

Chapter III: Evaluation for TB Infection and Disease

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A. Initial Patient Interview

The purpose of the initial patient interview is to determine if the patient has TB and to assess all individuals who 1) have, or are suspected of having active TB disease or, 2) have latent TB infection and are possible candidates for latent TB treatment.

1. Information to Collect

Patient demographics provide statistics used in program management at the clinic, state and national levels.

Other information to gather/record:

- Complete the TB Surveillance and Case Management Report (TB 17)
- Addresses and contacts in other cities, states or countries, such as Mexico
- Medical, family, and social history relevant to tuberculosis
- Symptoms pertaining to tuberculosis
- TST or IGRA results
- Relevant physical exam (usually weight, height, ideal body weight, and chest exam)
- Chest x-ray
- Sputa specimens when indicated (obtain 3 before treatment is started unless starting treatment is urgent)
- Other tests as needed including: blood, vision, and hearing tests (depending on medications to be prescribed) (See Chapter 6.B. Baseline Tests).

For those who are Class III or V (See Section's E.4 and E.5 or definitions), collect personal data for use in locating the patient should he or she become "lost". This may include: typical "hangouts", emergency contacts, phone numbers, and a copy of a photo ID or digital photo if one is not available and the individual is homeless.

2. Patient Education

The process of educating the patient about the disease and its consequences ideally begins at the initial interview and includes:

- Nature of tuberculosis (latent and active) and its infectiousness (including contact investigation)
- The importance of TB treatment and possible side effects of anti-TB drugs

- Legal responsibility of the health department to ensure safe and effective treatment of TB
- The patient's responsibilities to complete treatment, follow instructions on isolations, provide information for confidential contact investigation, notify providers of possible adverse drug effects or unexpected symptoms, and collaborate with transfer of care if moving

Note: Numerous resources exist to assist you in working with/educating individuals from different cultural backgrounds. Contact CDPHE for these resources. Find various TB documents in seven frequently-used languages here:

<http://www.colorado.gov/cs/Satellite/CDPHE-DCEED/CBON/1251607767510>

B. Medical Evaluation and Physical Examination

The pretreatment evaluation provides an opportunity to establish rapport with the patient, discuss the details of the patient's risk for TB, emphasize the benefits of treatment and importance of adherence to the drug regimen, and review possible adverse effects of the regimen, including interactions with other drugs. All individuals found to have a positive TST or IGRA reaction should be evaluated to rule out active TB disease and to assess the need for LTBI treatment.

A complete medical evaluation for TB includes a medical history with documentation of medical treatments being received including a description of contraception for women of childbearing years, a physical examination, TST, chest x-ray, and any appropriate bacteriologic or histologic examinations. Prior to receiving medications for tuberculosis (latent or active) a variety of laboratory tests, depending on the medications prescribed, may need to be done. All cases of TB must receive an HIV test or have a recent (last three months) HIV test result on file. HIV will necessitate changes to the standard anti-TB drug regimen.

 For more information, see *Chapter IV: Anti-tuberculosis Drugs in Current Use*.

1. Medical History

a. TB symptoms. Patients may be asymptomatic when diagnosed with TB due to screening such as done in contact investigations, immigration screening or targeted testing. Most other patients with active TB disease will have one or more of these symptoms:

- Prolonged cough (≥ 3 weeks)
- Chest pain

- Loss of appetite
- Fatigue
- Hemoptysis
- Unintended weight loss
- Fever / chills / night sweats
- Enlarged lymph nodes.

Approximately 17% of TB cases are exclusively extrapulmonary. The symptoms of extrapulmonary TB depend on the site affected. TB of the spine may cause pain in the back; TB of the kidney may cause blood in the urine. Extra-pulmonary TB should be considered in the differential diagnosis of any ill person who has systemic symptoms and who is at high-risk for TB.

b. TB infection is defined as a positive TST or IGRA. Risk factors for TB infection include:

- Close contact with a person who has TB disease
- Birth or residence in areas of the world with higher burden of TB
- Prolonged (3 months or more) travel to or frequent foreign visitors from high-burden TB countries in the home
- Children who are contacts to adults at high-risk for TB
- Substance abusers such as alcohol (ETOH) and intravenous drug use (IDU)
- Family history of TB
- Migrant farm and dairy workers
- Employee or resident (ongoing exposure) in long-term residential facility (nursing home, hospital, correctional facility, homeless shelter)

c. Previous treatment

All patients should be asked about previous LTBI or active TB treatment. If the patient has previously received treatment, it is important to determine:

- Drugs used
- Dates and duration of treatment
- Mode of treatment (self-administered, DOT, etc.)
- History of adverse reactions
- Reasons for discontinuation of treatment, and

- Prior drug susceptibility results.

Those who have completed a course of LTBI treatment in the past should be asked about recent close contact with a person who has active TB disease. If a patient describes having received treatment for LTBI or active TB, the nurse should contact CDPHE to assist in finding more information about previous TB treatment. Usually a person who has received a previous adequate course of LTBI treatment (minimum of 6 months of INH over a 9-month period) does not require re-treatment. If the patient is asymptomatic, he or she does not need another chest x-ray unless the patient is being evaluated in a contact investigation and needs to be excluded as a potential case.

