V. Screening for Tuberculosis Disease and Latent Tuberculosis Infection

A. INTRODUCTION

Screening for both tuberculosis (TB) disease and latent TB infection (LTBI) are important in the ultimate elimination of TB. Screening for TB disease allows for the identification and treatment of active cases, and screening for latent TB infection (LTBI) serves to identify individuals who would benefit from treatment to prevent progression to active disease. (AF; notes)

It is the policy of the Division of Tuberculosis Control (DTC) to endorse only those screening programs that:
1. Target specific, high-risk populations; and
2. Encompass a plan for testing and evaluation, a plan for appropriate treatment and follow-up, some means of assuring a high rate of treatment completion, and an evaluation component to assess program efficacy. Such planning should include arrangements for medical evaluation (*e.g.*, chest x-rays) of persons with positive tuberculin skin tests (TSTs) and for the medical supervision of the course of treatment.

(K; N; e-mail)

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B. SCREENING FOR TUBERCULOSIS DISEASE AND INFECTION

1. Levels of Screening

There are 2 levels of screening:
- Screening to identify persons who may have infectious TB disease so they can be isolated immediately and started on appropriate therapy. This level of screening is appropriate for all individuals.
- Screening to identify infected persons who are at high risk for progression to TB disease and who would benefit from LTBI therapy. This level of screening is appropriate only if completion of treatment can be ensured.

(N)

a. Screening for Disease

Screening for disease is appropriate in populations where the prevalence of active disease is high (*e.g.*, homeless persons, migrant and seasonal workers, foreign-born individuals from countries with a high prevalance of TB). (AF) (see **Evaluation for Treatment**)

Screening for disease begins with a clinical assessment for symptoms suggestive of TB. (AF) The index of suspicion for TB disease should be high when pulmonary symptoms are accompanied by general systemic symptoms of TB.

Symptoms Suggestive of Tuberculosis	
Pulmonary Symptoms	**General Systemic Symptoms**
➢ Productive, prolonged cough (lasting ≥ 3 weeks). ➢ Chest pain. ➢ Coughing up blood (hemoptysis).	➢ Weight loss. ➢ Night sweats, fever, or chills. ➢ Easy fatigability. ➢ Loss of appetite.

(N)

Any patient with symptoms suggestive of TB should be isolated and promptly evaluated for TB disease. (N; e-mail) An appropriate examination — including a clinical assessment, chest x-ray, sputum and culture examination, and other tests as needed — should be undertaken. (notes)

All persons with TB-like symptoms and sputum or x-ray results suggestive of TB disease should be started on a standard, 4-drug anti-TB regimen, pending final confirmation of the diagnosis. (AF)

In some circumstances, screening for disease with chest x-ray alone may be appropriate; however, this practice should be restricted to those settings where the risk of disease and transmission is high and where symptom evaluation is likely to be ineffective. DTC must be consulted before any radiographic screening program is initiated. (AF)

b. Screening for Infection

The Mantoux tuberculin skin test (TST) is the only diagnostic tool currently recommended in Virginia for detecting TB infection. The newly available *in vitro* test, the QuantiFERON-TB test, is not currently endorsed by DTC for use in Virginia. (see **Appendix: QuantiFERON-TB Test for Diagnosing Latent Tuberculosis Infection**) Because the Mantoux TST has poor predictive value in low-risk populations, patients must be carefully assessed for risk factors prior to administration of the test. (AF)

Persons being screened for infection should also be screened for TB disease. In these cases, screening for disease may consist of a symptom review and questioning the individual being screened. (notes)

2. Candidates for Screening

Screening is appropriate for individuals who are at risk of progression to disease once infected, or for members of a targeted population group (*e.g.*, homeless persons, foreign-born from high prevalence countries) in whom the incidence of infection or disease is increased. (AF; notes) (see **Targeted Testing Programs**, **Screening of Individuals**, and **Screening Among Specific Groups**, below) Candidates must be assessed for the likelihood of completing treatment if prescribed — in general, populations or individuals who will not or cannot complete a course of treatment of LTBI should not be screened for infection. (AF)

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Exemptions from Routine TST Screening	
Exempt from TST Screening*	**Not Exempt from TST Screening**
➢ Persons who have a documented positive TST result. ➢ Persons who have a documented history of TB disease. ➢ Persons who report a history of a severe necrotic reaction to tuberculin.	➢ Persons who have received the Bacile Calmette Guérin (BCG) vaccination.† ➢ History of positive TST without documentation.

