Self-Study Modules on Tuberculosis

Module 3 – Targeted Testing and the Diagnosis of Latent Tuberculosis Infection and Tuberculosis Disease

Module 3: Objectives
At completion of this module, learners will be able to:

1. Identify high-risk groups for targeted testing
2. Describe how to place, read, and interpret a Mantoux tuberculin skin test (TST)
3. Describe how to interpret an interferon-gamma release assay (IGRA)
4. Discuss considerations for using either the TST or IGRA for diagnosing latent tuberculosis infection (LTBI)
5. Describe the components of a medical evaluation for diagnosing TB disease

Module 3: Overview
• Targeted Testing
• Diagnosis of latent tuberculosis infection (LTBI)
  – TST
  – IGRA
  – TB Testing Programs, the Booster Phenomenon, and Two-Step Testing
• Diagnosis of TB Disease
• Reporting TB Cases
• Case Studies

Targeted Testing

Targeted Testing (1)
• Targeted testing is a TB control strategy used to identify and treat persons:
  – At high risk for latent TB infection (LTBI)
  – At high risk for developing TB disease once infected with *M. tuberculosis*

Targeted Testing (2)
• Identifying persons with LTBI is an important goal of TB elimination because LTBI treatment can:
  – Prevent the development of TB disease
  – Stop the further spread of TB to others
Targeted Testing (3)
A Decision to Test is a Decision to Treat

- TB testing activities should be done only when there is a plan for follow-up care
- Health care workers (HCWs) should identify and test persons who are at high risk
  - People who are not at high risk generally should not be tested

Targeted Testing (4)
High-Risk Groups

- High-risk groups can be divided into two categories:
  - People who are at high risk for exposure to or infection with *M. tuberculosis*
  - People who are at high risk for developing TB disease once infected with *M. tuberculosis*

Targeted Testing (5)
High-Risk Groups for TB Infection

- Contacts of people known or suspected to have TB disease
- People who have come to U.S. within 5 years from areas of the world where TB is common
- People who visit areas with a high prevalence of TB disease
- People who live or work in high-risk congregate settings

Targeted Testing (6)
High-Risk Groups for TB Infection

- HCWs who serve patients at increased risk for TB disease
- Populations defined locally as having an increased incidence of LTBI or TB disease (e.g., medically underserved, low income, or people who abuse drugs or alcohol)
- Infants, children, and adolescents exposed to adults in high-risk groups

Targeted Testing (7)
High-Risk Groups for TB Disease after Infection with *M. tuberculosis*

- People living with HIV
- Children younger than 5 years of age
- People recently infected with *M. tuberculosis* (within the past 2 years)
- People with a history of untreated or inadequately treated TB disease
- People receiving immunosuppressive therapy

Targeted Testing (8)
High-Risk Groups for TB Disease after Infection with *M. tuberculosis*

- Persons with silicosis, diabetes mellitus, chronic renal failure, leukemia, or cancer of the head, neck, or lung
- Persons who have had a gastrectomy or jejunoileal bypass
- Low body weight
- Cigarette smokers and persons who abuse drugs and alcohol
- Persons defined locally as having an increased incidence of disease due to *M. tuberculosis*
Diagnosis of Latent TB Infection (LTBI)

Available testing methods for *M. tuberculosis* infection:
- Mantoux tuberculin skin test (TST)
- Blood tests known as interferon-gamma release assays (IGRAs):
  - QuantiFERON®-TB Gold In-Tube (QFT-GIT)
  - T-SPOT.*TB* test (T-Spot)

Mantoux Tuberculin Skin Test (1)
- TST is administered by injection
- Tuberculin is made from proteins derived from inactive tubercle bacilli
- Most people who have TB infection will have a reaction at injection site

Mantoux Tuberculin Skin Test (2)
0.1 ml of 5 tuberculin units of liquid tuberculin are injected between the layers of skin on forearm

Mantoux Tuberculin Skin Test (3)
- Forearm should be examined within 48 to 72 hours by HCW
- Reaction is an area of induration (swelling) around injection site
  - Induration is measured in millimeters
  - Erythema (redness) is not measured
Module 3 – Targeted Testing and the Diagnosis of Latent Tuberculosis Infection and Tuberculosis Disease