Question the patient about:

- the onset of current symptoms
- all locations where they received care for symptoms (i.e. emergency room, primary care provider, walk-in-clinic) and
- The type of treatment received. Ask specifically about antibiotics, in particular fluoroquinolones (e.g. levofloxacin, moxifloxacin, gatifloxacin) and amikacin. Attempt to determine the timing, dose, and duration of treatment.

Obtain contact information for other health care providers so pertinent medical records may be requested. Have the patient sign a record release form as needed. Decisions about adequacy of LTBI and active TB treatment and the need for further treatment will be based on review of documentation of previous treatment and the history obtained from the patient.

d. Risk factors for progression to active TB

Ask about medical history, in particular risk factors associated with increased risk for reactivation of old TB.

 See “Candidates for Tuberculin Skin Testing” in *Chapter II: Testing for TB Infection*

- History of prior active TB without documentation of adequate completion of treatment
- Recent immigration from a country with a high TB burden who had abnormal pre-departure TB screening chest X-rays
- Close contact with a person who has TB disease
- Age: less than 5 years, adolescents/young adults, over 65 years of age
- TST conversion from negative to positive within 2 years (10 mm increase)
- Immunodeficiency - HIV infected, cancer of the head or neck, hematologic and reticuloendothelial disease (e.g., leukemia and Hodgkin's disease),

treatment with immunosuppressive medications such as infliximab (Remicade), etanercept (Enbrel), or long-term steroid use

- Diabetes mellitus
- Chronic renal failure/hemodialysis
- Organ transplantation
- Other chronic, debilitating conditions
- Injection drug use (IDU)
- Silicosis
- Gastrectomy/jejunoileal bypass surgery
- Malnutrition /chronic malabsorption syndromes/low body weight (10% or more below ideal).

e. Risk factors for drug toxicities and drug interactions

- Increased risk for hepatotoxicity. Alcohol abuse, end stage liver disease, hepatitis, cirrhosis, pregnancy and the first 3 months postpartum are all relative contraindications to the use of isoniazid (INH) for LTBI treatment. These will also affect the decisions made regarding what medications, including pyrazinamide (PZA) to use for treatment of active TB.

 For more information see “Monitoring Patients during LTBI Treatment” in *Chapter V: LTBI Treatment and Follow-up*. See also “Baseline Tests and Follow-up Evaluations” sections in *Chapter VI: Treatment and Follow-up for Suspect and Active TB Disease*. For contraindications to specific drugs used as LTBI treatment see *Chapter IV: Anti-tuberculosis Drugs in Current Use*.

- Peripheral neuropathies are more common in persons with diabetes, uremia, alcoholism, malnutrition, and HIV infection. Therefore, pyridoxine (vitamin B₆) should be given along with INH. Pregnant women, persons with seizure disorders, breastfeeding infants, and individuals with diets likely to be deficient in pyridoxine (meat/milk deficient diet, malnourished) should also take both pyridoxine and INH.
- Allergies and previous adverse drug effects. Rarely reported events (e.g. anaphylaxis, severe hepatotoxicity) should preclude the use of the drug suspected as the cause. Patients with other adverse effects (e.g. stomach pain, fatigue) may be eligible for medication re-challenge.
- Drug interactions. Rifampin is a potent inducer of hepatic enzymes that metabolize medications. This means that previously effective medications and doses may no longer be therapeutic when people are on rifampin.

Rifapentine is also a potent inducer of hepatic enzymes while rifabutin is much less potent than rifampin. Rifabutin levels are increased by some drugs, notably HIV protease inhibitors. INH is an inhibitor of similar hepatic enzymes. It is important to document all medications the patient is receiving and the method of contraception by women of childbearing age (the depot or implant of hormonal contraception might not be readily provided when asked about medications). This will allow one to assess the potential for drug-drug interactions for all medications being taken including prescription drugs, over-the-counter drugs, herbal medications, and supplements. Drug interaction programs are available on the internet.

f. Pregnancy and fertility assessment

Female patients should be asked whether they might be pregnant. Women with menses more than two weeks late should be referred for pregnancy testing. Women receiving rifampin while taking oral contraceptives for birth control are at increased risk of becoming pregnant and should be counseled to use another method of birth control.

g. Feasibility of LTBI treatment completion

Assess feasibility for completion of either 9 months of INH or 4 months of Rifampin (e.g., recent immigrants, homeless, incarcerated). Consider directly observed preventive therapy (DOPT) for selected populations at increased risk for progression to active TB or poor adherence to treatment.

h. Children

Evaluating children for active TB before treating for LTBI should take into account the different manifestations of TB in children. Signs and symptoms of TB may be subtle while the chest x-ray may be abnormal. TB may present as fever of unknown origin, pneumonia, failure to thrive, or as asthma with atelectasis on chest x-ray due to impingement on bronchi by enlarged lymph nodes. Extra-pulmonary TB is more common in children (25-35% of cases in 0 to 14 year olds) while in the overall population of TB cases, 17% are extra-pulmonary. Ask about fever, cough, malaise, bone pain, neurological changes, lymph node swelling and abdominal and flank pain. Examine the child looking for extra-pulmonary TB: ears, mastoids, eyes, spine and flank, neck and nodes and throat and abdomen.