* When treatment of LTBI is being considered, these persons should receive a chest x-ray to rule out active TB disease unless they have documentation of a previously completed course of treatment of LTBI. An annual chest x-ray is not necessary.

† See **Appendix: BCG Vaccine**.

(E; N; notes)

Candidates for screening should undergo a clinical assessment, including symptom review. TB disease must be excluded in patients in high-risk groups with TB-like symptoms, regardless of TST results. (AF)

Every person screened for TB infection must also be evaluated for HIV risks, as HIV infection significantly increases the speed and likelihood of progression from infection to disease. If risks are identified, confidential HIV counseling and testing must be offered. (H)

3. Targeted Testing Programs

As a strategic component of TB control, targeted tuberculin testing programs have a single purpose: to identify persons at risk for TB who would benefit from treatment of LTBI. (D; K; M; e-mail) DTC has established risk-based targeted tuberculin testing as the official TB screening policy for all state agencies

throughout the Commonwealth of Virginia, and as a result of these efforts, the unnecessary testing of individuals at low risk for either TB infection or progression to TB disease once infected was dramatically reduced. (CL) The planning and development of local programs to screen for TB disease or infection should always be carried out in consultation with DTC. (M; notes)

Certain factors place individuals at higher risk of TB exposure or infection — listed in the left column in the table below. Of these at risk for infection are persons who are at higher risk of progression to disease once infected — listed in the right column of the table — and the targeted testing approach focuses activities on these persons, for whom intervention (*i.e.*, treatment of LTBI) would be the most effective. These individuals should be targeted for testing. (notes)

High-Risk Groups for TB Infection and Disease	
Persons at Higher Risk for TB Exposure/Infection	**Persons at Higher Risk for TB Disease Once Infected**
➢ Close contacts of persons with known or suspected TB disease. ➢ Foreign-born persons, including children, from areas that have a high TB incidence or prevalence (*e.g.*, Asia, Africa, Latin America, Eastern Europe, Russia). ➢ Residents and employees of high-risk congregate settings (*e.g.*, correctional institutions, nursing homes, drug-treatment centers, homeless shelters). ➢ HCWs who serve high-risk clients. ➢ Some medically underserved, low-income populations as defined locally. ➢ High-risk racial or ethnic minority populations, defined locally as having an increased prevalence of TB (*e.g.*, Asians and Pacific Islanders, Hispanics, African Americans, Native Americans, migrant farm workers, homeless persons). ➢ Infants, children, and adolescents exposed to adults in high-risk categories. ➢ Persons who inject illicit drugs; any other locally identified high-risk substance users (*e.g.*, crack cocaine users).	➢ Persons who are HIV-positive or are at risk for HIV infection. ➢ Persons who were recently infected with *M. tuberculosis* (within the past 2 years, including skin test converters), particularly infants and very young children. ➢ Close contacts of persons with known or suspected TB disease. ➢ Foreign-born persons in the U.S. less than 5 years. ➢ Persons with other medical risk factors for progression to TB disease, such as diabetes mellitus, silicosis, prolonged corticosteroid therapy, cancer of the head and neck, hematologic and reticuloendothelial disease (*e.g.*, leukemia, Hodgkin's disease), end-stage renal disease, intestinal bypass or gastrectomy, chronic malabsorption syndromes, or low body weight (*i.e.*, 10% or more below ideal). ➢ Persons who inject illicit drugs and other groups of high-risk substance users (*e.g.*, crack cocaine users). ➢ Persons with radiographic findings of old, healed TB or who have a history of inadequately treated TB.