**Mantoux Tuberculin Skin Test**

**Study Question 3.1**
What is the TST used for?

**Study Question 3.2**
How is the TST given?

**Study Question 3.3**
With the TST, when is the patient’s arm examined?

**Study Question 3.4**
How is the induration measured?

**Diagnosis of Latent TB Infection (LTBI)**

**Mantoux Tuberculin Skin Test**
Interpreting the Reaction

Interpretation of TST reaction depends on size of induration and person’s risk factors for TB
Mantoux Tuberculin Skin Test (5)  
Interpreting the Reaction

- Induration of ≥ 5 mm is considered positive for:
  - People living with HIV
  - Recent contacts of people with infectious TB
  - People with chest x-ray findings suggestive of previous TB disease
  - People with organ transplants
  - Other immunosuppressed patients

Mantoux Tuberculin Skin Test (6)  
Interpreting the Reaction

- Induration of ≥ 10 mm is considered a positive reaction for:
  - People who have recently come to U.S. from areas where TB is common
  - People who abuse drugs
  - Mycobacteriology laboratory workers
  - People who live or work in high-risk congregate settings

Mantoux Tuberculin Skin Test (7)  
Interpreting the Reaction

- Induration of ≥ 10 mm is considered a positive reaction for:
  - People with certain medical conditions that increase risk for TB (e.g., silicosis, diabetes mellitus, severe kidney disease, certain types of cancer, and certain intestinal conditions)
  - Children younger than 5 years of age
  - Infants, children, or adolescents exposed to adults in high-risk categories

Mantoux Tuberculin Skin Test (8)  
Interpreting the Reaction

- Induration of ≥ 15 mm is considered a positive reaction for people who have no known risk factors for TB

Occupational Exposure

- For people who may be exposed to TB on the job (e.g., HCWs, staff of nursing homes or correctional facilities), interpretation of TST depends on:
  - The employee’s individual risk factors for TB
  - The risk of exposure to TB in the person’s job

Mantoux Tuberculin Skin Test Study Question 3.5

What two factors determine the interpretation of a skin test reaction as positive or negative? What additional factor is considered for people who may be exposed to TB on the job?
Module 3 – Targeted Testing and the Diagnosis of Latent Tuberculosis Infection and Tuberculosis Disease

**Mantoux Tuberculin Skin Test**

**Study Question 3.6**
Name 5 groups of people for which > 5 mm of induration is considered a positive reaction?

**Study Question 3.7**
Name seven groups of people for which > 10 mm of induration is considered a positive reaction.

**Study Question 3.8**
For which group of people is > 15 mm of induration considered a positive reaction?

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### Diagnosis of Latent TB Infection (LTBI)

#### Mantoux Tuberculin Skin Test

**Factors that Affect the Reaction**

- Factors that may cause people to have a positive reaction even if they do not have TB infection:
  - Infection with nontuberculous mycobacteria (NTM)
  - BCG vaccination
  - Administration of incorrect antigen
  - Incorrect measuring or interpretation of TST reaction

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**False-Positive Reaction**

- People who have been vaccinated with BCG may have a false-positive TST reaction
  - However, there is no reliable way to distinguish a positive TST reaction caused by BCG vaccination from a reaction caused by true TB infection

- Individuals should always be further evaluated if they have a positive TST reaction

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**BCG Vaccine**
Module 3 – Targeted Testing and the Diagnosis of Latent Tuberculosis Infection and Tuberculosis Disease

Mantoux Tuberculin Skin Test (11)
False-Negative Reaction

- Factors that may cause false-negative reactions:
  - Anergy
  - Recent TB infection (within past 8 to 10 weeks)
    - It can take 2 to 8 weeks after TB infection for body’s immune system to react to tuberculin
  - Very young age (younger than 6 months)
  - Recent live-virus measles or smallpox vaccination
  - Incorrect method of giving the TST
  - Incorrect measuring or interpretation of TST reaction

Mantoux Tuberculin Skin Test (12)
Anergy

- Inability to react to skin tests due to weakened immune system
- Anergy testing is no longer routinely recommended

Mantoux Tuberculin Skin Test (13)

Any patient with symptoms of TB disease should be evaluated for TB disease, regardless of his or her skin test reaction.

