diagnosis	Specimen Needed
<b>Pulmonary or laryngeal tuberculosis (TB)</b>	<p>Sputum (phlegm from deep in the lungs) samples for smear <b>AND</b> culture examination.</p> <p>A diagnosis of pulmonary TB cannot be established from sputum smear alone. When Acid Fast Bacilli (AFB) is seen on smear, other procedures may be necessary for identification, including nucleic acid amplification (NAA), bronchoscopy, and gastric aspiration in children.</p>
<b>Extrapulmonary TB</b>	<p>Depending on the anatomical site, other clinical specimens are necessary, such as:</p> <ul style="list-style-type: none"> <li>▪ Urine</li> <li>▪ Cerebrospinal fluid</li> <li>▪ Pleural fluid</li> <li>▪ Pus or other aspirated fluid</li> <li>▪ Biopsy specimens</li> <li>▪ Blood (heparinized) Ensure both AFB smear AND culture is requested. DO NOT put tissue specimens in formalin, as no culture can be obtained.</li> </ul>

Refer to Table 7 below for information on the bacteriology tests used to diagnose TB.

**Table 7: BACTERIOLOGY TESTS USED IN DIAGNOSING TUBERCULOSIS DISEASE**<sup>49</sup>

Test	Description	Laboratory Turnaround Times
<b>Acid-Fast Bacilli (AFB) Smear</b>	<ul style="list-style-type: none"> <li>▪ Provides the physician with a preliminary confirmation of the diagnosis. It usually is the first bacteriologic evidence of the presence of mycobacteria in a clinical specimen.</li> <li>▪ If positive, the laboratory gives a semiquantitative estimate of the number of bacilli being excreted (which is of vital clinical and epidemiologic importance in assessing the patient's infectiousness).</li> </ul>	<ul style="list-style-type: none"> <li>▪ On-site test: results available within 24 hours from specimen collection.</li> <li>▪ Off-site test: within 24 hours from laboratory receipt of specimen (time from specimen collection to laboratory receipt should be 24 hours or less).<sup>50</sup> Specimens are to be refrigerated while being stored and during transport to the lab.</li> </ul>
<b>Nucleic Acid Amplification (NAA) Assay</b> <sup>51</sup>	<ul style="list-style-type: none"> <li>▪ A test done on sputum specimens for the direct and rapid identification of the <i>Mycobacterium tuberculosis</i> complex.</li> <li>▪ Allows for the amplification of specific target sequences of nucleic acids that will be detected by a nucleic acid probe.</li> <li>▪ Does not replace the need for routine AFB smear and culture.<sup>52</sup></li> </ul>	<ul style="list-style-type: none"> <li>▪ Within 48 hours from positive smear result and specimen arrival at the laboratory performing NAA<sup>53,54</sup></li> </ul>
<b>Culture</b>	<ul style="list-style-type: none"> <li>▪ Usually necessary for species identification of all clinical specimens suspected of containing mycobacteria.</li> <li>▪ Is required for drug susceptibility testing and genotyping.</li> </ul>	<ul style="list-style-type: none"> <li>▪ Mycobacterial growth detection: usually within 14 days from specimen collection</li> <li>▪ Identification of mycobacteria: usually within 21 days from culture positive<sup>55,56</sup></li> </ul>
<b>Drug Susceptibility Testing</b>	<ul style="list-style-type: none"> <li>▪ For first-line drugs: Performed on initial isolates of all patients to identify an effective antituberculosis regimen.</li> <li>▪ For both first-line and second-line drugs: Repeated on interim isolates when a patient remains culture-positive after 2 months of treatment.<sup>57,58</sup></li> </ul>	<ul style="list-style-type: none"> <li>▪ First-line drugs: may be available within 30 days from specimen collection</li> <li>▪ Second-line drugs: within 4 weeks from date of request or specimen receipt at reference laboratory. The provider must specify drugs to be tested.</li> </ul>

Sources: ATS, CDC, IDSA. Controlling tuberculosis in the United States: recommendations from the American Thoracic Society, CDC, and the Infectious Diseases Society of America. *MMWR* 2005;54(No. RR-12):19; and Tenover, R., et al. The resurgence of tuberculosis: is your laboratory ready? *Journal of Clinical Microbiology* 1993:767–770.