(adapted from E; M; notes)

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By directing testing and screening programs toward at-risk individuals, the targeted testing approach improves the accuracy of screening procedures, ensures that available resources are not focused on low-risk areas, and further emphasizes the commitment to treat. (K; CL; e-mail; notes) Targeting other groups for screening is of low yield and is therefore not recommended. A larger number of positive reactions in low-risk persons are actually false-positives, (notes) and routine screening of low-risk persons diverts resources from activities of higher priority. (K)

Because health departments might lack access to high-risk populations and the resources necessary to undertake targeted testing programs, the participation of other health care providers is essential to ensure the successful implementation of community efforts to prevent TB in high-risk groups. (K) Populations at risk can be accessed at HIV treatment facilities, drug treatment centers, homeless shelters, community health centers and schools serving foreign-born persons, and selected community-based organizations. (K)

4. Screening of Individuals

While population groups may be targeted for screening, local health departments should perform a standardized risk assessment on every individual who presents for tuberculin skin testing, regardless of his/her stated reason. Only individuals with a demonstrated risk of TB exposure or a risk of progression to active TB disease once infected should be eligible for health department testing. (CL; notes) These individuals include those listed in both columns in the "High-Risk Groups for TB Infection and Disease" table. (adapted from E ; M; notes)

Individuals without risk factors should not eligible for testing by the local health department and should be advised to seek private care if tuberculin testing is absolutely required. To assist individuals whose

employers require screening, health departments should provide a signed letter stating that the individual has undergone a clinical evaluation for TB disease and that, based upon the absence of risk, a TST is not indicated. (CL)

5. Screening Among Specific Groups

Some screening programs that target high-risk populations for testing may also focus on additional groups.

a. Persons with HIV Infection

Co-infection with HIV is the most powerful risk factor for progression to TB disease in persons with TB infection, and TB screening among those known to be HIV-positive should be considered a high priority.

Screening should occur soon after HIV infection is detected and should consist of a TST and detailed symptom review. (AF) All HIV-positive individuals with a positive TST and/or TB-like symptoms must undergo a chest x-ray and/or sputum collection to exclude active TB disease. Once active TB has been excluded, individuals who are both HIV- and TST-positive should receive treatment for LTBI. (AF)

There is no indication for treatment of LTBI in the absence of a positive TST unless the HIV-positive individual is a close contact of a known case of TB disease. (AF)

b. Mobile Risk Groups

Screening among high-risk populations that are mobile or otherwise unlikely to complete a course of treatment for LTBI (*e.g.*, homeless persons, migrant or seasonal workers) should focus on finding disease rather than on detecting latent infection. Screening for TB infection among asymptomatic, immunocompetent members of these populations should not be pursued unless procedures are in place for assuring completion of therapy. With this assurance, screening for infection among young children (up to the age of 4 years) in this group should take priority. (AF)

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c. School Employees and Social Service Agencies, and Facilities

Existing state regulations that establish TB screening requirements for school employees and social service agencies and facilities — including group homes, detention centers, and adult and child day care centers — have been officially reinterpreted to allow screening for symptoms and risk factors *in lieu* of tuberculin testing where applicable. (CL)

Mandated skin-testing programs (*e.g.*, those formerly conducted among teachers and food-handlers) are discouraged unless the targeted groups contain substantial proportions of persons at high-risk. (K; notes)

c. Students: Preschool, Daycare, Primary/Secondary Schools, Colleges, and Universities

The routine screening of all children for TB infection prior to school entry or advancement is of low yield and is not recommended. Any screening of selected groups of children should focus on those who are at risk for progression to active TB disease once infected. (AF)