2. HIV testing

All patients being evaluated for active TB disease, including pregnant women and those without behavioral risk factors for HIV, should be counseled and offered HIV testing unless they have documentation of a positive HIV antibody test in the last three months. If the patient has received HIV testing result a short time (e.g. previous three months)

before the TB diagnosis and the documented results were negative for HIV, and the patient reports no risk factors for HIV, you do not need to repeat the HIV test. The length of time (before a TB diagnosis) that a negative HIV test result is acceptable should be based on clinical judgment of the patient's risk for TB, but the time should not exceed one year. State law does not require parental consent for STI testing of patients younger than 18 years and parental consent is not necessary for HIV testing of adolescents.

HIV-negative individuals who remain at risk for HIV infection during active TB treatment should be retested after three months of TB treatment.

 See *Chapter XIV: Chest X-Rays and Labwork* for more information on HIV testing.

C. TST and IGRAs

If there is no documentation that a tuberculin skin test (TST) or interferon gamma release assay (IGRA) has been performed, one or the other should be ordered unless the patient has culture-confirmed TB (when it is not needed). The TST and IGRA are useful for:

- Examining a person who is not ill but may be infected with *M. tuberculosis* such as (contacts to active TB, etc.
- Contributing diagnostic information about whether to isolate, start empiric therapy, and/or begin a contact investigation for a person who has symptoms of TB but negative sputum smears.

A negative reaction to the TST or IGRA does not exclude the diagnosis of TB, especially for patients with severe TB illness or HIV infection. Some persons may not react to the TST if they are tested too soon after being exposed to TB. Generally it takes up to 2 to 8 weeks after infection for a person to develop an immune response to tuberculin. Children younger than five years of age may not react to the TST because their immune systems are not yet fully developed.

BCG vaccination complicates the interpretation of TST results because it can produce a false-positive reaction to the TST, especially if BCG was given after the age of one year. (BCG given only at birth is less likely to cause a false-positive TST reactions in adults). There are no characteristics of the TST reaction that allow one to distinguish between a positive reaction due to BCG and a positive reaction due to true TB infection. In BCG-vaccinated persons, however, sensitivity to tuberculin is highly variable and tends to wane over time. The TST is interpreted the same in people with a history of BCG as in those without a prior BCG vaccination. A major advantage of the IGRAs is that BCG vaccinations do not cause false-positive IGRA results. Except for the greater expense of the IGRA, these tests are preferred in BCG-vaccinated persons.

 See Chapter 2 for more detail on the TST and the TST algorithm.

D. Chest X-Ray

A baseline chest x-ray should be obtained for all patients with a positive TST or IGRA and all those who are suspected of having active TB disease, whether or not their TST is positive. Patients should bring all previous chest x-rays. A written or oral report alone is not acceptable. Patients suspected of having extra-pulmonary TB should also undergo a chest x-ray to rule out pulmonary TB.

1. Timing

a. Patients who require a chest xray as soon as possible

- Those with symptoms or who are suspected of having active TB disease (including pregnant women)
- Children under 5 years with a positive TST or IGRA or recent exposure to infectious TB
- Immuno-compromised patients who have a positive TST or IGRA or recent exposure to infectious TB
- Recent contacts to active TB disease with positive TST or IGRA

A chest x-ray film taken within the past 2 weeks at another facility may be used if the film can be obtained easily from the other facility.

b. Patients who require a routine scheduled appointment for chest xray

- Routine positive TST or IGRA including asymptomatic pregnant women

In an asymptomatic person with LTBI, a film within the past 6 months may be adequate. If there are risk factors for progression, a film within the last 30 days may be required.

2. Views

A posterior-anterior (PA) chest x-ray is the standard view used for the detection and description of chest abnormalities. In some instances, other views (e.g., lateral, lordotic) or additional studies such as CT scans may be necessary.

a. PA and Lateral X-ray Views

Children 12 years of age or younger (i.e., up to and including the 13th birthday) should have both a PA and a lateral chest x-ray. The lateral view is important to help visualize adenopathy.

b. PA only

Adults and children 13 years of age or older only need a PA view, with additional views at the provider's discretion.

3. Findings

Radiographically, active TB is characterized by various combinations of hilar, mediastinal, and paratracheal lymphadenopathy; atelectasis, consolidation of lung parenchyma; mid- and lower lung zone infiltrates or scarring; nodules; calcifications; and pleural effusion. In pulmonary TB, x-ray 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 cavitation, especially in the immuno-suppressed/HIV-positive persons.

In HIV-infected persons, pulmonary TB may present atypically on the chest x-ray. For example, TB may cause infiltrates without cavities in any lung zone, or it may cause pleural effusion or mediastinal or hilar lymphadenopathy with or without accompanying infiltrates or cavities. In HIV-positive persons, almost any abnormality on a chest x-ray may indicate TB, and the chest x-ray of an HIV-positive person with TB disease may even appear entirely normal.

