

## 3.5 TUBERCULOSIS

<b>Tuberculosis</b>							
TST (mm):	<input type="text"/>	Plant Date:	<input type="text"/>	Read Date:	<input type="text"/>	Overseas chest X-ray:	<input type="checkbox"/> NL <input type="checkbox"/> ABNL BCG: <input type="text"/>
IGRA Type:	<input type="checkbox"/> QuantiFERON	<input type="checkbox"/> T-Spot	Date:	<input type="text"/>	Result:	<input type="checkbox"/> Negative <input type="checkbox"/> Positive <input type="checkbox"/> Indeterminate <input type="checkbox"/> Borderline	

### PURPOSE

To ensure effective prevention and control of tuberculosis (TB) among newly arrived refugees in Massachusetts

### BACKGROUND

TB is a major worldwide public health issue. One-third of the world's population is infected with *Mycobacterium tuberculosis* and TB is a leading infectious cause of death worldwide. For 2011, the World Health Organization estimated 8.7 million new cases of active TB (125 per 100,000 population), with an estimated 13% co-infected with HIV. There were 1.4 million deaths from TB. Refugees are at particularly high risk of exposure to tuberculosis. In addition, progress in the response to multi-drug resistant strains of TB is slow.<sup>1</sup>

For decades, TB rates declined steadily in United States but several complex social and medical factors caused TB morbidity to increase during the late 1980s into the mid 1990s, after which the decline of TB resumed. In 2012, 215 cases (case rate 3.2 per 100,000 population) of active TB disease were reported to and verified by the Massachusetts Department of Public Health, Division of TB Prevention and Control. Although the TB case rate increased in 2012, Massachusetts has had a decreasing trend in case rate from 4.0 to 3.2 since 2008, representing a 19% decrease overall. Case rates in the United States have declined more steeply and, in 2012, the state and national rates aligned at 3.2.

Non-U.S. born persons (defined as persons born outside the United States and its territories) remain the group at highest risk for TB disease in Massachusetts. In 2012, 186 (87%) TB cases occurred in persons born outside the U.S. Over the years, non-US born persons have accounted for an increasing proportion of the TB cases in Massachusetts from 35% in 1984 to 87% in 2012. While the proportion of cases occurring among the non-U.S. born has increased the absolute number of such cases has been relatively stable since 2002.

**Transmission** of TB is person-to-person through the air by droplet nuclei particles 1-5µm in diameter that contain *M.*

<sup>1</sup> [http://www.who.int/tb/publications/global\\_report/en/](http://www.who.int/tb/publications/global_report/en/)

**Section 3: CLINICAL PROGRAM**

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*tuberculosis*. Droplet nuclei are produced when an individual with pulmonary or laryngeal TB coughs, sneezes, speaks or sings.

**Latent TB infection** (LTBI) occurs when an individual is harboring *M. tuberculosis* in a latent (dormant) form contained by the immune system, but does not have systemic or local manifestations of tuberculosis disease. Such individuals will usually have a positive TB test (tuberculin skin test [TST] or interferon gamma release assay [IGRA]).

**Disease** occurs when there is an active process of bacterial replication and invasion of an organ or organs in an individual who is harboring *M. tuberculosis*. The most common radiologic findings in pulmonary tuberculosis are upper lobe (often cavitory) lesions, increased density in the lung parenchyma (a "pneumonia") that may occur anywhere, and/or regional (hilar or mediastinal) lymph node enlargement. Other findings can include other lymphadenopathy (particularly in the neck), pleural effusion, and lesions at other body sites.

The **tuberculin skin test** (TST) is the only acceptable skin test for the diagnosis of LTBI. The test requires intradermal injection of 5 TU of PPD, a complex mixture of *M. tuberculosis* proteins by a trained provider, followed by measurement of induration at the skin test site after 48-72 hours. An essential aspect of TST testing is that the induration also is measured by a trained health care worker (not a parent or relative).

**Interferon-gamma release assays** (IGRAs) are approved blood tests for the diagnosis of LTBI. Two tests generally are available, the QuantiFERON®-TB Gold In-Tube test, and the T-SPOT.TB test. In most situations an IGRA may be used in place of, or in conjunction with, the TST to diagnose LTBI in children 5 years of age or older (see below).