Similarly, pre-matriculation screening for TB infection of all college and university students is not recommended, unless an appropriate risk category is identified **and** measures are in place to monitor and ensure compliance with treatment of LTBI. (AF)

d. Prenatal Clinics

Pregnancy does not confer an added risk of TB infection or progression to active disease, and so is not by itself an indication for skin test screening. However, pregnant women with any of the following conditions or characteristics are at risk for TB infection or disease:

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

(E; AF)

Pregnant women — particularly those at increased risk for TB disease — should be screened (*i.e.*, symptom evaluation) and undergo an appropriate evaluation to exclude active disease if symptoms are present. (notes) Although tuberculin skin testing is safe during pregnancy, testing should be delayed until the third trimester or the postpartum period (*i.e.*, the first 3 months following delivery), in order to:

- Prevent exposing the unborn child to x-ray.
- Minimize the interval between diagnosis and potential initiation of treatment of LTBI.
- Eliminate the need for multiple x-rays.

(notes)

Notation should be made in the patient's record so this test is not forgotten. (notes)

However, regardless of stage of pregnancy, **women with a newly identified positive TST must receive a chest x-ray without delay to rule out active TB disease**, as untreated TB poses a greater risk to the fetus than does x-ray with proper shielding. (notes)

e. Patients with a History of Prior TB Infection or Disease (Treated and Cured)

There is no indication for routine, follow-up chest x-rays in asymptomatic persons with a history of treated LTBI or previous TB disease that has been treated and cured. However, if there is subsequent, post-treatment exposure to TB, these individuals should be screened with a symptom assessment, and those with TB-like symptoms should be evaluated further with a chest x-ray and/or sputum collection. (AF; notes)

Patients with a history of treated and cured multidrug-resistant TB (MDR-TB) are important exceptions and may require a more thorough annual evaluation — including chest x-ray — to document the absence of recurrence. (AF)

C. TESTING

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The Mantoux tuberculin skin test (TST) is the current standard diagnostic tool for identifying persons infected with *M. tuberculosis*. (M) This test has been used for years as an aid in diagnosing LTBI by measuring the delayed-type hypersensitivity (DTH) response 48-72 hours after intradermal injection of tuberculin purified protein derivative (PPD). (CH) Although the currently available TST antigens are less than 100% sensitive and specific for detection of infection, no better diagnostic method is widely available. (AG)

While the *in vitro* QuantiFERON-TB test (QFT) was approved in 2001 by the U.S. Food and Drug Administration (FDA) as a tool for diagnosing LTBI, (CH), the TST and QFT do not measure the same components of the immunologic response and are not interchangeable. (CJ) **The QFT test is not recommended for use in Virginia**. (see **Appendix: QuantiFERON-TB Test for Diagnosing Latent Tuberculosis Infection**)

In some circles, the Mantoux TST has erroneously been referred to as a "PPD" (purified protein derivative) test. As "PPD" more accurately describes the antigen used in the skin test rather than the test itself, DTC uses the standard term "TST" to refer to the Mantoux tuberculin skin test and "PPD" and/or "tuberculin" to describe the antigen used. (notes)

A multiple puncture test — such as the TINE test — should not be used to determine if an individual is infected with *M. tuberculosis*. The multiple puncture test introduces tuberculin into the skin either by puncture with multiple antigen-coated needles or by multiple needles puncturing through a thin film of antigen placed on the skin at the puncture site. As the quantity of tuberculin injected intradermally cannot be precisely controlled, diagnostic and treatment decisions cannot currently be based on the results of such tests; people whose multiple puncture test results are positive should be re-tested using the Mantoux TST. (M; AG; notes)

1. The Mantoux Tuberculin Skin Test

Infection with *M. tuberculosis* confers the ability to mount a DTH reaction to *M. tuberculosis* antigens. Using the TST, PPD tuberculin — a complex mixture of antigens derived from *M. tuberculosis* and capable of eliciting a DTH response — is injected intradermally. A reaction usually begins within 5-6 hours, reaches its maximum in approximately 48-72 hours, and subsides over a period of a few days. (O; AG; notes) In a few individuals (*e.g.*, the elderly, those being tested for the first time), the reaction may not peak until after 72 hours. (AG)