Laboratories are required to report positive smears or positives cultures, and primary healthcare providers are required to report suspected or confirmed cases of TB to the health department, as specified in the “Reporting Tuberculosis” topic in the Surveillance section. Prompt reporting allows the health department to organize treatment and case management services and to initiate a contact investigation as quickly as possible.<sup>59</sup>



For additional information on use of NAA Testing of sputum or other specimens, see ATS, CDC, IDSA, “Updated Guidelines for the Use of Nucleic Acid Amplification Tests in the Diagnosis of Tuberculosis” (*MMWR* 2009;58[01]; 7-10). Available at: <https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5801a3.htm>



For information on reporting, see the “Reporting Tuberculosis” topic in the Surveillance section.



For a list of all the laboratory services available and information on specimen collection and shipment, see Chapter 9, *Laboratory*.



For laboratory services available in Nevada, contact The Nevada State Public Health Laboratory at (775) 682-6218.

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## **Tuberculin Skin Testing (Mantoux Test)**

The Mantoux method of tuberculin skin testing has been used since the 1930's as the standard diagnostic test for detecting infection with *Mycobacterium tuberculosis*. It does not distinguish between latent or active TB infection.

In general, it takes 2 to 10 weeks after a person becomes infected to develop a delayed-type immune response to tuberculin that can be measured with the Mantoux tuberculin skin test (TST).

During the test, tuberculin is injected into the skin. The immune system of most persons infected with tuberculosis (TB) will recognize the tuberculin purified protein derivative (PPD), causing a measurable reaction in the skin. The size of the measured induration (a hard, dense, raised formation) and the patient's individual risk factors are used to determine whether TB infection is diagnosed.

### **Candidates for Tuberculin Skin Testing (Mantoux TST)**

The Mantoux TST can be administered to all persons, including pregnant women and persons who have previously been vaccinated with Bacille Calmette-Guérin (BCG). It is not possible to determine a true positive reaction from a false positive reaction in a BCG vaccinated person.

A Mantoux TST may be administered to eligible clients when: their risk assessment and/or symptoms indicate the possibility of *M. tuberculosis* infection, they will be in a congregate setting, i.e., group home, jail or prison, or they are employees that are at risk for exposure to tuberculosis i.e. healthcare workers, laboratorians and for persons whose employers require it as pre-employment protocol.

TST of individuals and groups should be undertaken only if the diagnostic evaluation and a course of preventative therapy can be completed. **Routine testing of low risk individuals is not recommended.**

The Mantoux TST should not be administered until a minimum of four weeks after vaccination with live-virus vaccines.

If the person being tested is a contact to an active case, follow the procedures outlined in the Contact Investigation section, chapter 8.

### **Documented Prior Positive Tuberculin Skin Test**

Persons who have tested positive in the past and can provide documentation of their status do not need to have another TST. Instead, administer a TB symptom assessment questionnaire to identify any symptoms of TB disease. Persons who are symptomatic require a chest radiograph to determine the presence of active TB disease.

Evidence of severe scarring at an old TST site denotes a prior positive reaction and a repeat TST may not be indicated.

Patients should be advised to retain documentation of positive TST results to avoid having repeat TST's performed unnecessarily.

## **Pregnancy**

The risk of unrecognized tuberculosis in an expectant woman and the close post partum contact between a mother (with active TB disease) and an infant can put the infant in grave danger of becoming infected with tuberculosis and complications, such as TB meningitis. Therefore, the prescribing physician should consider if the potential benefits outweigh the possible risks for performing the TST on a pregnant woman

Tuberculin skin testing is considered safe and reliable throughout pregnancy by the Advisory Council for The Elimination of Tuberculosis. It is recommended that pregnant women at high risk for TB infection or disease be tested when 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

## **Things That Can Affect Mantoux Test Are:**

### **Live-Virus Vaccines**

The Mantoux TST can be administered in conjunction with all vaccines. However, the measles, mumps, rubella (MMR) vaccine, varicella, and live attenuated influenza vaccines—may transiently suppress the response to PPD. Therefore, if a vaccine containing live virus 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 wait to give the MMR until the TST has been measured

## **Anergy Testing**

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 that have been proven to be feasible for application in public health TB screening programs.