Cavitary lesions and upper lobe infiltrates, which are typical in adult TB cases, are occasionally seen in children and adolescents.

Old, healed (inactive) TB usually presents a different radiographic appearance from active TB, but the distinction of active versus inactive TB is a clinical and microbiological one. Inactive pulmonary TB can produce various radiographic findings. Dense pulmonary nodules, with or without visible calcification, may be seen in the hilar area or upper lobes. Smaller nodules, with or without fibrotic scars, are often seen in the upper lobes. Upper-lobe volume loss often accompanies these scars. Nodules and fibrotic lesions of inactive TB have well-demarcated, sharp margins and are often described as "hard." Bronchiectasis of the upper lobes is a nonspecific finding that sometimes occurs from previous pulmonary TB. Inactive TB may be associated with pleural scarring, but this finding is less specific for TB than upper lobe fibrotic lesions and may have been caused by trauma or prior pneumonia.

Nodules and fibrotic scars may contain slowly multiplying tubercle bacilli with the potential for future progression to active TB. The risk of progression is significant, and persons who have nodular or fibrotic lesions consistent with inactive TB on chest x-ray and have a positive TST reaction should be considered high-priority candidates for treatment of LTBI regardless of age. Despite documented x-ray stability and lack of symptoms, lesions typical of inactive TB may actually be culture-positive, chronic active TB. Sputa cultures and clinical evaluation are required to diagnose inactive TB. Conversely, isolated calcified nodular lesions (calcified granuloma) and/or apical pleural

thickening pose minimal increased risk for current active TB or future progression to active TB. Patients with these findings and no symptoms should be considered for LTBI treatment based on their other risks for progression to active TB disease.

Abnormalities on chest x-rays may be suggestive of, but are never diagnostic of active TB. However, chest x-rays may be used to exclude the diagnosis of pulmonary TB in a person who has a positive reaction to the TST and no symptoms of disease.

E. Diagnostic Microbiology

1. Specimen Collection

a. Respiratory samples

Persons suspected of pulmonary or laryngeal TB should have sputa collected for microbiological evaluation.

Generally, at least 3 sputa specimens of 3-5 cc each should be collected to be examined by smear and culture. It is often recommended to obtain a series of early-morning specimens, collected on 3 consecutive days, but this was more easily accomplished when patients were hospitalized for prolonged periods. A more timely diagnosis can be achieved by more frequent sampling, such as every four to eight hours, especially when it is important for clinical or public health reasons to start treatment promptly. If you are planning to collect specimens in a shorter time-frame than every 24 hours, discuss it with CDPHE's TB Program first. Specimens should be obtained in an isolated, well-ventilated area or a sputum collection booth.

In some cases, children who are unable to produce sputum spontaneously or cannot use the sputum induction machine, may be admitted to the hospital for early morning gastric aspirates to be taken on three consecutive days.

b. Other Clinical Specimens

Because TB can occur in almost any anatomical site, a variety of clinical specimens other than sputum (e.g., urine, cerebrospinal fluid, pleural fluid, pus, or biopsy specimens) may be submitted for examination when extrapulmonary TB disease is suspected. Formalin or other preservatives should not be used because these solutions kill or inhibit the growth of *M. tuberculosis*.

2. Methods for Collection of Respiratory Samples

a. Spontaneous sputum collection

A health care worker should coach and supervise the patient the first time sputum is collected. Patients should be properly instructed in how to produce a good specimen. Patients should be informed that sputum is the material brought up from the lungs and that mucus from the nose or throat and saliva are not good specimens. Patients collecting sputum samples at home should refrigerate the samples and return them to the clinic as soon as possible within 2 to 3 days. Samples should be sent as they are collected and should be received at the laboratory within 24 hours of collection.

Do not ship samples on Fridays as they will not be refrigerated over the weekend. See Chapter 12 on Miscellaneous Protocols/Administrative Issues for details on how to obtain specimen containers and shipping instructions from CDPHE lab.

b. Sputum induction

For patients unable to cough up sputum, deep coughing may be induced by inhalation of an aerosol of bacteriostatic water or hypertonic saline. Check with your local hospital to determine if this service is available. Please consult the CDPHE TB Program prior to arranging this procedure so that payer source can be discussed.

c. Bronchoscopy

A bronchoscopy may be performed if there is suspicion of TB and the patient cannot cough up sputum. Adequate infection control precautions should be taken when performing a bronchoscopy for the purpose of diagnosing TB disease. Bronchial washings, brushings, and biopsy specimens may be obtained, depending on the diagnostic possibilities and findings. Sputum collected after bronchoscopy may also be useful for a diagnosis. Please contact the CDPHE TB program prior to arranging a bronchoscopy so that payer source can be discussed. CDPHE does not generally provide funding for this procedure.

d. Gastric aspiration

Gastric aspiration may also be used to obtain specimens of swallowed sputum. Although it is uncomfortable, it is less expensive and less invasive than a bronchoscopy. It is the best way to obtain specimens from infants and some young children who cannot produce sputum with aerosol inhalation. When using gastric aspiration to obtain specimens from children, the procedure should be done in the morning before the patient gets out of bed or eats.