In accordance with the current American Thoracic Society (ATS) and Centers for Disease Control and Prevention (CDC) guidelines, [\*Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection\*](#), refugees are at high risk for developing TB disease and would benefit from treatment of latent TB infection, if detected.<sup>2</sup>

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<sup>2</sup> American Thoracic Society. 2000. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med*. 161:S221-S247.

**PROGRAM  
REQUIREMENTS**

In brief, the RHAP requires the following of providers:

1. **Review** overseas medical examination forms for TB evaluations. Review all immunization records for the date of the most recent live viral vaccination (MMR or varicella).

**Children and contacts evaluated overseas using the 2007 Technical Instructions will have TST results documented on their overseas records.**

2. **Test** for TB using IGRA or TST at first visit, with IGRA being the preferred test for eligible individuals (see below for exceptions). Providers are responsible for IGRA or TST testing of RHAP patients to identify *M. tuberculosis* infection.

**Exceptions (no TB test required):**

- A *positive TST* or IGRA is documented on the overseas medical forms. IGRA may be used to "confirm" a positive TST from overseas.
- There is a clear, documented history of treatment for clinical TB disease on the overseas medical examination form.

**Exception to TB test at first RHAP visit:**

- Fewer than 28 days have elapsed since the most recent live viral vaccination. **Schedule TB testing for the second visit or earlier if feasible.**

**No exception to TB test:**

- Refugees with an overseas diagnosis of TB of any class based solely on an overseas chest x-ray should have IGRA or TST done.
- Refugees with a documented *negative* TST overseas should have IGRA or TST repeated during the RHAP.

Any deferral should be recorded on the RHAP form in the **COMMENTS/REFERRALS** Section.

a) *Administer TB test (IGRA or TST) if no exceptions*

**IGRAs** currently approved by the FDA for use in the United States include the Quantiferon TB Gold In-Tube

test (QFT-GIT) and T-SPOT. These tests measure the patient's immune response after stimulation of white blood cells in a test tube or on a plate with 2-3 relatively TB specific antigens. The interpretations are based on the amount of IFN-g that is released or on the number of cells that release IFN-g.

**Persons for whom IGRA tests are *not* recommended, should have a TST:**

- a. Children < 5 years old
- b. Persons with the following medical conditions: diabetes mellitus, chronic renal failure, hematologic malignancy (e.g., leukemia) and other specific malignancies (carcinoma of the head or neck and lung).
- c. Health care workers and others who will undergo sequential or periodic testing

**TST** should receive 0.1 ml of 5 tuberculin units (TU) PPD injected intradermally via the Mantoux technique and read by qualified personnel at 48-72 hours.

Record the date the TST is planted, the date read, and diameter of induration in millimeters at the TST injection site across the forearm (perpendicular to the long axis) on the RHAP form. Record the absence of induration as 0mm. Erythema should not be measured. Only one dimension (perpendicular to the long axis of the forearm) should be measured and recorded.

**When reading a TST, measure induration (not erythema) perpendicular to the long axis of the forearm (i.e. across the arm).**

3. **Interpret** the test results:

**IGRAs** have a standard qualitative test interpretation that should be reported in the RHAP form:

- a. Positive - suggests that *M. tuberculosis* infection is likely
- b. Negative - suggests that infection is unlikely

- c. Indeterminate or Borderline - indicates an uncertain likelihood of *M. tuberculosis* infection or test failure. *Repeat IGRA or TST is needed.*

**TST:** The following are guidelines for interpreting TST results for newly arrived refugees.

≥ 5 mm induration is considered positive for:

- Persons who have had recent close contact with a known or suspected case of infectious TB
- Persons with overseas chest x-rays consistent with active or previous TB
- Persons with clinical evidence of TB
- Persons with HIV infection or other immunosuppressive conditions

≥ 10 mm induration is considered positive for:

- Persons who, if infected, are at increased risk for progression to active TB because of specific clinical conditions<sup>3</sup>
- Persons from TB endemic regions (i.e., Africa, Asia, Central America, South America, Mexico, Caribbean, Eastern Europe, Middle East).
- Persons exposed to individuals who are HIV-infected, homeless, users of illicit drugs, medically indigent city dwellers, residents of nursing homes, incarcerated or institutionalized persons, and migrant farm workers

4. Refer all persons with positive TB test results and those with any overseas diagnosis or treatment of TB for TB evaluation. This evaluation must be performed at a state TB Clinic or approved alternative.