Anergy testing is not routinely recommended in conjunction with TST for HIV-infected persons in the U.S.

### **Do not rule out TB infection or disease based on results of anergy testing**

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
- Overwhelming disease can cause false negative TST results, as well as anergy tests.

### **Boosting**

In some individuals infected with *M. tuberculosis*, the ability to react to the TST may gradually diminish over the years. If skin tested at this point, these individuals may have a false negative reaction. However, that skin test stimulates (the booster phenomenon) the person's ability to react to tuberculin tests placed after that, causing a positive reaction to subsequent tests.<sup>1</sup> This reaction may be misinterpreted as a new infection to a recent exposure (conversion).

For this reason, the 2-step TST is performed which establishes an accurate baseline on persons who will be routinely tested (i.e. group home residents, healthcare workers). If the reaction to the first test is positive, consider the individual infected. If the reaction to the first test is negative, a second test should be given 1 to 3 weeks later.

The booster phenomenon may occur at any age, but is more common in persons over the age of fifty-five. Two step testing reduces the likelihood of interpreting a boosted reaction as a new infection.

Boosted reactions may occur in persons infected with nontuberculous mycobacteria or in persons who have had a prior BCG vaccination.<sup>2</sup>

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<sup>1</sup> Centers for Disease Control and Prevention (2000) Core Curriculum on Tuberculosis: What the Clinician Should Know, 4<sup>th</sup> edition; pp. 32-33

<sup>2</sup> [http://www.cdc.gov/tb/pubs/corecurr/Chapter4/Chapter\\_4\\_Skin\\_Testing.htm](http://www.cdc.gov/tb/pubs/corecurr/Chapter4/Chapter_4_Skin_Testing.htm)

## Bacille Calmette-Guérin Vaccine

BCG vaccines are live vaccines derived from a strain of *Mycobacterium bovis*. They are not recommended as a TB control strategy in the United States because their effectiveness in preventing infectious forms of TB has never been demonstrated, except under rare circumstances. They are however, used commonly in other countries that have high incidence of TB infections and disease. A history of BCG vaccination is not a contraindication for performing a tuberculin skin test, nor does it influence the indications for a TST.

Administer and measure the TST 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 if they are:

- 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)
- born or have lived in a country with a high prevalence of TB
- exposed to someone with infectious TB, particularly if that person has transmitted TB to others.

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.

## The Two-Step Tuberculin Skin Test

Two-step testing should be used for the **initial** skin testing of adults who will be retested periodically, such as healthcare workers.

Two-step testing is used to reduce the likelihood that a boosted reaction will be misinterpreted as a recent infection.

Testing is recommended for staff and volunteers who meet the following criteria:

- 1) May be exposed to persons with TB on the job (e.g., staff of correctional facilities, healthcare, and congregate living facilities). Testing the residents of some long-term care facilities is also recommended.
- 2) Would pose a risk to large numbers of susceptible persons if they developed infectious TB (e.g., staff of AIDS hospices).

Such persons should receive a two-step tuberculin skin test upon initial employment and annually thereafter. This testing is done for two reasons:

- To detect TB infection or disease in staff so that they may be given treatment
- To determine whether TB is being transmitted in the facility (indicated by skin test conversions among staff)

