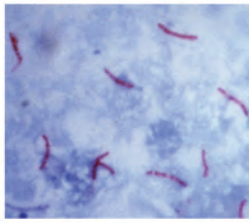
Core Curriculum on Tuberculosis:
What the Clinician Should Know



Sixth Edition 2013

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of Tuberculosis Elimination

CS234269

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Introduction to the Core Curriculum on Tuberculosis: What the Clinician Should Know

Sixth Edition 2013

Centers for Disease Control and Prevention

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention

Division of Tuberculosis Elimination

Introduction to the Core Curriculum on Tuberculosis: What the Clinician Should Know

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About the Core Curriculum on Tuberculosis: What the Clinician Should Know

Purpose

The *Core Curriculum on Tuberculosis: What the Clinician Should Know (Core Curriculum)* presents information about tuberculosis (TB) for health-care professionals. This document, produced by the Centers for Disease Control and Prevention (CDC) Division of Tuberculosis Elimination (DTBE), updates the 2000 *Core Curriculum*. It is intended for use as a reference manual for clinicians caring for persons with or at high risk for TB disease or infection. In addition, it was designed to be useful in developing educational programs. It is **not** meant to provide detailed answers to all public health or clinical questions about TB, **nor** is it meant as a substitute for any specific guidelines. It is anticipated that new guidelines will be published at future dates that will supersede information in the *Core Curriculum*, and these new guidelines will be posted on the CDC DTBE website: www.cdc.gov/tb.

An update on TB for clinicians is critical today. Research to find new treatment regimens and more effective use of current ones continues as multidrug-resistant and extensively drug-resistant TB cases challenge the public health community. The increased complexity of TB and HIV co-infection has required updated guidelines for prevention and treatment. Testing, diagnosis, and patient management and public health practice have also been revised.

Target Audience

The audience for this course includes clinicians who are caring for persons with or at high risk for TB disease or infection.

Goal

The goal of the *Core Curriculum* is to provide the reader with information about TB. Upon completion of this educational activity, the reader should possess a clear working knowledge of the diagnosis, treatment, and prevention of TB infection and disease.

Materials

The Curriculum

The *Core Curriculum* includes the following materials:

- Print-based self-study manual with the following 8 chapters:
  - Chapter 1. Overview of Tuberculosis Epidemiology in the United States
  - Chapter 2. Transmission and Pathogenesis of Tuberculosis
  - Chapter 3. Testing for Tuberculosis Infection and Disease
  - Chapter 4. Diagnosis of Tuberculosis
  - Chapter 5. Treatment of Latent Tuberculosis Infection
  - Chapter 6. Treatment of Tuberculosis Disease
  - Chapter 7. Tuberculosis Infection Control
  - Chapter 8. Community Tuberculosis Control
- Each chapter includes
  - Chapter objectives
  - Content topics with study questions
  - Chapter summary
  - References
- Appendix A–Glossary
- Appendix B–Answers to the study questions
- Appendix C–PowerPoint slides

Estimated Time for Completion

The curriculum is designed in a self-study format so that each person can work at his or her own pace. The actual time it takes to complete the *Core Curriculum* may differ from person to person. Listed below are estimates of the time needed to complete each chapter and the entire 8-chapter course.

Core Curriculum on Tuberculosis: What the Clinician Should Know
Estimated Time for Completion

Chapter	Title	Estimated Time for Completion
1	Overview of Tuberculosis Epidemiology in the United States	**15 minutes**
2	Transmission and Pathogenesis of Tuberculosis	**25 minutes**
3	Testing for Tuberculosis Infection and Disease	**45 minutes**
4	Diagnosis of Tuberculosis	**50 minutes**
5	Treatment of Latent Tuberculosis Infection	**55 minutes**
6	Treatment of Tuberculosis Disease	**100 minutes**
7	Tuberculosis Infection Control	**65 minutes**
8	Community Tuberculosis Control	**35 minutes**
	TOTAL	**6 hours and 30 minutes**

Study Questions

Study questions are included throughout each chapter to provide a review of the content and help the reader apply the content to real-life situations. The format of the questions includes either multiple choice or matching. For each question, select the ONE BEST ANSWER. Answers to the study questions are available in Appendix B.

PowerPoint Slide Set

The *Core Curriculum* is accompanied by a PowerPoint slide set for use in presentations and training programs. Images of the slides are included in Appendix C. The slide set may be downloaded from the CDC DTBE website at .