*a) Refer for TB evaluation as appropriate*

The role of the provider during the health assessment is to determine whether or not a patient (regardless of age or gender) should be referred for TB evaluation at a state TB clinic [See [list of TB referral clinics](#)] through the local health department or an approved alternative site. State TB clinics provide comprehensive, expert services to Massachusetts residents who require evaluation, treatment and follow-up for tuberculosis.

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<sup>3</sup> Diabetes mellitus, silicosis, gastrectomy/jejunoileal bypass, chronic renal failure, some hematologic disorders (e.g. leukemias and lymphomas) other specific malignancies (e.g., carcinoma of the head, or neck and lungs), weight loss of ≥ 10% of ideal body weight

Refugees meeting any of the following criteria must be referred for TB evaluation:

- Clinical evidence of TB disease
- Abnormal overseas chest x-ray consistent with TB (Class A TB/Class B TB) regardless of the TST result
- Treatment for active or latent TB started overseas
- Positive IGRA or TST result (regardless of age, gender or overseas chest x-ray) either from testing overseas or during the RHAP

*All cases of suspected active TB must be reported to the Massachusetts Department of Public Health.*

*To report TB, call:*

**617-983-6813**

**Latent TB infection is also reportable. The electronic reporting TeleForm is provided to all RHAP sites.**

Logistics for TB screening and evaluation vary in the state. Specific RHAP provider responsibilities are clearly outlined for each site in coordination with the Refugee and Immigrant Health Program.

### **Note on BCG Vaccination**

The Massachusetts Department of Public Health, Division of Tuberculosis Prevention and Control IGRA guidelines note that the antigens used for the IGRA tests are not present in BCG vaccines, so false positive results due to prior sensitization to BCG do not occur. Thus, IGRA is the preferred test for individuals who have received BCG vaccine.

The Massachusetts Department of Public Health, Division of Tuberculosis Prevention and Control, has an earlier policy [statement on BCG and PPD](#).<sup>4</sup> The policy states that TST reactions should be interpreted without regard to BCG history in almost all circumstances. TST reactions of 10mm or more in adults or children who are from high prevalence countries are likely to be due to TB infection.

The requirements of the RHAP are consistent with this policy, yet place an increased emphasis on acknowledging and discussing BCG. Providers should obtain a BCG history,

<sup>4</sup> *BCG AND PPD*. Policy of the Massachusetts Department of Public Health, Division of Tuberculosis Prevention and Control. September 6, 1986.

including age at vaccination and number of vaccinations, if possible. Record the most recent BCG vaccination date on the health assessment form.

Decisions around treatment for latent TB infection will take into account BCG history. Providers may want to cover the following points relative to BCG:<sup>5</sup>

- BCG protects against the most severe forms of TB in infants and very young children. Protection against TB in the lungs in both children and adults is not proven.
- Nearly all countries where BCG is used have high rates of TB.
- IGRAs do not cross-react with BCG, so false-positive tests due to sensitization to BCG antigens are unlikely to occur.
- Positive TST reactions are generally not due to BCG:
  - Not all persons who are vaccinated convert their PPD;
  - The reaction to BCG is usually <10mm; and,
  - The sensitivity (reaction) wanes over time.

### **TB Clinic Role**

The purpose of TB clinics is to assess, evaluate, and determine treatment for all refugees with an overseas diagnosis of TB, abnormal overseas chest x-ray, or a positive IGRA or TST.

Refugees for whom treatment for latent TB infection is recommended may be managed at the primary care site following initial evaluation at the TB clinic. In such cases, the TB clinic will be available for further consultation.

Treatment guidelines are outlined in the [ATS/CDC statements on testing<sup>6</sup>](#) and treatment.<sup>7</sup>

### **CHILDREN**

Infants and young children with latent TB infection have, by definition, been infected recently. This places them at increased risk for progression to disease, especially if under the age of 5 years. Further, infants and young children are more likely than older children and adults to develop severe forms of TB, e.g., TB meningitis or disseminated TB. The risk for disease appears to decline after 5 years of age.

