Guidelines for Screening for Tuberculosis Infection and Disease during the Domestic Medical Examination for Newly Arrived Refugees

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Scope

These guidelines briefly describe the overseas medical screening process for refugees resettling to the United States, and outlines the guidelines for clinicians evaluating refugees for tuberculosis (TB) during the domestic medical examination for newly arrived refugees. This document does not replace guidelines for the general US patient population but is meant to highlight specific needs in refugees and be used in conjunction with existing guidelines from national authorities (American Thoracic Society [ATS]/Centers for Disease Control and Prevention [CDC]/ Infectious Diseases Society of America [IDSA]) and state TB control programs.

Background

From 2016 to 2017, the number of TB cases in the United States decreased by 1.6% [1]. Additionally, in 2017 the TB rate was 2.8 per 100,000 people, the lowest rate on record since 1953 [1]. While TB is decreasing overall in the United States, there has been an increase in the percentage of TB cases in foreign-born individuals. For example, in 2017, 70% of TB cases were diagnosed in foreign-born persons in the United States, as opposed to 30% in 1993. In cities that are home to many newly arriving immigrants and refugees, rates of TB can be well above the national average. Additionally, the prevalence of drug-resistant TB or extrapulmonary TB cases, which are more challenging to diagnosis and manage, is higher among foreign-born persons [2]. Studies have indicated that reactivation of latent tuberculosis infection (LTBI), rather than recent transmission, is the primary driver of TB disease in the United States, accounting for >80% of all TB cases [2]. The risk of TB disease appears to remain high for many years after immigration, making it essential that clinicians identify and treat LTBI before TB disease develops [3]. Because of the continued risk of reactivation and the time-limited nature of a single medical exam, healthcare providers who serve refugees (including those treating refugees after the initial domestic medical screening) should maintain a high index of suspicion for TB disease, regardless of the results of their medical examination performed overseas [4].

Overview of Overseas Tuberculosis Screening for Refugees

Before departure for the United States, all refugees undergo an overseas medical examination. This examination identifies individuals with conditions that, by law, necessitate exclusion from, or treatment before, departure for the United States. CDC stipulates the content of this examination through Technical Instructions (TIs) issued to panel physicians and organizations that perform the medical screening examinations. Table 1 outlines the required TB screening components for refugees being resettled to the United States.

Table 1. Tuberculosis screening for refugee applicants to the United States

	Countries with a WHO-estimated TB incidence rate of ≥20 cases per 100,000 population	**Countries with a WHO-estimated TB incidence rate of <20 cases per 100,000 population**
2–14 years of age	All applicants must have a medical history, physical exam, and interferon-gamma release assay (IGRA)* for *Mycobacterium tuberculosis*. Applicants with a positive IGRA, signs/symptoms of TB disease, or known HIV infection must have a chest x-ray (CXR). Those with a documented history of TB disease must undergo a CXR, even if their IGRA result is negative. Applicants with a CXR suggestive of TB, signs/symptoms of TB, or known HIV infection must have three sputum smears and three cultures for *M. tuberculosis*. Those with positive cultures must undergo drug susceptibility testing and complete directly observed therapy (DOT) before immigration (unless a waiver is granted).	All applicants must have a medical history and physical examination. An IGRA*, CXR, and three sputum smears and three cultures for *M. tuberculosis* are required for all persons with signs/symptoms of TB or known HIV infection. Those with a history of documented TB disease must undergo a CXR. Those with positive cultures must undergo drug susceptibility testing and complete DOT before immigration (unless a waiver is granted).
≥15 years of age	All applicants must have a medical history, physical exam, and CXR. Applicants with a CXR suggestive of TB, signs/symptoms of TB, or known HIV infection must have three sputum smears and three cultures for *M. tuberculosis*. Those with positive cultures must undergo drug susceptibility testing and complete DOT before immigration (unless a waiver is granted).	All applicants must have a medical history, physical exam, and CXR. Applicants with a CXR suggestive of TB, signs/symptoms of TB, or known HIV infection must have three sputum smears and three cultures for *M. tuberculosis*. Those with positive cultures must undergo drug susceptibility testing and complete DOT before immigration (unless a waiver is granted).
***As of October 1, 2018, an IGRA must be used if one is licensed in the country where screening occurs. Overseas, CDC will only allow use of an IGRA approved by the US Food and Drug Administration (FDA). Currently, QIAGEN QuantiFERON® (any iteration approved by FDA) or Oxford Immunotec T-SPOT®.*TB* are the only tests with FDA approval.** **Note: All contacts must receive an IGRA (or TST if IGRA is not licensed) within 2 weeks of diagnosis of the potential source case. Contacts whom have clinical or CXR findings suggestive of TB disease, or known HIV infection must provide at least three sputum specimens for acid-fast bacilli (AFB) microscopy and mycobacteria culture.**		