Mantoux Tuberculin Skin Test Study Question 3.9

Name four factors that may cause false-positive reactions to the TST.

Mantoux Tuberculin Skin Test Study Question 3.10

Is there a reliable way to distinguish a positive TST reaction caused by vaccination with BCG from a reaction caused by true TB infection?

Mantoux Tuberculin Skin Test Study Question 3.11

Name 6 factors that may cause false-negative reactions to the TST.
Mantoux Tuberculin Skin Test
Study Question 3.12

What is anergy?

Mantoux Tuberculin Skin Test
Study Question 3.13

After TB germs have been transmitted to someone, how long does it take before TB infection can be detected by the TST?

Mantoux Tuberculin Skin Test
Study Question 3.14

What should be done if a patient has a negative TST result, but has symptoms of TB disease?

Diagnosis of Latent TB Infection (LTBI)

Interferon-Gamma Release Assays (IGRAs)

Types of IGRAs

• QuantiFERON®-TB Gold In-Tube (QFT-GIT)
  – Approved in 2007
• T-Spot®.TB test (T-SPOT)
  – Type of ELISpot assay
  – Approved in 2008
• CDC guidelines for IGRAs published in 2010

IGRAs (1)

• Blood tests that help diagnose \textit{M. tuberculosis} infection
• Measures a person’s immune reactivity to \textit{M. tuberculosis}
Module 3 – Targeted Testing and the Diagnosis of Latent Tuberculosis Infection and Tuberculosis Disease

IGRAs (2)
Conducting the Test

- Confirm arrangements for testing in a qualified laboratory
- Arrange for delivery of the blood sample to the laboratory in the time the laboratory specifies
- Draw a blood sample from the patient according to the manufacturer’s instructions
- Schedule follow-up appointment for patient to receive test results
- Based on test results, provide follow-up evaluation and treatment as needed

IGRAs (3)
How it Works

- Blood samples are mixed with antigens (protein substances that can produce an immune response) and incubated
- If the person is infected with M. tuberculosis, blood cells will recognize antigens and release interferon gamma (IFN-\(\gamma\)) in response

IGRAs (4)
Interpreting Results

- QFT-GIT Results
  - Based on amount of IFN-\(\gamma\) released in response to M. tuberculosis antigens and control substances
- T-Spot Results
  - Based on number of IFN-\(\gamma\) producing cells (spots) produced

IGRAs (5)
Interpreting Results

- Qualitative test interpretation and quantitative assay measurements should be reported
- Laboratories use software provided by manufacturer to calculate results
- Results are sent to requesting health care provider

IGRAs (6)
Report of Results

<table>
<thead>
<tr>
<th>IGRA Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>M. tuberculosis infection likely</td>
</tr>
<tr>
<td>Negative</td>
<td>M. tuberculosis infection unlikely, but cannot be</td>
</tr>
<tr>
<td></td>
<td>excluded especially if</td>
</tr>
<tr>
<td></td>
<td>1. Patient has signs and symptoms of TB</td>
</tr>
<tr>
<td></td>
<td>2. Patient has a high risk for developing TB</td>
</tr>
<tr>
<td></td>
<td>disease once infected with M. tuberculosis</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>The test did not provide useful information about</td>
</tr>
<tr>
<td></td>
<td>the likelihood of M. tuberculosis infection.</td>
</tr>
<tr>
<td></td>
<td>Repeating an IGRA or performing a TST may be useful.</td>
</tr>
<tr>
<td>Borderline</td>
<td>The test did not provide useful information about</td>
</tr>
<tr>
<td>(T-Spot only)</td>
<td>the likelihood of M. tuberculosis infection.</td>
</tr>
<tr>
<td></td>
<td>Repeating an IGRA or performing a TST may be useful.</td>
</tr>
</tbody>
</table>

IGRA Recommendations (1)