Treatment for latent TB infection is effective and well-tolerated in children. The recommended regimen for treatment in HIV-

<sup>5</sup> Centers for Disease Control and Prevention. The role of BCG vaccine in the prevention and control of tuberculosis in the United States: a joint statement by the Advisory Council for the Elimination of Tuberculosis and the Advisory Committee on Immunization Practices. *MMWR*. 1996;45(RR-4).

<sup>6</sup> American Thoracic Society/Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Am J Respir Crit Care Med*. 2000;161:S221-S247.

<sup>7</sup> American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America. Treatment of tuberculosis. *Am J Respir Crit Care Med*. 2003;167:603-662.

uninfected children is a 9-month course of isoniazid (INH) self-administered daily or by directly observed therapy (DOT) twice-weekly.<sup>8</sup> In the US, INH is available in liquid form only as a suspension formulated at 50mg/5ml in a sorbitol-based vehicle. Since sorbitol may cause diarrhea, crushed tablets suspended in something tasty to the child like pudding generally are preferred.

As noted in the section on tuberculin skin testing and BCG, TST reactions over 10mm in young children are, under nearly all circumstances, interpreted as resulting from TB infection. Likewise, the decision to treat a young refugee child with latent TB infection is not affected by the history of BCG.

According to current guidelines, IGRA is not recommended for children less than 5 years of age.

TB diagnosis in children relies on TB test (IGRA or TST), chest radiography, and evaluation for clinical symptoms and signs, and often follows discovery of an adult case. A child with a positive TB test, then, is a sentinel event potentially indicating an adult with active disease. However, one may not immediately be able to determine if exposed children are infected because the development of delayed-type hypersensitivity to TB infection may take up to 3 months. Clinical symptoms are often nonspecific, and chest radiographs are difficult to interpret though they remain the most reliable tool for diagnosing tuberculosis in children. Because the diagnosis of TB in children is often made on clinical grounds, both over- and under-diagnosis are possible. Routine laboratory tests are not helpful. Young children with disease rarely produce sputum as they are usually unable to expectorate voluntarily, and gastric aspirations result in a positive culture only 40 percent of the time.<sup>9</sup> Recent attempts to induce sputum through inhalation of nebulized hypertonic saline and oropharyngeal suctioning have proven successful, but the technique is not yet in common practice.

## **ELDERLY**

Providers should get an accurate history of previous TB exposure and an accurate medical history, including history of TB disease. There are co-existing medical conditions such as previous gastrectomy, diabetes mellitus, or on-going therapy with immunosuppressive drugs that may predispose reactivation of old infection or development of new foci of infection. Providers should maintain a high index of suspicion when assessing the elderly.

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<sup>8</sup> ATS/CDC/IDSA, 2003.

<sup>9</sup> Khan EA, Starke JR. Diagnosis of tuberculosis in children: increased need for better methods. *Emerging Infectious Diseases*. 1995;1:115-123.

Many healthy elders react vigorously to PPD testing, especially if infected recently. However, TB skin test reactivity declines with age; therefore, TB reaction may develop slowly and not peak until approximately 72 hours. Furthermore, the TST reaction may be negative secondary to decline in delayed hypersensitivity with age.<sup>10</sup> *Two-step testing* with a second test planted a week or more after an initial negative test with minimal or no induration on the first test may often be positive because the initial test triggered immune memory. The second test, if positive, indicates true TB infection, most likely from many years earlier. Note that 2-step testing is not a routine part of the refugee health assessment.

The ATS/CDC guidelines on treatment of latent TB infection consider all persons at high risk for developing TB as candidates for treatment, regardless of age. In addition to isoniazid, clinicians have treatment options with a less hepatotoxic drug regimen (*i.e.* Rifampin) that may be used with older patients. In select, high risk circumstances, a short course, 12 week regimen consisting of once-weekly INH and rifapentine administered by DOT may be considered as an alternative to daily INH or rifampin ( see: MDPH website guideline for 3HP).

Predominant symptoms of TB disease in the elderly include unexplained weight loss, fevers, sweats at night, cough (often non-productive), and progressive dyspnea. Treatment tends to be successful for pulmonary TB, though drug toxicity is higher among the elderly.