The classification of the Mantoux TST reaction depends on the size of the reaction, the person's risk factors for TB, and, for people who may be exposed to TB on the job, the risk of exposure to TB. (V) (see **Reading and Classifying the Test Reaction**, later this section)

Immunization with a live virus vaccine — such as MMR (measles, mumps, and rubella), oral polio, varicella, yellow fever, BCG, and oral typhoid vaccines — can interfere with the TST and produce a false-negative TST reaction. (E; M; CK; CY; notes) While the TST can be given prior to or concurrently with a live virus vaccine without influencing the TST result, the TST cannot be read accurately if given after the vaccine. (notes) If the TST cannot be administered and read prior to the vaccine, the TST should be deferred until at least 4-6 weeks after the live virus vaccine is administered. (E; M; notes) (see **Skin Test Accuracy and Specificity**, later this section)

2. Administering the Test

The tuberculin test, like all medical tests, is subject to variability, but many of the inherent variations in administration and reading of tests can be avoided by careful attention to detail. (AG) Additionally, when administering the TST, institutional guidelines regarding universal precautions for infection control (*e.g.*, the use of gloves, sharps disposal) should be followed. (E; M; O)

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Prior to administering the TST, the individual receiving the test should be informed of the requirement to return in 48-72 to have the result read and should be asked about his/her history of previous TST or live virus vaccine. (notes) After administering the TST, the patient should be instructed not to scratch, rub or put a bandage on the test site, although the area may be washed and patted dry. (E; O)

The Mantoux TST is performed by the intradermal injection of 0.1 ml of PPD containing 5 tuberculin units (TU) into the inner surface of the forearm. The injection should be made with a disposable tuberculin syringe (*e.g.*, a short disposable 26-gauge needle), just beneath the surface of the skin, with the needle bevel facing upward. This should produce a discrete, pale elevation of skin — a firm, white wheal — of 6-10 mm in diameter. (E; M; O; AG)

If the test is improperly administered, another test dose can be given at once, selecting a site several centimeters away from the original injection. A note in the record should indicate the site chosen for the second test. (AG)

3. Reading and Classifying the Test Reaction

The test result should be read only by a trained health worker; patients should never be allowed to read their own reaction. The following procedure should be used:

1. The result should be read 48 - 72 hours after administering the test.
2. Only the hard, swollen area known as induration should be measured. Redness, which does not necessarily indicate TB infection, should not be measured.
3. The induration must be measured at its widest point — transversely, across the forearm — using a flexible ruler. The size of the induration should be recorded in millimeters; the reaction should also be classified as positive or negative, based on the table below. If there is no induration, the result should be recorded as “00 mm.” Only one measurement should be recorded.

(A; E; O; notes)

Classification of a Mantoux TST reaction is dependent upon the size of the induration and the person's medical and epidemiological risk factors for TB, regardless of BCG status. (E) There are 3 cut-off measurements: 5 mm, 10 mm, and 15 mm. (O)

Guidelines for Determining a Positive TST Reaction (regardless of BCG status)		
Individuals Positive at ≥5 mm Induration	Individuals Positive at ≥10 mm Induration	Individuals Positive at ≥15 mm Induration
➢ HIV positive persons and patients at risk for HIV. ➢ Recent close contacts to persons with potentially infectious TB. ➢ Those with fibrotic changes on the chest x-ray consistent with prior TB. ➢ Patients with organ transplants and other immunosuppressed patients (receiving >15 mg/d of prednisone for more than a month).	➢ Recent immigrants from high prevalence countries. ➢ Injection drug users known to be HIV-negative. ➢ Persons from medically underserved, low-income communities. ➢ Residents and employees of high-risk congregate settings.* ➢ Mycobacteriology laboratory personnel. ➢ Persons with particular medical conditions.** ➢ Children younger than 4 years. ➢ Infants, children, and adolescents exposed to adults in high-risk categories.	➢ People with no identified risk factors.