During specimen collection, patients produce an aerosol that may be hazardous to health care workers or other patients in close proximity. For this reason, precautionary measures for infection control must be followed during sputum

induction, bronchoscopy, and other common diagnostic procedures. CDPHE does not generally provide funding for this procedure.

3. Laboratory Examination

a. Smear

Detection of acid-fast bacilli (AFB) in stained smears examined microscopically may provide the first bacteriologic clue of TB. Smear examination is an easy and quick procedure. Results should be available within 24 hours after specimen collection. However, smear examination allows only the presumptive diagnosis of TB because the AFB in a smear may be mycobacteria other than *M. tuberculosis*. Furthermore, many TB patients have negative AFB smears.

b. Rapid molecular diagnostic tests

Currently, the only rapid diagnostic tests for TB, Nucleic Acid Amplification (NAA) tests, that have been approved by the Food and Drug Administration are the Roche Polymerase Chain Reaction (PCR) Test (Amplicor®) and the Amplified Mycobacterium tuberculosis Direct (MTD) Test (Gen-Probe®). Both tests are approved for smear-positive respiratory samples but only the MTD is approved for use on smear negative samples. The CDC recommends that NAA testing be performed on all smear-negative patients with clinical signs consistent with TB when the result will lead to changes in management. Additionally, laboratory developed NAA tests are available. A positive result with one of these tests should be confirmed by culture. The MTD test is performed at National Jewish Health laboratory, Colorado Department of Public Health and Environment (CDPHE), LabCorp, ARUP, and possibly other reference labs. Samples may be sent by special request from one of the ID/TB physicians. Results are usually out within 48 hours (not including weekends). A positive NAA test result indicates a high likelihood of TB, but a negative result does not exclude TB, particularly in patients at high risk for TB. NAA tests cannot replace clinical judgment or be relied on as the only guide for therapy or isolation practices. The tests may enhance diagnostic certainty, but should be interpreted in a clinical context.

The Gene Xpert test has been validated by the laboratory at Colorado Department of Health and Environment (CDPHE) and is currently available for detecting rifampin-resistance in patients at higher risk for MDR TB.

c. Culture and identification

Positive cultures for *M. tuberculosis* confirm the diagnosis of TB. However, TB may also be diagnosed on the basis of clinical signs and symptoms in the absence of a positive culture. Culture examinations should be done on all specimens, regardless of AFB smear results.

In the CDPHE microbiology lab, the BACTEC® MGIT 960 System is the primary liquid medium culture detection method for MTB, with a solid medium backup for each specimen (Middlebrook 7H10 selective media). The liquid medium system allows for the detection of mycobacterial growth in an average of 4 to 14 days. Tubes entered into the BACTEC MGIT 960 System are continuously incubated at 37°C and monitored every 60 minutes for growth. Culture tubes which remain negative for a minimum of 42 days and which show no visible signs of positivity are reported as negative. The solid medium backup is also incubated for six weeks. Isolates of acid-fast bacilli (AFB) detected by the MGIT 960 system, or subsequently grown on solid medium, are identified by probe testing (AccuProbe, Gen-Probe, Inc) for MTB complex and *M. avium-intracellulare* complex (MAC).

In addition, smear positive and select smear-negative specimens undergo nucleic acid amplification method using the Gen-Probe MTB Direct amplification assay.

An older test, used in some labs that do not have the DNA Probe available, is a test for inhibition by p-nitro- α -acetyl-amino- β -hydroxypropio-phenone (*NAP Test*). It can identify *M. tuberculosis* in 3-4 days.

If the lab cannot identify the organism in an AFB positive culture they will send it to the CDC lab for confirmation (16s rRNA sequencing).

d. Drug susceptibilities

For all patients, the initial *M. tuberculosis* isolate, regardless of source, should be tested for drug resistance. It is crucial to identify drug resistance as early as possible in order to ensure appropriate treatment. Drug susceptibility testing should be repeated for patients who do not respond adequately to therapy or who have positive culture results despite 3 months of therapy.

The BD MGIT 960 System, which uses a liquid medium, is faster than conventional methods for determining susceptibility to first-line TB medications. Usually, susceptibility results can be obtained from the CDPHE laboratory within two to three weeks after the identification of *M. tuberculosis*. Second line drug susceptibilities processed through National Jewish Hospital usually require one month. National Jewish Hospital also performs 2nd line drug susceptibility testing in its lab.

Groups at an increased risk for drug resistance include:

- Persons who have a history of treatment with TB drugs
- Contacts to persons known to have drug-resistant TB
- Foreign-born persons from areas of the world where the prevalence of drug-resistant TB is high
- Persons whose smears or cultures remain positive despite 3 months of therapy with TB drugs

- Persons receiving inadequate treatment regimens (e.g. single drug therapy for LTBI) for more than 2 weeks.