## **PREGNANCY**

The clinical presentation of TB in pregnant women is similar to that in non-pregnant women and pregnancy does not increase the risk of progression to active disease. Providers should question pregnant women about symptoms and proceed to test with IGRA or TST routinely. If the TB test is positive, the woman should be referred to a TB clinic for evaluation. If the patient has symptoms of TB or if she falls into a high risk group (e.g. recent TST conversion by CDC criteria, infected close contact to an infectious case, immune compromised, insulin-dependent diabetes), a clinical evaluation with a chest radiograph (single PA view with shielding is sufficient) should not be delayed. If the patient does not have symptoms or is not at high risk, the radiograph may be delayed until after the 12th week of gestation.

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<sup>10</sup> American Thoracic Society/Centers for Disease Control and Prevention. Diagnostic standards and classification of tuberculosis in adults and children. *Am J Respir Crit Care Med.* 2000;161:1376-1395.

**TST and IGRA testing are considered valid and safe throughout pregnancy.**

A newly arrived pregnant refugee whose IGRA or TST is positive, with a normal chest x-ray, is a candidate for treatment of latent TB infection. The infant does not require special evaluation for TB if the mother is asymptomatic.

A woman who has been diagnosed with active TB during pregnancy and has been culture-negative for 3 months before delivery poses little risk of infection to the newborn. The infant should be evaluated following birth for signs of disseminated tuberculosis placental transmission by a trained pediatric specialist and have a TST placed at 3 month intervals but does not require further evaluation, unless the TST is positive. If the mother has not been culture-negative for three months before delivery, the child should be evaluated by a TB specialist for possible congenital disease.<sup>11</sup> For care of the newborn, please refer to the *2012 Red Book: Report of the Committee on Infectious Diseases, 29<sup>th</sup> Edition*, or seek consultation from an infectious disease specialist.

## **ISSUES ASSOCIATED WITH TB**

While the understanding of TB by any group of people varies considerably and reflects the group culture and socio-economic status, the social stigma of TB is nearly universal. The belief that a positive TST is caused by BCG is a source of much confusion among refugees. Refugees who are identified as infected or diseased may have a difficult time accepting the diagnosis, particularly if there are no symptoms. It may ease a refugee's anxiety to learn that a third of the world's population is TB-infected and that infection could have occurred during their stay in an overcrowded refugee camp or during periods of unrest in their home country.

An empathetic bond with a refugee who is newly-identified as having latent TB infection or TB disease will help encourage adherence with preventive and curative protocols.<sup>12</sup> Cultural and behavioral factors affecting both parties, patients and providers, should be taken into account and an appropriate network of support and education should be provided to medical staff, patients and their families. Education should be aimed to empower people to understand the complex nature of TB and not just to promote adherence to medication regimens.

<sup>11</sup> ATS/CDC/IDSA, 2003.

<sup>12</sup> Thorensen CE. Overview. In: Matarazzo JD, Weiss SM, Herd JA, eds. *Behavioral Health: A Handbook of Health Enhancement and Disease Prevention*. John Wiley and Sons, 1984.

Socio-behavioral studies have demonstrated that people in developing countries tend to describe TB as a multi-causal and multi-factorial disease.<sup>13</sup> As the disease can present in many ways and is greatly stigmatized around the world, symptoms are often attributed to other, more benign causes. Weight loss and fatigue can be attributed to hard work and lack of sleep. Also, loss of weight, back pain, intermittent headache, coughing, fatigue, or rhinorrhea can be attributed to *gripe* (common cold) or *susto* (fright illness) in some Latin American cultures. The same symptoms and signs can be attributed to *piang*, or weak lungs, in the Philippines and witchcraft in India. Such cultural attributions should be acknowledged by the provider.

## RESOURCES

### [Division of TB Prevention & Control](#)

Massachusetts Department of Public Health  
305 South Street, Jamaica Plain, MA 02130  
617-983-6970

### [Division of TB Elimination](#)

Centers for Disease Control and Prevention  
Atlanta, GA 30333  
404-639-8140

### [International Union Against TB & Lung Disease](#)

Paris FRANCE

### [STOP TB Program](#)

World Health Organization

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<sup>13</sup> Jaramillo E. Anthropological issues and their impact on tuberculosis control in developing countries. Paper presented at the International Union Against Tuberculosis and Lung Disease (IUATLD), North American Regional Meeting, Chicago, March 1-2, 1996.