- IGRAs are the preferred method of testing in
  - Groups of people who might be less likely to return for TST reading and interpretation
  - Persons who have received the BCG vaccine
- TST is the preferred method of testing for children younger than 5 years of age
Module 3 – Targeted Testing and the Diagnosis of Latent Tuberculosis Infection and Tuberculosis Disease

IGRA Recommendations (2)
- Routine testing using both TST and IGRAIs is NOT recommended
- Certain situations where results from both tests may be useful:
  - When the initial test is negative and:
    - Risk for infection, progression to disease, or a poor outcome is high
    - There is clinical suspicion for TB disease and confirmation of *M. tuberculosis* infection is desired

IGRA Recommendations (3)
- Certain situations where results from both tests may be useful
  - When the initial test is positive and:
    - Additional evidence of infection is required to encourage the patient’s acceptance and adherence to treatment
    - Person has a low risk of both infection and progression from infection to TB disease

IGRA Advantages
- Requires single patient visit to conduct test
- Results can be available in 24 hours
- Does not cause booster phenomenon which can happen with repeat TSTs
- BCG vaccination does not affect IGRA results

IGRA Disadvantages and Limitations (1)
- Blood samples must be processed within 8 to 30 hours after collection
- Errors in collecting or transporting blood specimens or in running and interpreting test can decrease accuracy
- Limited data on its use in certain populations (e.g., children younger than 5, persons recently infected, immunocompromised persons, and serial testing)

IGRA Disadvantages and Limitations (2)
- Limited data on its use to predict who will progress to TB disease
- Tests may be expensive

What are the steps for conducting an IGRA?
How are IGRA results interpreted?

Study Question 3.16

How should negative IGRA results be interpreted?

Study Question 3.17

What are 5 advantages for using an IGRA as compared to the TST?

Study Question 3.18

Many residential facilities, health care settings, and other settings have TB testing programs:

- Employees and residents are periodically given TSTs or IGRAs
- Testing programs:
  - Identify people who have LTBI or TB disease so they can be given treatment as needed
  - Determine whether TB is being transmitted in facility

TB Testing Programs (1)

- Employees or residents are given TSTs or IGRAs when they first enter facility
  - If person is negative, they may be retested at regular intervals thereafter

TB Testing Programs (2) Baseline Test

Diagnosis of Latent TB Infection (LTBI)

TB Testing Programs, the Booster Phenomenon, and Two-Step Testing
Module 3 – Targeted Testing and the Diagnosis of Latent Tuberculosis Infection and Tuberculosis Disease

TB Testing Programs (3) Conversion

- Persons whose TST or IGRA result converts from negative to positive may have been infected with *M. tuberculosis*
  - TST or IGRA conversions may indicate that TB is being transmitted in facility

Booster Phenomenon

- Phenomenon in which people who are skin tested many years after they became infected with TB have:
  - Negative reaction to initial TST
  - Positive reaction to subsequent TST given up to one year later
- Occurs mainly in older adults
- May affect accuracy of baseline skin test
- TST can boost subsequent IGRA results

Two-Step Testing

- Only conducted when TST is used
- Distinguishes between boosted reactions and reactions caused by recent infections
  - Should be used for initial skin testing of persons who will be retested periodically
    - If person’s initial skin test is negative, they should be given a second test 1 to 3 weeks later
      - Second test positive: probably boosted reaction
      - Second test negative: considered uninfected

What is the booster phenomenon?
Two-Step Testing
Study Question 3.20
What is the purpose of two-step testing?

Two-Step Testing
Study Question 3.21
In what type of situation is two-step testing used?

Two-Step Testing
Study Question 3.22
How is two-step testing done?