Molecular Detection of Drug Resistance (MDDR): CDC is performing a molecular testing service using DNA sequencing for the identification of drug resistance associated mutations in isolates of *M. tuberculosis* Complex (MTBC). This service (MDDR) will allow rapid confirmation of MDR TB through the identification of genetic mutations associated with rifampin (RIF) and isoniazid (INH) resistance. In addition, genetic loci associated with resistance to the most effective second-line drugs, fluoroquinolones (FQ) and the injectables amikacin (AMK), kanamycin (KAN), and capreomycin (CAP) will be examined. The key advantage of the molecular tests is that they can provide results within 24 to 48 hours. The sequencing panel was selected to be able to detect resistance associated mutations for the first- and second-line anti-tuberculosis drugs that define MDR- and XDR-TB. (MDR-TB is defined as resistance to at least RIF and INH; XDR-TB is defined as MDR-TB plus resistance to a FQ and at least one of the second-line anti-TB injectable drugs: KAN, CAP or AMK). This test must be pre-approved by the CDC laboratory by emailing the appropriate completed CDC form.

MDDR submission criteria: Isolates may be submitted for molecular detection of drug resistance if one of the following criteria is met:

- High-risk of RIF resistance or MDR-TB (including previously treated TB case, drug resistant TB contact, foreign-born from area with high rates of MDR TB)
- Known RIF resistant isolates
- High profile patients (e.g. daycare workers, nurses)
- Adverse reactions (e.g. patient allergic to RIF)
- Mixed or non-viable cultures
- other situations considered on case by case basis

e. DNA fingerprinting

DNA fingerprinting can be used to identify specific strains of *M. tuberculosis* and thus track TB transmission during outbreaks. DNA fingerprinting can also be used to detect lab contamination by determining if the isolates from the contaminating source culture and the suspect culture are related. If the isolates have differing DNA fingerprint patterns, cross-contamination is very unlikely to have taken place. There are two labs performing fingerprinting: Michigan and California. Colorado isolates are sent to the California lab. Fingerprinting is performed by spoligotyping and sequencing of Mycobacterial Interspersed Repetitive Units (MIRU). Results from both methods are available in approximately 10 working days. Restriction fragment

length polymorphism (RFLP) can be performed to confirm the results using other methods upon request, or as needed.

- Spoligotyping is spacer oligonucleotide typing. It is a polymerase chain reaction (PCR) assay that identifies specific single nucleotide polymorphisms, or unique spacer sequences in the mycobacterial genome.
- MIRU VNTR is analysis of mycobacterial interspersed repetitive units-variable number of tandem repeats. It is also a PCR-based assay that targets repeated base pairs in the Mycobacterial genome.
- RFLP (Restriction Fragment Length Polymorphism). The restriction enzymes used in this technique cleave the Mycobacterial genome at certain sites to produce fragments of various lengths. These fragments are separated by size to produce a pattern, or "fingerprint", that is specific for each bacterial strain. Related isolates show the same pattern. This test is more time-consuming, although it is the most specific.

F. Special Populations

1. Prenatal, Pregnant, and Post-Partum Patients

Pregnant women who have a positive TST or IGRA reaction are often referred for evaluation to local public health agencies from OB/GYNs in the community. For most patients, a shielded chest x-ray should be taken after the first trimester. A chest x-ray should be done immediately, *even during the first trimester*, for pregnant women who:

- Have symptoms that are highly suggestive of TB disease (cough, fever, night sweats, chest pain, etc.), or
- Are HIV-positive regardless of TST/IGRA result, but have been in close contact with a person who has pulmonary or laryngeal TB disease, or
- Are HIV-negative, TST/IGRA-positive and have been in close contact with a person who has pulmonary or laryngeal TB disease.

If the chest x-ray is normal, discuss LTBI treatment with the patient. If she is a candidate for LTBI treatment and willing to take it, then schedule for a follow-up appointment 6 to 8 weeks after her expected delivery date/expected date of confinement (EDC) for a repeat chest x-ray and to start LTBI treatment.

Due to a greater risk of hepatotoxicity, a baseline alanine transaminase (ALT/SGPT) should be drawn if LTBI treatment will start within 3 months after delivery.

2. TB Screening for Immigrants, Refugees, Status Adjustors

a. Required TB screening for migration to the United States

All immigrants, refugees and certain non-immigrants, including fiancés, coming to the United States must have a physical and mental examination abroad by a Panel Physician selected by a United States embassy or consulate to conduct medical examinations of aliens applying for visas. Persons already in the United States who are applying for adjustment of status to a permanent resident of the United States must have a physical and mental examination in the United States by a Civil Surgeon, a physician in the United States designated by the Department of Homeland Security U.S. Citizenship and Immigration Service.