* High-risk congregate settings include: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with HIV, and homeless shelters.
** Such medical conditions include: silicosis, diabetes mellitus, chronic renal failure, some hematologic malignancies (*e.g.*, lymphoma, leukemia), some other specific malignancies (*e.g.*, carcinoma of head, neck, and lung), weight loss of ≥10% ideal body weight, gastrectomy, and jejunoileal bypass.
(E; M; O; notes)

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Positive reactions often persist for at least 7 days. (A) If the patient fails to appear for the scheduled reading but returns at a later time, the test site should be examined and any present induration measured. If this measurement is large enough to be classified as positive, the result should be recorded, with no further testing required. If there is no reaction or if it is too small to be classified as positive, the TST should be repeated — **a repeat TST can be given immediately**. (E; O; notes)

Patients who have a positive TST reaction should receive a clinical evaluation, including chest x-ray, to rule out TB disease and to be considered for treatment of LTBI. (E) (see **Evaluation for Treatment**)

In general, these guidelines for interpreting TST reactions should also be applied to persons who may have occupational exposure to TB (*e.g.*, HCWs or staff of nursing homes, drug treatment centers, or correctional facilities). The appropriate cutoff for defining a positive reaction depends on the employee's individual risk factors for TB, including recent TB exposure, and the prevalence of TB in the facility. (M) (see **Infection Control: Occupational Screening**)

4. BCG Vaccinated Individuals

Many countries still use BCG (Bacille Calmette–Guerin) as part of their TB control programs, especially for infants. While data suggests that the BCG vaccine protects children against disseminated TB and meningitis, protection against active TB disease in children or adults has not been proven, (AG) and the BCG vaccine provides no protection against infection. (notes) (see **Appendix: BCG**)

Tuberculin skin testing is not contraindicated for persons who have been vaccinated with BCG, (M) and, in general, a history of BCG vaccination should not influence the need for tuberculin skin testing, the interpretation of the reaction, or clinical decisions regarding the management of TST-positive individuals. (E)

While BCG vaccination may sometimes cause a positive TST reaction, (E; O) a reaction to tuberculin in a person with a history of BCG vaccination is more likely to be due to infection with *M. tuberculosis* **if any of the following are true**:

- The induration is large.
- The person was vaccinated a long time ago.
- The person is a recent contact of a person with infectious TB.
- There is a family history of TB.
- The person comes from an area of the world where TB is common (*e.g.*, Asia, Africa, Latin America).
- The chest radiograph findings show evidence of previous TB.

(N)

All persons with positive TST reactions — meeting the cutoff size of induration for the respective risk group — should be considered to have latent TB infection and be treated accordingly. (O) TST-positive, BCG-vaccinated children should be evaluated with both a posterior-anterior and a lateral chest x-ray. (E; notes) (see **Evaluation for Treatment**)

5. Skin Test Conversion

Skin test conversion refers to situation in which an individual's TST result converts from negative to positive between 2 tests — this conversion to positive is defined by an increase in induration of 10 mm or more between the first and second tests. Due to the increased risk of progression to disease in those recently infected, a skin test conversion is considered significant when it is documented to have occurred within a period of 2 years. (notes)

Examples of Skin Test Conversion

Initial TST		Second TST†		Comments
Induration	**Classification***	**Induration**	**Classification***	
6 mm	Negative	10 mm	Negative	With an increase of only 4 mm between the initial and second TSTs, and with no change in risk factors, this individual's result is still considered negative.
6 mm	Negative	16 mm	Positive	As the second TST shows an increase in induration of 10 mm, this individual's result is considered positive and indicative of recent infection.