**Table 8: FOUR APPOINTMENT SCHEDULE FOR TWO-STEP TESTING**

Appointments	Tasks
<b>First appointment</b>	Apply the first tuberculin skin test (TST).
<b>Second appointment</b> 48 to 72 hours after applying the first TST	Measure the reaction. <ul style="list-style-type: none"> <li>▪ If the reaction is negative, schedule a third appointment.</li> <li>▪ If the reaction is positive, do not repeat the TST. Obtain a chest radiograph.</li> </ul>
<b>Third appointment</b> 1 to 3 weeks after measurement of the first TST	Apply the second TST. <ul style="list-style-type: none"> <li>▪ If the reaction is negative and the patient returns over a week after the first TST was applied, apply the second TST.</li> <li>▪ Use the same dose and strength of tuberculin. Inject the tuberculin on the other forearm, or at least 5 cm from the original test site.</li> </ul>
<b>Fourth appointment</b> 48 to 72 hours after applying the second TST	Measure the reaction. <ul style="list-style-type: none"> <li>▪ If the reaction is negative, classify the individual as uninfected.</li> <li>▪ If the reaction is positive, obtain a chest radiograph.</li> </ul>

The number of visits required may be reduced to **3** by using the following protocol:

**Table 9: THREE APPOINTMENT SCHEDULE FOR TWO-STEP TESTING**

Appointments	Tasks
<b>First appointment</b>	Apply the first tuberculin skin test (TST).
<b>Second appointment</b> 7 days after applying the first TST	Measure the reaction. <ul style="list-style-type: none"> <li>▪ If the reaction is negative, apply the second TST.</li> <li>▪ Use the same dose and strength of tuberculin. Inject the tuberculin on the other forearm, or at least 5 cm from the original test site.</li> <li>▪ If the reaction is positive, do not repeat the TST. Obtain a chest radiograph.</li> </ul>
<b>Third appointment</b> 48 to 72 days after applying the second TST (day 9 or 10)	Measure the reaction. <ul style="list-style-type: none"> <li>▪ If the reaction is negative, classify the individual as uninfected.</li> <li>▪ If the reaction is positive, obtain a chest radiograph.</li> </ul>
<b>Sensitivity of this method</b>	
The majority of significant TST reactions will remain "positive" 7 days after application. Those that have diminished or disappeared by day 7 will be boosted back to positive by the 2 <sup>nd</sup> TST. Reducing the number of visits from 4 to 3 will not reduce the sensitivity of the two-step TST.	
Francis J. Curry National Tuberculosis Center <a href="http://www.nationaltbcenter.edu">http://www.nationaltbcenter.edu</a> Updated March 2004	

A positive reaction to the second test probably represents a boosted reaction (past infection or prior BCG vaccination). Based on this second test result, the person should be classified as previously infected and once active disease is ruled out, the person should be offered LTBI treatment (unless previously treated).

In persons who have tested negative for both steps of the two step TST method, a positive reaction to any subsequent test is likely to represent new infection with *M. tuberculosis* (skin test conversion).

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## Administration of the Tuberculin Skin Test

CDC guidelines are used in the administration and evaluation of the Mantoux Tuberculin Skin Test (TST). CDC recommended Mantoux Skin Test Training can be found at: <https://npin.cdc.gov/pages/mantoux-tuberculin-skin-test-training-materials-kit>

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

### Tuberculin Purified Protein Derivative



Read the PPD vial label carefully before administering a TST, including the tuberculin unit strength. The packaging of tetanus toxoid-containing vaccines (TTCVs) is similar to Tubersol<sup>®</sup> and Aplisol<sup>®</sup>, and all are refrigerated.

In order to maintain the potency of the tuberculin reagent, store and transport vials between 35-46° F or 2-8° C and avoid exposure to light.

PPD tuberculin vials must be dated upon opening and discarded 30 days after.

### Placing the Tuberculin Skin Test

1. Discuss why the skin test is given, what is involved in the procedure, and when the patient should return for the test to be read. If a patient cannot return 48 to 72 hours after the test is administered for the test to be read, reschedule the administration. Encourage the patient to ask questions and talk about any anxieties (s)he may have. If the patient's written consent is required, obtain it, per health department requirements.
2. Wipe the top of the vial with a new alcohol swab before drawing up the tuberculin solution. Place the vial on a flat surface and insert a disposable tuberculin safety needle and syringe (needle and syringe are one unit) through the neoprene stopper. Invert the vial, the tip of the needle should be below the fluid level in the vial. Pull back on the plunger and draw out slightly more than the one tenth of a milliliter needed for the test. Remove the needle from the vial. Draw back slightly on the plunger to create an air space in the syringe. Tap the syringe slightly to release any

air bubbles then push forward to expel the air and the small amount of excess fluid, leaving exactly one tenth of a millimeter of tuberculin solution in the syringe.