Classifications and Travel Clearance

All refugee applicants must be assigned one or more TB classifications on the US Department of State (DS) forms. TB classification is determined by screening results, and treatment, if required. Table 2 describes the TB classifications and travel clearance for all refugee applicants.

Table 2. TB Classifications and Travel Clearance

Classification	Clinical Findings	Travel Clearance
No TB Classification	Applicants without current clinical findings of TB disease, without known HIV infection, and with a normal CXR (and for applicants who require it, a negative IGRA) with normal TB disease screening examinations	Valid for 6 months from the time the evaluation is complete
Class A TB Disease	All applicants who have TB disease, including applicants with extrapulmonary TB who have a CXR suggestive of pulmonary TB disease regardless of sputum smear and culture results	Applicants are not cleared for travel until completion of treatment unless a waiver is granted
Class B0 TB, Pulmonary	Applicants who were diagnosed with TB disease by the panel physician or presented to the panel physician while on TB treatment and successfully completed Division of Global Migration and Quarantine (DGMQ)-defined DOT* under the supervision of a panel physician before immigration	Valid for 3 months from the date final cultures are reported as negative
Class B1 TB, Pulmonary	Applicants who have signs or symptoms, physical exam, or CXR findings suggestive of TB disease, or known HIV infection, but have negative sputum smears and cultures and are not diagnosed with TB disease. This classification also includes applicants diagnosed with TB disease by the panel physician who refused DOT treatment and are returning after treatment and completion of 1-year wait.	Valid for 3 months from the date final cultures are reported as negative
Class B1 TB, Extrapulmonary	Applicants diagnosed with extrapulmonary TB with a normal CXR and negative sputum smears and cultures	Valid for 3 months from the date final cultures are reported as negative
Class B2 TB, LTBI	Applicants who have a positive IGRA or TST but otherwise have a negative evaluation for TB	Valid for 6 months from the time the evaluation is complete
Class B3 TB, Contact Evaluation	Applicants who are recent contacts of a known TB disease case, regardless of IGRA or TST results	Valid for 6 months from the time the evaluation is complete
*Directly observed therapy (DOT) is the required form of treatment for applicants diagnosed with tuberculosis disease during medical screening. Treatment of tuberculosis disease must be administered following DGMQ-defined DOT policies and practices during the entire course of therapy. Note: Applicants can be both Class B1 and Class B3, or Class B2 and Class B3. However, other combinations of TB classifications are not permitted.		

The TB TIs were implemented in priority countries on a rolling basis, as determined by factors such as refugee volume and burden of tuberculosis disease. Since 2013, all countries are required to comply with the TB TIs. The complete TB TIs, which additional details on TB classifications and travel clearance, can be found on the CDC Immigrant, Refugee, and Migrant Health website.

Documentation of Overseas TB Evaluation

Panel physicians must document TB screening and treatment results on the DS 2054 (Medical Examination), DS 3030 (TB Worksheet), and DS 3026 (Medical History and Physical Examination Worksheet). All medical documentation, including original laboratory reports, must be included with the required DS forms. Refugees receive copies of these documents and should provide them to the evaluating provider in the United States. In addition, the information is available through CDC's Electronic Disease Notification (EDN) system to state and/or local health departments. Evaluating providers in the United States who are not receiving this information should contact the state refugee health program for guidance. Overseas medical documents should always include screening information, as well as any diagnostic procedures and treatment rendered, including such data as:

- Pre-resettlement medical screening evaluations
    - Medical history and physical examination
    - IGRA (if indicated) OR TST documentation (including name of product, expiration date, amount administered, and type of product used, such as 5TU PPD-S or 2TU of RT 23) if IGRA is not licensed in the country where screening is conducted
    - CXR, for all applicants ≥15 years of age and younger applicants when indicated
    - Sputum smears and cultures for TB, if required
- Overseas treatment information
    - DOT regimen received, including doses of all medications, start and completion dates, and periods of interruption
- CXR findings before, during, and after treatment
- Laboratory results
    - Sputum smear AFB microscopy results obtained before, during, and after treatment
    - Cultures for mycobacteria obtained before, during, and after treatment, including any that were contaminated
    - Drug susceptibility test results performed on any positive culture
- Clinical course, including such information as clinical improvement or lack of improvement during and after treatment