Diagnosis of TB Disease

Medical Evaluation
- Anyone with TB symptoms or positive TST or IGRA result should be medically evaluated for TB disease
- Components of medical evaluation:
  1. Medical history
  2. Physical examination
  3. Test for TB infection
  4. Chest x-ray
  5. Bacteriological examination

Diagnosis of TB Disease

Medical Evaluation
- 1. Medical History
- 2. Physical Examination
- 3. Test for TB Infection
1. Medical History (1)

- Clinicians should ask patients if they have:
  - Symptoms of TB disease
  - Been exposed to a person with infectious TB or have risk factors for exposure to TB
  - Any risk factors for developing TB disease
  - Had LTBI or TB disease before

1. Medical History (2)

General Symptoms of TB Disease

- Fever
- Appetite loss
- Chills
- Fatigue
- Night sweats
- Malaise
- Weight loss

1. Medical History (3)

Symptoms of Pulmonary TB Disease

- Cough lasting 3 or more weeks
- Chest pain
- Coughing up sputum or blood

1. Medical History (4)

Symptoms of Extrapulmonary TB Disease

- Symptoms of extrapulmonary TB disease depend on part of body that is affected
- For example:
  - TB disease in spine may cause back pain
  - TB disease in kidneys may cause blood in urine

2. Physical Examination

A physical examination cannot confirm or rule out TB disease, but can provide valuable information

3. Test for TB Infection (1)

- Types of tests available for diagnosing TB infection in U.S.:
  - Mantoux TST
  - IGRAs
    - QFT-GIT
    - T-SPOT
3. Test for TB Infection (2)

- Patients with symptoms of TB disease should always be evaluated for TB disease, regardless of their TST or IGRA test result
  - Clinicians should not wait for TST or IGRA results before starting other diagnostic tests
  - TST or IGRA should be given at the same time as other steps in the diagnosis of TB disease

Diagnosis of TB Disease
Study Question 3.23
What are the 5 components for conducting a medical evaluation for diagnosing TB disease?

Diagnosis of TB Disease
Study Question 3.24
What parts of a patient’s medical history should lead a clinician to suspect TB?

Diagnosis of TB Disease
Study Question 3.25
What are the symptoms of pulmonary TB disease? What are the symptoms of extrapulmonary TB disease?

Diagnosis of TB Disease
Study Question 3.26
For patients with symptoms of TB disease, should clinicians wait for TST or IGRA results before starting other diagnostic tests?

Diagnosis of TB Disease
Medical Evaluation
4. Chest X-Ray
When a person has TB disease in the lungs, the chest x-ray usually appears abnormal. It may show:

- **Infiltrates** (collections of fluid and cells in lung tissue)
- **Cavities** (hollow spaces within the lung)

Chest x-rays can:

- Help rule out possibility of pulmonary TB disease in persons who have a positive TST or IGRA result
- Check for lung abnormalities

Chest x-rays cannot confirm TB disease

- Other diseases can cause lung abnormalities
- Only bacteriologic culture can confirm patient has TB disease
- Chest x-ray may appear unusual or even appear normal for persons living with HIV

Can the results of a chest x-ray confirm that a person has TB disease? Why or why not?
5. Bacteriologic Examination (1)

- TB bacteriologic examination is done in a laboratory that specifically deals with *M. tuberculosis* and other mycobacteria
  - Clinical specimens (e.g., sputum, urine) are examined and cultured in laboratory

5. Bacteriologic Examination (2)

- Bacteriologic examination has 5 parts
  - Specimen collection
  - Examination of acid-fast bacilli (AFB) smears
  - Direct identification of specimen (nucleic acid amplification)
  - Specimen culturing and identification
  - Drug susceptibility testing

5. Bacteriologic Examination (3)

Specimen Collection

- For pulmonary TB, specimens can be collected by:
  - Coughing up sputum sample
  - Inducing sputum sample
  - Bronchoscopy
  - Gastric washing

5. Bacteriologic Examination (4)

Sputum Sample Specimen Collection

- Easiest and least expensive method is to have patient cough into sterile container
- HCWs should coach and instruct patient
- Should have at least 3 sputum specimens examined
  - Collected in 8 to 24 hour intervals
  - At least one early morning specimen

5. Bacteriologic Examination (5)

Induced Sputum Collection

- Induced sputum collection should be used if patient cannot cough up sputum on their own
- Patient inhales saline mist, causing deep coughing
- Specimen often clear and watery, should be labeled “induced specimen”

5. Bacteriologic Examination (6)

Bronchoscopy

- Bronchoscopy may be used:
  - If patient cannot cough up enough sputum
  - If an induced sputum cannot be obtained
- Procedure: instrument is passed through the mouth into the diseased portion of the lung to obtain sputum or lung tissue
5. Bacteriologic Examination (7) Gastric Washing