3. The Mantoux Tuberculin Skin Test is an intradermal injection and should be placed on the palm-side-up surface of the forearm, about two to four inches below the elbow. 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 or alternative skin cleanser by circling from the center of the site outward. Allow the site to dry completely before the injection.
5. Stretch taut the selected area of skin between the thumb and forefinger. Inject 0.1 ml (one tenth of a milliliter) PPD tuberculin containing 5 tuberculin units (TU) intradermally. Do this by inserting the needle, bevel facing up slowly at a 5-15-degree angle (the angle is important because this layer of skin is very thin). The needle bevel is advanced through the epidermis, the superficial layer of skin, approximately 3 mm so that the entire bevel is covered and lies just under the skin (the injection will produce inadequate results if the needle angle is too deep or too shallow). Slowly inject the tuberculin solution. It is not unusual for a drop of blood to appear at the site of the injection.
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. Do not: blot, dab, press, massage or place a bandage over the wheal, as some of the tuberculin reagent may be inadvertently drawn out of the injection site. Allow the entire 0.1 ml injection to be absorbed naturally. The wheal should be at least 6 mm in diameter, if it is not the test must be repeated.
7. Appropriately dispose of syringe and other supplies used and wash hands thoroughly.
8. Record the date and time of TST administration, location of injection site, dose, name of person who administered the test, name and manufacturer of tuberculin product used, lot number, expiration date, and reason for testing.
9. Remind patient of importance of the 48-72-hour appointment to have the test result read (A patient who does not return within 72 hours will need another skin test). Explain that mild itching, swelling, irritation or erythema (reddening of the skin) may occur and that these are normal reactions that do not require any treatment. These reactions usually go away within a week. Explain that caring for the injection site includes keeping the site clean and dry, avoid scratching, and do not apply creams, lotions or adhesive bandages. Normal washing is appropriate but avoid vigorous wiping or scrubbing.

**TABLE 10: OVERVIEW OF ADMINISTERING A TUBERCULIN SKIN TEST**

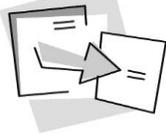
<b>Overview of a TST Administration</b>	
<b>Preparation</b>	<p>Review Information:            CDC. <i>Mantoux Tuberculin Skin Test Facilitator Guide</i> at <a href="https://www.cdc.gov/tb/education/Mantoux/default.htm">https://www.cdc.gov/tb/education/Mantoux/default.htm</a></p> <ul style="list-style-type: none"> <li>▪ Infection control procedures per institutional policies (including hand washing before and after the procedure and the use of gloves and a sharps container)</li> </ul> <p>Gather Equipment</p> <ul style="list-style-type: none"> <li>▪ Personal protective equipment (i.e. gloves, sharps container, etc)</li> <li>▪ Alcohol pads or alternative skin cleanser</li> <li>▪ Single-dose disposable tuberculin syringe with a short bevel 27-gauge needle (Because some of the tuberculin solution can adhere to the inside of the plastic syringe, do not pre-draw tuberculin into syringes.)</li> <li>▪ Purified Protein Derivative (PPD) (Tubersol® or Aplisol®: See the warning in the text below in this table.)</li> </ul> <p>Prepare Patient</p> <ul style="list-style-type: none"> <li>▪ Educate patient and make return appointment 48-72 hours post placement for reading test results</li> <li>▪ Locate and clean injection site</li> <li>▪ Prepare syringe</li> </ul>
<b>Placing TST</b>	<p>Injecting the tuberculin solution</p> <ul style="list-style-type: none"> <li>▪ Inject the tuberculin Purified Protein Derivative (PPD) (Tubersol® or Aplisol®: See the warning in the text below in this table.) at a 5-15-degree angle</li> <li>▪ Discard the needle and syringe properly</li> <li>▪ Check that the skin test was administered properly</li> <li>▪ Repeat test if needed</li> </ul>
<b>Final Steps</b>	<ul style="list-style-type: none"> <li>▪ Wash your hands</li> <li>▪ Record information</li> <li>▪ Remind patient about the return visit</li> <li>▪ Provide patient educational information and answer any questions</li> <li>▪ Return unused portion of tuberculin solution to refrigerated storage</li> </ul>