Domestic Refugee Screening for Tuberculosis

The primary goal of the domestic refugee medical screening evaluation for TB is to identify individuals with LTBI or TB disease, to facilitate timely treatment and control. Individuals with LTBI or TB disease, and contacts of known cases of TB disease, should be treated according to US standards of care. Cases of confirmed or suspected TB disease must be reported to appropriate authorities (i.e., state or local health department) for monitoring and further public health intervention, such as contact investigation. Some areas also require reporting of individuals with LTBI.

Medical History and Physical Examination of Refugees for Tuberculosis during the Domestic Medical Screening Evaluation

Tuberculosis disease should be encountered infrequently during the domestic refugee medical screening evaluation. When identified, it may represent primary pulmonary or extrapulmonary disease. Patients with TB disease may be minimally symptomatic, particularly those with extrapulmonary disease. In fact, some individuals with tuberculosis disease, particularly children, may be asymptomatic. Others may deny symptoms because of cultural issues, fears, or other concerns.

Symptoms of pulmonary tuberculosis are often indolent and include malaise, weight loss, night sweats, cough, pleuritic chest pain, fever, and hemoptysis. Symptoms of extrapulmonary disease generally reflect the organ involved (e.g., abdominal pain with gastrointestinal TB). Although extrapulmonary TB can be found in virtually any organ of the body, statistically, lymphadenopathy is the most commonly identified extrapulmonary manifestation. Symptoms may also be nonspecific, such as failure to thrive in children.

All predeparture medical records for the refugee should be closely reviewed. A thorough post-arrival medical history must be obtained. In addition to current signs or symptoms of disease (e.g., weight loss, night sweats, fever, cough), specific information may be helpful in identifying a person at higher risk of TB disease or LTBI:

- Previous history of TB
- Illness suggestive of TB (i.e., cough >3 weeks, dyspnea, weight loss, fever, night sweats, or hemoptysis)
- Prior treatment suggestive of TB treatment
- Prior diagnostic evaluation suggestive of TB
- Family or household contact with a person who has or had TB disease, treatment, or diagnostic evaluation suggestive of TB

In addition, in children, a history of recurrent pneumonias, failure to thrive, or recurrent or persistent fevers should increase the provider's index of suspicion. Providers should keep in mind that children experience higher rates of extrapulmonary TB disease, including meningitis, and disease of the middle ear and mastoid, lymph nodes, bones, joints, and skin.

The physical examination should include height, weight, temperature, respiratory rate, blood pressure, thorough pulmonary examination, and inspection and palpation of all major palpable lymph node beds (see History and Physical Examination Screening Guidelines). In addition, a careful skin examination is important, as it may reveal cutaneous disease, scars from scrofula or bacille Calmette-Guérin (BCG) vaccination, or hints of prior chest surgery that may alert the clinician.

Testing Newly Arrived Refugees for Tuberculosis Infection and Disease

TB testing at the domestic medical screening is unusual since pre-departure screening is universal and results should be available. For completeness, screening protocols are discussed below, but repeat screening is not necessary in asymptomatic individuals.

Screening Tests

Domestic screening can be performed by using one of two modalities: an interferon-gamma release assay (IGRA) for *M. tuberculosis* or the Mantoux tuberculin skin test (TST). A summary of recommended uses, benefits, and limitations for IGRA and TST can be found in the ATS/CDC/IDSA Clinical Practice Guidelines: Diagnosis of Tuberculosis in Adults and Children. QuantiFERON®-TB Gold (In-Tube or Plus) test and T-SPOT®.*TB* are the two IGRAs currently approved in the United States. Either an IGRA or TST should be performed during the domestic refugee medical screening, if pre-departure testing results are unavailable. All children 2–14 years of age examined overseas on or after October 1, 2018, should have overseas IGRA results, if living in a country with a WHO TB rate of ≥20 TB cases per 100,000 population. Additionally, children 2–14 years of age living in a country with a WHO TB rate of <20 TB cases/100,000 population who have known HIV infection or signs or symptoms of TB disease at the time of overseas examination should also have IGRA results. TST can be used as a substitute for IGRA only when an FDA-approved IGRA product is not licensed for use by the country of overseas

examination, or in children under 2 years of age (when testing is indicated). The TST should be repeated if no specific documentation of a result (in mm induration) is available; however, if the refugee reports a history of a previous severe reaction to a TST (e.g., blistering, ulceration), repeating the TST is contraindicated. It should be noted that a negative TST or IGRA does not eliminate TB disease from the differential diagnosis in a patient with signs or symptoms of TB disease.