- Usually only used if sample cannot be obtained from other procedures
- Often used with children
- Tube is inserted through nose and into stomach to obtain gastric secretions that may contain sputum

5. Bacteriologic Examination (8) Extrapulmonary TB

- Specimens other than sputum may be obtained
- Depends on part of body affected
- For example:
  - Urine samples for TB disease of kidneys
  - Fluid samples from area around spine for TB meningitis

5. Bacteriologic Examination (9) Examination of AFB Smears

- Specimens are smeared onto glass slide and stained
- AFB are mycobacteria that remain stained after being washed in acid solution

5. Bacteriologic Examination (10) Examination of AFB Smears

- Number of AFB on smear are counted
- According to number of AFB seen, smears are classified as 4+, 3+, 2+, or 1+
  - For example, 4+ smear has 10 times as many AFB than 3+ smear
- If very few AFB are seen, the smear is classified by the actual number of AFB seen
- A negative smear does not rule out the possibility of TB

5. Bacteriologic Examination (11) Examination of AFB Smears

<table>
<thead>
<tr>
<th>Classification of Smear</th>
<th>Smear Result</th>
<th>Infectiousness of Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>4+</td>
<td>Strongly positive</td>
<td>Probably very infectious</td>
</tr>
<tr>
<td>3+</td>
<td>Strongly positive</td>
<td>Probably very infectious</td>
</tr>
<tr>
<td>2+</td>
<td>Moderately positive</td>
<td>Probably infectious</td>
</tr>
<tr>
<td>1+</td>
<td>Moderately positive</td>
<td>Probably infectious</td>
</tr>
<tr>
<td>Actual number of AFB seen (no plus sign)</td>
<td>Weakly positive</td>
<td>Probably infectious</td>
</tr>
<tr>
<td>No AFB seen</td>
<td>Negative</td>
<td>May not be infectious</td>
</tr>
</tbody>
</table>

Study Questions 3.29

What are the 4 ways to collect sputum specimens? Indicate which procedure is the least expensive and easiest to perform.
**Module 3 – Targeted Testing and the Diagnosis of Latent Tuberculosis Infection and Tuberculosis Disease**

**Study Question 3.30**
What do laboratory personnel look for in a smear?

**Study Question 3.31**
What does a positive smear indicate about a patient’s infectiousness?

### Diagnosis of TB Disease

**Medical Evaluation**

5. **Bacteriologic Examination (continued)**

#### 5. Bacteriologic Examination (12)
**Nucleic Acid Amplification Tests (NAA)**
- NAA tests directly identify *M. tuberculosis* from sputum specimens by:
  - Amplifying (copying) DNA and RNA segments
  - Can help guide clinician’s decision for patient therapy and isolation
  - Does not replace need for AFB smear, culture, or clinical judgment

#### 5. Bacteriologic Examination (13)
**Nucleic Acid Amplification Tests (NAA)**
- If NAA test and AFB smears are positive:
  - Patient is presumed to have TB and should begin treatment
- If NAA test is negative and AFB smears are positive:
  - Patient may have nontuberculous mycobacteria infection (NTM)

#### 5. Bacteriologic Examination (14)
**Xpert MTB/RIF Assay**
- Xpert MTB/RIF assay is a NAA test that simultaneously detects *Mycobacterium tuberculosis* complex (MTBC) and resistance to rifampin
  - To conduct this test, a sputum sample is mixed with the reagent that is provided with the assay
  - A cartridge containing the mixture is placed in the GeneXpert machine
  - Results are available in less than 2 hours
5. Bacteriologic Examination (15) Xpert MTB/RIF Assay

- Results that are positive for MTBC and for rifampin resistance indicate that the bacteria have a high probability of resistance to rifampin
  - Should be confirmed by additional rapid testing
- If rifampin resistance is confirmed, rapid molecular testing for drug resistance to both first-line and second-line drugs should be performed so an effective treatment regimen can be selected

5. Bacteriologic Examination (16) Culturing and Identifying Specimen

- Culturing:
  - Determines if specimen contains \textit{M. tuberculosis}
  - Confirms diagnosis of TB disease
- All specimens should be cultured