## Reading the Tuberculin Skin Test

The TST should be read by a trained healthcare worker 48 to 72 hours after the intradermal injection. Patients should never be allowed to read their own TST.<sup>60</sup>

- 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.



For additional information, review the CDC's *Mantoux Tuberculin Skin Test Facilitator Guide*

at <https://www.cdc.gov/tb/education/Mantoux/default.htm>

## How to Measure a Tuberculin Skin Test

1. Collect the following supplies: a small plastic flexible ruler marked in millimeters, a pen to mark the edges of the induration, and an alcohol pad to clean off the pen marks. You will also need the documentation for recording the result, as well as, culturally appropriate educational materials for the patient to reinforce information, answer questions, and provide supplementary information for follow-up evaluation, should it be required.
2. Inspect the arm in good light and slightly flex the arm at the elbow to locate the skin-test site.
3. The basis of reading the skin test is the presence or absence of an induration. An induration is a hard, dense, raised formation with definite edges which may not be visible, it must be felt. Measure only induration hardness and **not** swelling around the site of the injection. **Do not** measure erythema (redness). A TST with erythema and or soft swelling, but no induration, is nonreactive. Keep in mind there may not be an induration.
4. Reactions will range from no induration to a large well-defined induration.
5. Using a light, gentle motion, sweep fingertip over the surface of the forearm in a 2-inch diameter in all four directions to locate the margins of edges of the induration.
6. If an induration is present, use a zigzag, feather-like touch over the area, in order to outline the margins of the induration.
7. 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 an induration, do not round off the reading, but record it exactly as read.
8. 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 <http://www.fda.gov/medwatch/>
9. Cold packs or over the counter topical steroid preparations may be used for the relief of pruritus and local discomfort.

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## Interpretation of the Tuberculin Skin Test

TST's should be interpreted by a trained healthcare worker. Use Table 11 below to interpret TST's.



Call your regional TB Control Program or the Nevada DPBH Tuberculosis Program, (contact information is located in the *Introduction*, Chapter 1) regarding TST reactions when interpretation and/or medical follow-up are unclear.



Before interpreting a TST, information can be reviewed in the CDC's *Mantoux Tuberculin Skin Test Facilitator Guide* at <https://www.cdc.gov/tb/education/Mantoux/default.htm>.

### How to Interpret a Tuberculin Skin Test

Based on the sensitivity and specificity of the Purified Protein Derivative (PPD), the patients' immune response capabilities, 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
- Greater than or equal to 10 mm
- Greater than or equal to 15 mm of induration

Use **Table 11: Positive Tuberculin Skin Test Reactions** below, to determine what size induration cut-point to use to interpret the TST measurement and ultimately decide whether the test is positive or negative.