Category	Definition	Medical Examination Required	Examination Location
Immigrant (also known as Permanent resident alien)	An alien* admitted to the U.S. as a lawful permanent resident	Yes	Overseas Panel Physician completes the DS 2053
Refugee	A person outside his or her country of nationality who is unable or unwilling to return because of a well-founded fear of persecution	Yes	Overseas Panel Physicians
Asylee	A person who has entered the U.S. and who is unable or unwilling to return because of a well-founded fear of persecution	May not be until change of status	Civil Surgeon during change of status
Status adjusters	Individual already in the U.S. who is in the process of changing their status to that of lawful permanent resident	Yes	In the U.S., the Civil Surgeon completes the I-693 form
Non-immigrants	An alien granted temporary entry to the U.S. for a specific purpose. (Most common visa classifications for non-immigrants are visitors for pleasure, visitors for business, temporary workers, students, and exchange visitors)	No	Medical examination may be required at the discretion of the consular officer overseas or immigration officer at the U.S. port of entry
Short-term Transit	An alien in immediate and continuous transit through the U. S. with or without a visa, including those going to and from the United Nations headquarters and foreign government officials and family members in transit.	No	--
Others	Includes migrants who entered the U. S. without inspection, including those who entered with & without proper documentation (e.g., those who overstay their visa and illegal immigrants)	No	--

* Alien = A person who is not a citizen of the United States.

Source: U.S. Department of Homeland Security <http://www.uscis.gov/portal/site/uscis>. Accessed November 18, 2008.

b. TB Classifications/Screening for Overseas Evaluations

Classification	Clinical and laboratory findings	TB screening requirements
Class A – Pulmonary TB, Active, Infectious	<ul style="list-style-type: none"> ▪ Abnormal chest radiograph(s) suggestive of active TB disease ▪ Either one or more sputum smears positive for AFB or one or more cultures positive for <i>M. tuberculosis</i> 	<ul style="list-style-type: none"> ▪ Must be treated before departure from their country of origin. Once smear-negative or active TB treatment completed they may travel if still overseas ▪ Health department follow-up required ▪ I-693 may be signed by health department if applying for “change of status”
Class B1 - Pulmonary TB, Active, Non-Infectious	<ul style="list-style-type: none"> ▪ Abnormal chest radiograph(s) suggestive of active TB disease ▪ Three sputum smears negative for AFB and three cultures negative for <i>M. tuberculosis</i>. 	<ul style="list-style-type: none"> ▪ Allowed to travel but referred to a health department in the state of their intended residence for further evaluation ▪ Health department follow-up required ▪ I-693 may be signed by health department if applying for “change of status”
Class B1- Extrapulmonary TB, Active, Non-infectious	<ul style="list-style-type: none"> ▪ Radiographic or other evidence of extrapulmonary TB disease ▪ No pulmonary TB 	<ul style="list-style-type: none"> ▪ Allowed to travel but referred to a health department in the state of their intended residence for further evaluation ▪ Health department follow-up required ▪ I-693 may be signed by health department if applying for “change of status”
Class B2 – Pulmonary TB, Inactive	<ul style="list-style-type: none"> ▪ Abnormal chest radiograph(s) suggestive of inactive TB disease (discrete nodules without calcification, fibrotic scars, linear opacities all with or without volume loss or retraction) ▪ No sputum smears or cultures required 	<ul style="list-style-type: none"> ▪ Allowed to travel but referred to a health department in the state of their intended residence for further evaluation ▪ Health department follow-up required ▪ I-693 may be signed by health department if applying for “change of status”
Class B – Latent TB Infection Needing evaluation for treatment (LTBI)	<ul style="list-style-type: none"> ▪ TST reaction ≥ 10 mm in recent U.S. arrivals (within 5 years) or any group where ≥ 10 mm is considered positive ▪ TST reaction ≥ 5 mm in specific groups (HIV infected, recent contact, patients with transplants, other immuno-suppressed) <p>AND</p> <ul style="list-style-type: none"> ▪ No evidence of active TB disease 	<ul style="list-style-type: none"> ▪ Allowed to travel but referred to a health department in the state of their intended residence for further evaluation ▪ Health department follow-up recommended ▪ I-693 may be signed by health department if applying for “change of status”
Class B – Other chest condition (non-TB)	<ul style="list-style-type: none"> ▪ Abnormal chest radiograph, not suggestive of TB disease but needing follow-up 	<ul style="list-style-type: none"> ▪ Allowed to travel ▪ I-693 may be signed by civil surgeon if applying for “change of status” specify condition (e.g. cardiomegaly, scoliosis) ▪ Advise the applicant about the findings and the type of medical referral needed
<p>If the applicant has TB signs or symptoms, he or she should be referred to CDPHE’s TB Program for further evaluation regardless of TST result or chest radiograph appearance.</p>		

c. Evaluation of Class A, B1, and B2

Before the 2007 revised Technical Instructions for overseas TB screening of immigrant applicants, active TB was diagnosed in 3-14% of Class B1 immigrants (chest x-ray suggesting active TB and 3 negative sputum smears, cultures not done). Studies have not been done to evaluate the prevalence rate of immigrants who were screened overseas with cultures, but it is likely that active TB will be less frequent in immigrants screened by sputum culture.

Immigrants, refugees or asylees with a classification of **Class A** (active, pulmonary TB) will have been treated before arrival, usually to completion and cure; these may then travel as a Class B1.