5. Bacteriologic Examination (17) Culturing and Identifying Specimen

- Step 1: Detect growth of mycobacteria
  - Solid media: 3 to 6 weeks
  - Liquid media: 4 to 14 days
- Step 2: Identify organism that has grown
  - Nucleic acid probes: 2 to 4 hours

5. Bacteriologic Examination (18) Culturing and Identifying Specimen

- Positive culture: \textit{M. tuberculosis} identified in patient’s culture
  - Called \textit{M. tuberculosis} isolate
  - Confirms diagnosis of TB disease

5. Bacteriologic Examination (19) Culturing and Identifying Specimen

- Negative culture: \textit{M. tuberculosis} NOT identified in patient’s culture
  - Does not rule out TB disease
  - Some patients with negative cultures are diagnosed with TB based on signs and symptoms

5. Bacteriologic Examination (20) Culturing and Identifying Specimen

- Bacteriological examinations are important for assessing infectiousness and response to treatment
- Specimens should be obtained monthly until 2 consecutive cultures are negative
- Culture conversion is the most important objective measure of response to treatment
5. Bacteriologic Examination (21)
Drug Susceptibility Testing

- Conducted when patient is first found to have positive culture for TB
- Determines which drugs kill tubercle bacilli
- Tubercle bacilli killed by a particular drug are susceptible to that drug
- Tubercle bacilli that grow in presence of a particular drug are resistant to that drug

5. Bacteriologic Examination (22)
Drug Susceptibility Testing

- Tests should be repeated if:
  - Patient has positive culture after 3 months of treatment; or
  - Patient does not get better

5. Bacteriologic Examination (23)
Types of Drug-Resistant TB

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mono-resistant</td>
<td>Resistant to any one TB treatment drug</td>
</tr>
<tr>
<td>Poly-resistant</td>
<td>Resistant to at least any two TB drugs (but not both isoniazid and rifampin)</td>
</tr>
<tr>
<td>Multidrug-resistant (MDR TB)</td>
<td>Resistant to at least isoniazid and rifampin, the two best first-line TB</td>
</tr>
<tr>
<td></td>
<td>treatment drugs</td>
</tr>
<tr>
<td>Extensively drug-resistant</td>
<td>Resistant to isoniazid and rifampin, PLUS resistant to any fluoroquinolone</td>
</tr>
<tr>
<td>(XDR TB)</td>
<td>AND at least 1 of the 3 injectable second-line drugs (e.g., amikacin,</td>
</tr>
<tr>
<td></td>
<td>kanamycin, or capreomycin)</td>
</tr>
</tbody>
</table>

5. Bacteriologic Examination (24)
Growth-Based Drug Susceptibility Testing

- Growth-based susceptibility testing can be done using a liquid or solid medium method
- Organisms that grow in media containing a specific drug are considered resistant to that drug
- Liquid medium methods are faster than solid media methods for determining susceptibility to first-line TB medications
- Results can be obtained within 7 to 14 days for liquid medium method and up to 21 days for solid medium method

5. Bacteriologic Examination (25)
Molecular Detection of Drug Resistance

- Molecular tests provide preliminary guidance on effective therapy for TB patients
- These tests should be considered for patients with the following characteristics:
  - High risk of rifampin resistance, including MDR TB;
  - First-line drug susceptibility results are available and show resistance to rifampin;
  - Infectiousness poses a risk to vulnerable contacts; and
  - Contraindications to essential first-line medications

Culture Specimen
Study Question 3.32

Why is it necessary to culture a specimen?
Culture Specimen
Study Question 3.33
What does a positive culture for \textit{M. tuberculosis} mean? How is this important for the TB diagnosis?

Drug Susceptibility
Study Question 3.34
Why are drug susceptibility tests done?

Drug Susceptibility
Study Question 3.35
How often should drug susceptibility tests be done?