**Table 11: POSITIVE TUBERCULIN SKIN TEST REACTIONS**

Induration Size	Considered Positive For:
5 mm or more	<ul style="list-style-type: none"> <li>▪ Persons with human immunodeficiency virus (HIV) infection/acquired immunodeficiency syndrome (AIDS)</li> <li>▪ Recent contacts of an infectious case of tuberculosis (TB) disease</li> <li>▪ Persons with fibrotic lesions on chest radiograph consistent with healed TB</li> <li>▪ Persons with organ transplants or other immunosuppressed persons (such as those receiving the equivalent of &gt;15 mg/day of prednisone for &gt;1 month)</li> <li>▪ Persons receiving treatment with tumor necrosis factor-alpha (TNF-<math>\alpha</math>) antagonists</li> </ul>
10 mm or more	<ul style="list-style-type: none"> <li>▪ 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, Russia, or from refugee camps)</li> <li>▪ Persons who inject drugs or use other high-risk substances, such as crack cocaine</li> <li>▪ Alcoholics</li> <li>▪ Residents and employees in high-risk, congregate settings (e.g., correctional institutions; long-term residential care facilities, such as nursing homes, mental institutions, etc.; hospitals and other healthcare facilities; homeless shelters; and refugee camps)</li> <li>▪ Mycobacteriology laboratory personnel</li> <li>▪ Persons with other medical conditions that increase the risk of TB disease</li> <li>▪ Children younger than 5 years of age, or children and adolescents exposed to adults in high-risk categories</li> </ul>
15 mm or more	<ul style="list-style-type: none"> <li>▪ Persons with no known risk factors for TB</li> <li>▪ Individuals with no risk factor for TB disease who increase their mm reading by 10mm or more during a two-year period (converter)</li> <li>▪ Workers in occupational settings that are classified as minimal or low risk</li> <li>▪ All contacts to extrapulmonary TB with no other risk factor for TB disease</li> </ul>

Every effort should be made to test only those persons at the highest risk for infection but certain individuals may require testing for employment or school attendance. An approach independent of risk assessment is not recommended by Centers for Disease Control (CDC) or The American Thoracic Society (ATS).

When interpreting TST results, be aware of the following.

### **Skin test conversions**

For persons with documentation of a previous skin test, an increase in induration of 10 mm or more within a two-year period is classified as a conversion to positive.

## False-Negative Reactions

**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 6 months of age, because the immune system is not fully developed)
- Overwhelming TB disease
- Vaccination with live viruses (e.g., measles, mumps, rubella, varicella, smallpox, oral polio, or yellow fever and live attenuated influenza vaccines).



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

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

## False-Positive Reactions

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

- 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.

## Persons at Risk for Progressing from Latent TB Infection (LTBI) to TB Disease<sup>3</sup>

Every effort should be made to test only those persons at risk, interpret tuberculin skin test (TST) reactions accurately, ensure appropriate treatment, and completion of the recommended treatment regimen.

Generally, persons at risk for developing TB disease fall into two categories: those who have been recently infected and those with clinical conditions that increase the risk of progression from LTBI to TB disease.

### Suspect recent infection in the following:

- Close contacts of a person with infectious TB
- Persons who have immigrated from areas of the world with high rates of TB
- Children < 5 years of age who have a positive TST result
- Recent converters (those with an increase of 10 mm or more in size of TST reaction within a 2-year period)
- Groups with high rates of *M. tuberculosis* transmission, such as homeless persons, injection drug users, and persons with HIV infection
- Persons who work or reside with people who are at high risk for TB in facilities or institutions such as hospitals, homeless shelters, correctional facilities, nursing homes, and residential homes for those with HIV

### Clinical conditions that have been reported to increase the risk of progression from LTBI to TB disease:

- HIV infection
- Radiographic evidence of prior TB
- Low body weight ( $\geq 10\%$  below ideal)
- Silicosis
- Diabetes mellitus
- Chronic malabsorption syndrome
- Chronic renal failure or being on hemodialysis
- Gastrectomy or Jejunioileal bypass
- Leukemia, lymphomas, Hodgkin's disease
- Solid organ transplant
- Cancer of the head or neck
- Prolonged use of immunosuppressive agents (e.g., prednisone, TNF- $\alpha$  antagonists)

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<sup>3</sup> <https://www.cdc.gov/tb/publications/factsheets/testing/skintestresults.htm>

## **Evaluating persons with positive skin tests**

**See section 3.9, Diagnosis of Tuberculosis Disease, of this Chapter, for more details**

### Sections:

Medical history .....	3.10
Physical examination .....	3.13
Human immunodeficiency virus screening .....	3.13
About the Tuberculin skin test and interferon gamma release assays .....	3.13
Chest radiography.....	3.14
Bacteriologic examination .....	3.15

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# Resources and References

## Resources

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