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* The initial TST result is classified as either positive or negative based on the induration and the individual's risk factors.
† The second TST is administered within 2 years following the initial TST.
(adapted from notes)

Clinicians may deviate from these general principles based on individual circumstances. For instance, if an HIV-negative person with an initial TST reaction of 5 mm subsequently becomes HIV-positive, a second TST reaction of 5 mm may be considered positive — even though there is no increase in induration — due to the person's increased risk factor for progression to TB disease. (notes)

6. Two-Step Tuberculin Skin Testing

Sensitivity to tuberculin may wane over time, and a TST given many years after infection may boost immune response in people infected with *M. tuberculosis*. For example, a TST given years after a person is infected may yield a negative reaction, though a subsequent TST may show a positive reaction. (E; M) Boosted reactions may also occur in persons infected with nontuberculous mycobacteria (NTM) or in persons who have had a prior BCG vaccination. (M)

Two-step testing reduces the likelihood that a boosted reaction will be misinterpreted as recent infection with *M. tuberculosis*. (M) This procedure should be restricted to those populations at continual risk of exposure — including health care workers and residents of congregate settings (*e.g.*, correctional facilities) who are enrolled in a serial TST screening program and will be tested periodically. (M; notes) (see **Infection Control: Occupational Screening**) The two-step skin test process is as follows:

- If the reaction to the first TST is classified as negative, a second TST should be given using the same dose and strength of tuberculin either on the other forearm or at least 5 cm from the initial test site. The second TST should be administered within 1-3 weeks, to ensure that a subsequent positive TST is not the result of recent infection.

- If the second TST result is also negative, this person should be classified as uninfected.
- A positive reaction to the second TST probably represents a boosted reaction (*i.e.*, past infection or prior BCG vaccination). This person should be classified as previously infected — regardless of BCG status — and should be given an evaluation and prescribed treatment, as appropriate.

(M; O)

Individuals who can provide documentation of a negative TST reaction within the preceding year should be given a TST and classified on the basis of that result; a second TST is not necessary because the earlier test is, in effect, the baseline of a two-step test. (E)

Following the two-step procedure, a positive reaction to any subsequent TST is likely to represent new infection with *M. tuberculosis* (M; O) and should warrant an investigation for the possible source of recent exposure at the facility. Individuals should also be questioned about the potential for recent exposure in the community. (notes)

7. Skin Test Accuracy

The TST is a valuable tool, but various factors affect its precision, (notes) and currently available TST antigens are less than 100% sensitive and specific for the detection of *M. tuberculosis* infection. (AG)

The sensitivity of a test is the likelihood of the results being positive if the condition being testing for is actually present, while the specificity of a test is the likelihood that the results will be negative if the condition is absent. Thus, tests with low sensitivity produce more false-negative results, and tests with low specificity produce more false-positive results. (notes)

a. TST Sensitivity

The TST has a reported false-negative rate as high as 25% during the initial evaluation of persons with active TB. (AG) This lowered sensitivity appears to be due to poor nutrition and general health, overwhelming acute illness, or immunosuppression, among other health-related factors. (AG)

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Other factors that may cause false-negative TST results are related to the tuberculin used in the test, the method of test administration, and the reading and recording of test results.