Reporting TB Cases

• TB programs report TB cases to CDC using a standard case report form called the \textit{Report of Verified Case of Tuberculosis} (RVCT)
  – All cases that meet criteria are called verified TB cases

Criteria for Reporting TB Cases (1)
Cases that meet one of these four sets of criteria are counted as verified TB cases:

1. Patient has positive culture for \textit{M. tuberculosis}
2. Patient has positive NAA test for \textit{M. tuberculosis}
   • NAA test must be accompanied by culture for mycobacteria species
Criteria for Reporting TB Cases (2)

3. Patient has positive AFB smear, but culture has not been obtained or is falsely negative or contaminated

4. In the absence of laboratory confirmation, patient meets all of the following criteria:
   - Positive TST or IGRA,
   - Other signs and symptoms of TB disease,
   - Treatment with 2 or more TB drugs, and
   - A completed diagnostic evaluation.

Criteria for Reporting TB Cases (3)

• Cases that do not meet any of these sets of criteria may be counted as a verified TB case if health care provider has reported the case and decided to treat the patient for TB disease

Module 3: Case Study 3.1
Which of the following patients have a positive TST reaction? Circle the best answer(s).

a. Mr. West, 36 yrs. old, HIV infected, 8 mm induration
b. Ms. Hernandez, 26 yrs. old, native of Mexico, 7 mm induration
c. Ms. Jones, 56 yrs. old, diabetic, 12 mm induration
d. Mr. Sung, 79 yrs. old, nursing home resident, 11 mm induration
e. Mr. Williams, 21 yrs. old, no known risk factors, 13 mm induration
f. Ms. Marcos, 42 yrs. old, chest x-rays findings suggestive of previous TB, 6 mm induration
g. Ms. Rayle, 50 yrs. old, husband has pulmonary TB, 9 mm of induration

Module 3: Case Study 3.2 (1)

A 30 year-old man who recently immigrated to the United States from India is given a TST and found to have 14 mm of induration. He reports that he was vaccinated with BCG as a child. He also says that his wife was treated for pulmonary TB disease last year.

Module 3: Case Study 3.2 (2)

How should this man’s results be interpreted?

What factors make it more likely that this man’s positive reaction is due to TB infection?
Module 3: Case Study 3.3 (1)

Mr. Bell comes to the TB clinic for a TST. He believes that he has been exposed to TB, and he knows he is at high risk for TB because he is HIV infected. He is given a TST, and his reaction is read 48 hours later as 0 mm of induration.

Module 3: Case Study 3.3 (2)

What are 3 ways to interpret this result?

Module 3: Case Study 3.4 (1)

Ms. Wilson is a 60-year-old nurse. When she started a job at the local hospital, she was given a TST, her first test in 25 years. Her reaction was read 48 hours later as 0 mm induration. Six months later, she was retested as part of the TB testing program in the unit where she works. Her skin test reaction was read 48 hours later as 11 mm of induration.

Module 3: Case Study 3.4 (2)

What are 2 ways to interpret this result?

Module 3: Case Study 3.5 (1)

Mr. Lee has a cough and other symptoms of TB disease, and he is evaluated with a chest x-ray. However, he is unable to cough up any sputum on his own for the bacteriologic examination.

Module 3: Case Study 3.5 (2)

What should be done?
Module 3: Case Study 3.6 (1)

Ms. Thompson gave three sputum specimens, which were sent to the laboratory for smear examination and culture. The smear results were reported as 4+, 3+, and 4+.

Module 3: Case Study 3.6 (2)

What do these results tell you about Ms. Thompson’s diagnosis and her infectiousness?

Module 3: Case Study 3.7 (1)

Mr. Sagoo has symptoms of TB disease and a cavity on his chest x-ray, but all of his sputum smears are negative for acid-fast bacilli.

Module 3: Case Study 3.7 (2)

Does this rule out the diagnosis of pulmonary TB disease?

Why or why not?

Module 3: Case Study 3.8 (1)

In the public health clinic, you see a patient, Ms. Sanchez, who complains of weight loss, fever, and a cough of 4 weeks duration. When questioned, she reports that she has been treated for TB disease in the past and that she occasionally injects heroin.

Module 3: Case Study 3.8 (2)

What parts of Ms. Sanchez’s medical history lead you to suspect TB disease?

What diagnostic tests should be done?