IGRA

The interferon-gamma release assays (IGRAs) use *M. tuberculosis* complex-specific antigens to stimulate patient T- lymphocytes. Importantly, IGRAs do not cross-react with antigens related to the *M. tuberculosis* BCG vaccine. Sensitized cells, in someone previously exposed to *M. tuberculosis*, will produce the cytokine interferon (IFN)-γ. The QuantiFERON®-TB Gold (In-Tube or Plus) tests test (Qiagen, Germany) are based on the quantification of IFN-γ produced by T-lymphocytes in whole blood stimulated by *M. tuberculosis* complex-specific antigens (e.g., ESAT-6, CFP-10, and TB7.7). The T-Spot TB Test (Oxford Immunotec, Marlborough, MA) measures the number of T-lymphocytes producing IFN-γ when stimulated by *M. tuberculosis* complex-specific antigens.

A positive result by an IGRA (indicating infection with the TB mycobacterium) demands further evaluation to exclude TB disease.

Tuberculin Skin Test

Interpreting the results of the TST depends on the patient's risk factors. In otherwise healthy refugees from areas of the world where TB is common, ≥10 mm of induration is considered positive. A cutoff of ≥5 mm of induration is considered positive in persons with HIV infection, those with recent close contact with a known case of infectious TB, persons with fibrotic changes on CXR consistent with prior TB, persons with organ transplants, and other immunosuppressed persons. Many refugees from TB-endemic areas have been vaccinated against TB with BCG vaccine. Although previous BCG vaccination may influence TST results, especially in infants, a history of vaccination with BCG should not influence interpretation of the TST. The clinician must thoroughly explain to the patient the reasons for not considering the BCG vaccination in the interpretation of the test. A positive result by TST demands further evaluation to exclude TB disease.

TST testing can be performed in all persons, including children and pregnant women. False negative results may be more frequent in young children and in persons with a compromised immune system. False negatives also may occur more commonly in persons at high risk for TB (a high pretest probability). A TST should be administered and read by a trained healthcare provider. For additional information about performing a TST, visit the CDC TB website.

Diagnostic Evaluation

Chest Radiography

If the pre-departure IGRA (or TST if IGRA is not licensed in the country where screened occurred) was negative and the refugee has no signs or symptoms of TB disease or known HIV infection, a CXR is not necessary. Any patient with signs or symptoms of TB disease, including those with a Class A or B TB designation, should undergo evaluation for TB disease including a CXR. If CXRs from the overseas medical exam are available and there has been no change in clinical status (no new signs or symptoms of pulmonary or extrapulmonary TB disease), there is no need to repeat the CXR. If documentation is not available at the initial screening visit, providers should contact their State Refugee Coordinator, or the Centers for Disease Control and Prevention to obtain overseas testing. If overseas results cannot be

obtained, either IGRA or TST should be done at the new arrival screening and, if positive, a CXR should be performed.

When a CXR is performed, a posterior-anterior (PA) radiograph should be the primary image obtained in adults and older children. In children too young to cooperate with PA positioning, an anteroposterior (AP) view should be obtained. Additionally, a lateral chest radiograph is recommended in children less than 10 years of age, because hilar adenopathy, a common pediatric TB finding, can be difficult to visualize on a PA or AP view. Any new CXR should be compared to previous films. Pregnant women with a positive TST or IGRA or other CXR indication should be protected with wraparound abdominal and pelvic lead shielding during chest radiography.