Other individuals who arrive with **Class B1 and B2-pulmonary TB** classification will need an evaluation based upon whether they had sputa cultures done overseas (not all countries implemented AFB sputum cultures during 2008). Follow-up recommendations are:

- **Class B1-pulmonary TB, negative overseas sputum AFB smears, cultures not done:** obtain a current chest x-ray and 3 sputum specimens for AFB smear and culture unless the chest X-ray overseas and/or in the U.S. are not considered to be consistent with TB. The physician should decide if a repeat chest x-ray and/or other testing is necessary before decisions about TB classification and treatment are made.
- **Class B1-pulmonary TB, negative overseas AFB smears and cultures:** obtain a current chest x-ray and an initial sputum AFB smear and culture unless the assessment is that the overseas and current chest x-rays are determined not to be consistent with active or inactive TB. The need for additional sputum specimens will be determined based upon the individual's prior treatment history, presence of symptoms, and comparison of current and overseas x-ray findings.
- **Class B2- pulmonary, no sputum specimens tested overseas:** obtain a current chest x-ray and AFB sputa specimens for smear and culture based upon whether there are lesions consistent with active TB.
- **Class B2 - extrapulmonary TB:** assess whether treatment was given overseas and base the need for sputum collection upon the records of diagnosis and treatment as well as the results of a current chest x-ray.
- **Patients with positive TST and parenchymal fibrotic lesions on chest x-ray abnormalities compatible with inactive TB** are at high risk for reactivation and are candidates for preventive therapy regardless of age.

There are occasionally patients with typical clinical and radiological features of inactive pulmonary TB but who have negative TST or IGRA. Repeat TST or IGRA can be considered in selected patients before discharging the patient from follow-up.

The immigrant, refugee or asylee who is referred with **Class B-Latent TB Infection** (usually only children receive TSTs overseas), a normal overseas chest x-ray and positive TST of at least 10 mm, should ideally have an IGRA test since over 50% of such patients will have a negative IGRA, a repeat X-ray can be avoided and they can be discharged as “no TB infection, Class 0.” If the IGRA is positive or TST result used because the IGRA is not available, the patient should receive a repeat chest x-ray and if this is stable, they are candidates for LTBI treatment regardless of age.

d. Follow-up for applicants in the United States

Immigration applicants already in the United States seeking a permanent residency visa by change of status must be screened and found free of infectious TB before they can change their immigration status and get permanent residency. Civil Surgeons must perform the screenings. The procedure consists of an initial TST/IGRA. If the induration size is greater than or equal to 5 mm (rather than the 10 mm cut-off used by overseas Panel Physicians), a chest x-ray is required. This cut-off is used to detect the individuals with fibrotic lung lesions for whom a 5 mm cut-off is recommended. The 5-9 mm TST readings are considered negative if the chest X-ray is normal. Persons whose chest radiograph is abnormal must be evaluated by the local health department. Referral for possible LTBI treatment to the health department or the individual’s primary care provider is recommended (but not required by USCIS) for persons with TST reactions of greater than or equal to 10 mm. If the individual is motivated to receive treatment for TB infection, an IGRA should be done if feasible to exclude false-positive TST due to prior BCG vaccination.

G. Decision to Initiate Treatment

The decision to initiate treatment for tuberculosis is based on:

- a patient’s medical and social history
- clinical signs and symptoms
- chest x-ray
- the initial series of AFB smears (preferably 3)
- subsequent cultures for mycobacteria, and
- public health considerations.

On the basis of this information, the likelihood that a given patient has tuberculosis can be estimated. For example, a patient who has emigrated recently from a country with a high-burden of TB, and has a history of cough and weight loss, and has characteristic findings on chest x-ray should be considered highly likely to have tuberculosis. In such situations, the initiation of combination drug therapy should strongly considered, even before AFB smears and mycobacteria culture results are known. Treatment should be initiated quickly in a patient seriously ill with a disorder that is thought possibly to be tuberculosis. Initiation of treatment should not be delayed because of negative AFB smears. Disseminated (miliary) tuberculosis, for example, is often associated with negative sputa AFB smears, and only half of the patients diagnosed with TB meningitis have the diagnosis confirmed by culture. Public health considerations often indicate a patient with suspected tuberculosis and a high risk of transmitting the disease should be empirically started on combination drug treatment despite negative AFB smears with cultures pending to minimize potential transmission.

A positive AFB smear provides strong inferential evidence for the diagnosis of tuberculosis. The TB treatment regimen can be continued to complete a standard course of therapy if the TB diagnosis is confirmed by identification of *M. tuberculosis* or is strongly inferred from clinical or chest x-ray improvement consistent with a response to treatment. A TST or IGRA may be done at the time of initial evaluation, but a negative test does not exclude the diagnosis of active tuberculosis. However, a positive TST or IGRA supports the diagnosis of culture-negative pulmonary tuberculosis, or in persons with stable abnormal chest x-ray consistent with inactive tuberculosis, a diagnosis of latent tuberculosis infection.

In low-suspicion patients not initially treated, if cultures remain negative, the TST (5 mm or greater), or IGRA is positive and the chest x-ray is unchanged after 2 months, there are two treatment options:

- INH for 9 months or
- RIF with or without INH for 4 months.

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