Factors Causing False-Negative Tuberculin Skin Tests	
Factors related to the person being tested: ➢ Viral infection (*e.g.*, measles, mumps, chicken pox, HIV). ➢ Bacterial infection (*e.g.*, typhoid fever, brucellosis, typhus, leprosy, pertussis, overwhelming TB, tuberculous pleurisy). ➢ Fungal (*e.g.*, South American blastomycosis). ➢ Live virus vaccinations (*e.g.*, measles, mumps, rubella, oral polio, varicella, yellow fever, smallpox, BCG, oral typhoid). ➢ Metabolic derangements (*e.g.*, chronic renal failure). ➢ Low protein states (*e.g.*, severe protein depletion, afibrinogenemia). ➢ Diseases affecting lymphoid organs (*e.g.*, Hodgkin's disease, lymphoma, chronic leukemia, sarcoidosis). ➢ Drugs (*e.g.*, corticosteroids, many other immunosuppressive agents). ➢ Age (*e.g.*, newborns, elderly patients with "waned" sensitivity). ➢ Stress (*e.g.*, surgery, burns, mental illness, graft-versus-host reactions). ➢ Anergy.	Factors related to the tuberculin used: ➢ Improper storage (*e.g.*, exposure to light and heat). ➢ Improper dilutions. ➢ Chemical denaturation. ➢ Contamination. ➢ Adsorption (partially controlled by adding Tween 80). Factors related to the method of administration: ➢ Injection of too little antigen. ➢ Subcutaneous injection. ➢ Delayed administration after drawing into syringe. ➢ Injection too close to other skin tests. ➢ Leakage of antigen due to improper technique. Factors related to reading the test and recording results: ➢ Inexperienced reader. ➢ Conscious or unconscious bias. ➢ Error in recording. ➢ Improper site selection near veins and tendons.

(M; AG; notes)

b. TST Specificity

False-positive TSTs — lowered TST specificity — may occur in individuals who have been infected with other mycobacteria, including vaccination with BCG. Some antigens in the PPD tuberculin are shared with the other mycobacteria and thus can elicit a skin test response. These cross-reactions tend to result in smaller amounts of induration than reactions due to *M. tuberculosis*, but the overlap may be considerable in areas of the world where the other mycobacteria are common. In these populations, the specificity of the test is highly dependent on the criterion used to define a "positive" test, and the specificity of the test can be improved by progressively increasing the cut point for positivity. (AG)

In any population, the likelihood that a positive test represents a true infection is influenced by the prevalence of infection with *M. tuberculosis*. The TST has a specificity of approximately 99% in populations that have no other mycobacterial exposures or BCG vaccination, but the specificity decreases to 95% in populations where cross-reactivity with other mycobacteria is common. The general U.S. population as a whole currently has an estimated *M. tuberculosis* infection rate of 5–10%, thus causing the TST to have a low positive predictive value. Children entering school in many areas of the country have a 0.1–1% likelihood of being infected, and the yearly incidence of new TB infection in the general U.S. population without known exposure to TB is estimated to be 0.1–0.01%. Therefore, screening of groups without a known or likely exposure to *M. tuberculosis* is not recommended — in these groups, a false-positive result is more likely than a true positive result. (AG)

Positive Predictive Value of the Mantoux TST		
	Positive Predictive Value	
Prevalence of TB infection (%)	Specificity of 0.95	Specificity of 0.99
90	0.99	0.999
50	0.95	0.99
25	0.86	0.97
10	0.67	0.91
5	0.50	0.83
1	0.16	0.49
0.1	0.03	0.10
0.01	0.002	0.09

(AG)

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9. Anergy Testing

Anergy testing is not recommended by DTC and should not be used by any health department in Virginia. (notes) Ordering an anergy panel subjects the patient to superfluous testing, (notes) and the lack of standardization and outcome data limit its effectiveness. (E; M)

Previously, anergy testing was used to confirm a negative TST as a "true negative" — defined as a negative TST with a positive anergy panel. A person who had a negative TST and a negative anergy panel was said to be "anergic," and his/her TST results were considered unreliable. (notes)

The use of anergy testing was based on the following assumptions:

- A person infected with *M. tuberculosis* will exhibit a reaction to the TST unless s/he is unable to react to other antigens.
- There is no occurrence of specific skin test anergy.
- Specific anergy is uncommon.

(notes)

However, since specific skin test anergy does occur in individuals infected with *M. tuberculosis* — and occurs commonly among those with active TB disease — the use of anergy testing is largely ineffective and does not improve diagnostic accuracy. The value of anergy testing is questionable at best.

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