Specimen Collection and Mycobacterial Culture

If a refugee is symptomatic or has CXR or physical findings suggestive of pulmonary TB disease, attempts should be made to collect sputum specimens for AFB smear and mycobacterial culture. Three sputum samples should be collected at least 8–24 hours apart, with at least one being an early morning specimen. In addition, current CDC domestic guidelines recommend nucleic acid amplification testing be performed on the initial respiratory specimen from each patient suspected of having pulmonary TB [5]. Rapid molecular drug susceptibility testing for rifampin with or without isoniazid, using the specimens of persons who are either AFB smear positive or Hologic Amplified Mycobacterium Tuberculosis Direct (MTD) test positive and who meet certain criteria, is also recommended [5]. Sputa should be induced in adults unable to expectorate spontaneously. Specimens should be collected in either a well-ventilated area or a sputum collection booth or room with negative pressure. Collection of early morning specimens is preferred because of the overnight accumulation of secretions. Sputum should be collected under direct observation to ensure that the patient is being properly coached and is giving a good coughing effort, as well as to ensure that patients are producing their own sputum for examination. Children less than 2 years of age are often unable to expectorate voluntarily, so gastric aspirates or aerosolized hypertonic saline-induced sputum may need to be obtained in lieu of a standard expectorated sputum sample [6]. Children frequently must be hospitalized to collect adequate gastric aspirate samples. Because diagnosis and management of children can be very challenging, consultation with an experienced and knowledgeable expert in pediatric TB is encouraged.

In the setting of suspected extrapulmonary disease, consideration should be given to obtaining one or more specimens of body fluid or tissue from the suspected site of disease, if it can be done with an acceptable risk of complications. In general, if there are multiple options for obtaining a specimen, the least invasive method should be used first (e.g., obtain urine before performing a renal biopsy). Because of the increased risk for drug-resistant TB among many refugees, strong efforts should be made to obtain adequate specimens for TB culture, so that drug susceptibility testing may be performed. At least one culture-positive specimen from each patient should have conventional drug susceptibility testing. Rapid drug susceptibility testing of positive culture isolates can be obtained from CDC after consultation with the state health department and may be particularly useful in some circumstances (e.g., suspect MDR-TB, or history of previous treatment). In addition, some state health department laboratories offer rapid drug susceptibility testing of direct specimens from patients who are at high risk for drug resistance.

Suspected or Confirmed TB Disease

Screening results indicating suspected or confirmed TB disease may include a combination of a positive IGRA or TST, abnormal CXR or computed tomography (CT) scan, pathology findings consistent with TB disease (e.g., caseating granuloma), signs or symptoms consistent with either pulmonary or extrapulmonary disease, and sputum or tissue smear positive for AFB or a culture positive for *M. tuberculosis.* Immediate treatment is needed for confirmed or clinically diagnosed cases of TB. All

suspected or confirmed cases (pulmonary or extrapulmonary) should be reported to the local health authorities within 24 hours of determination so that appropriate public health measures can be implemented. Do not wait for culture confirmation to report suspected TB disease. When pulmonary or laryngeal TB is suspected, the patient should be isolated in an appropriate setting to prevent spread of infection until the patient is no longer considered infectious.

Overview of Treatment

National treatment guidelines state that a provider undertaking to treat a patient with TB disease is assuming a public health function that includes not only prescribing an appropriate regimen but also ensuring adherence to the regimen until treatment is completed. TB disease should be treated in consultation with the public health department and a medical expert in the treatment of TB. All patients with TB disease should receive DOT. All treatment should be administered in accordance with the ATS/CDC/IDSA guidelines for treatment of TB.

LTBI

Most TB cases in the United States are believed to be the result of infection acquired years previously [3]. It is estimated that 92.5% of TB among foreign-born persons is caused by reactivation of LTBI [7]. Therefore, most TB cases among foreign-born persons (including refugees) is likely attributable to infections acquired overseas [3]. The CDC and US Preventative Services Task Force (USPSTF) recommend screening and treatment of persons with LTBI who were born in, or have lived in, countries with high TB prevalence, regardless of time since arrival in the United States [3, 8]. Some states require reporting of LTBI. Refugees should be offered treatment for LTBI, in accordance with CDC guidelines, unless contraindicated. Treatment regimens are by mouth and include the 12-dose (isoniazid and rifapentine [RPT]) regimen (known as 3HP), a 4-month rifampin regimen, and isoniazid (INH) for 6 or 9 months. Information on how to choose the most effective treatment regimen for each patient, adverse drug effects, monitoring, and assessing adherence is available on the CDC TB website.

Sources of Additional Information

Additional information regarding tuberculosis can be found on the CDC TB website or at the WHO website.

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