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If you would like to request a print copy of the *Core Curriculum*, please use the CDC publication online ordering system at www.cdc.gov/tb.

All copies are free of charge.

Course Objectives

The overall objectives for the entire *Core Curriculum* are listed below.

- Identify TB disease trends in the United States.
- Describe the transmission and pathogenesis of TB.
- Identify appropriate TB testing methods.
- Describe the five components of a TB medical evaluation.
- Describe LTBI treatment regimens.
- Describe treatment regimens for TB disease.
- List common adverse drug reactions to TB medications.
- Discuss the three levels of an effective TB infection control program.
- Describe the roles and responsibilities for TB control and prevention in the public and private health care sectors.

Continuing Education

Continuing education (CE) is offered free of charge for various professions based on approximately 6.5 hours of instruction. In order to receive CE credit/contact hours, you must complete an exam and course evaluation. No minimum score is necessary to receive credit/contact hours. Upon successful completion of the course, exam, and evaluation, your CE certificate will be issued by CDC Training and Continuing Education Online.

Continuing Education Registration and Test

You can register and take the test for CE credits/contact hours online for the Core Curriculum.

- Origination Date: February 15, 2011
- Renewal Date: February 15, 2013
- Expiration Date: Check the online registration website to determine the expiration date of the CE credits/contact hours.

Continuing Education Credits/Contact Hours

The following CE credits/contact hours are available free of charge for the *Core Curriculum*:

- **Continuing education units (CEUs)**
  The CDC has been approved as an Authorized Provider by the International Association for Continuing Education and Training (IACET), 1760 Old Meadow Road, Suite 500, McLean, VA 22102. The CDC is authorized by IACET to offer **0.6** ANSI/IACET CEUs for this program.
- **Continuing medical education (CMEs)**
  The CDC is accredited by the Accreditation Council for Continuing Medical Education (ACCME®) to provide continuing medical education for physicians.

The CDC designates this **enduring material** for a maximum of **6.5** *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

- **Continuing nursing education (CNEs)**
  The CDC is accredited as a provider of Continuing Nursing Education by the American Nurses Credentialing Center's Commission on Accreditation.

  This activity provides **6.5** contact hours.
- **Continuing education contact hours in health education (CECH)**
  Sponsored by the CDC, a designated provider of continuing education contact hours (CECH) in health education by the National Commission for Health Education Credentialing, Inc. This program is designed for Certified Health Education Specialists (CHES) and/or Master Certified Health Education Specialists (MCHES) to receive up to **6.5** Category I continuing education contact hours. Maximum advanced level continuing education contact hours available are **0**. CDC provider number **GA0082**.

Online Registration and Test

To receive continuing education, you must register for this specific course and submit an evaluation at the CDC Training and Continuing Education Online website.

- Go to www2a.cdc.gov/TCEonline
- Log in as a participant. (Note: If you are a first-time user of this online system, you will need to log in as a new participant and create a participant profile.)
  - » When you receive your reset password by e-mail, log in as a participant and change the password.
- At Participant Services, click on Search and Register, type a keyword from the course title into the keyword search, such as "Core," and click View. You can also find the course by typing in the course number. The course number for this activity is **SS1604**.
- Click on the title, *Core Curriculum on Tuberculosis*, select the type of credit/contact hours you wish to receive at the bottom, and click Submit.
- Verify the demographic information and click Submit at the bottom.
- Complete the course evaluation.
- Complete the course posttest (if applicable).
- At Participant Services, click on Certificates and Transcripts and print your continuing education certificate.

For assistance with the online system, call 1(800)-41-TRAIN Monday through Friday from 8:00 AM to 4:00 PM Eastern Standard Time, or e-mail ce@cdc.gov.

Disclosure Statement

CDC, our planners, and our reviewers wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters. Planners have reviewed content to ensure there is no bias.

Content does not include any discussion of the unlabeled use of a product or a product under investigation with the exception of Levofloxacin, Moxifloxacin, Gatifloxacin, and Rifabutin.

The CDC does not accept commercial support.

Key Tuberculosis Resources

Tuberculosis Reporting, Guidelines, and Recommendations

Clinicians should immediately contact their state health department if they have a patient with suspected or confirmed TB disease. The health department can assist in providing guidance and overall public health management of the patient. Contact information for each state TB control office can be found at www.cdc.gov/tb/links/tboffices.htm.

For additional information about TB guidelines and recommendations, contact the following sources:

- CDC DTBE website: www.cdc.gov/tb
- TB Regional Training and Medical Consultation Centers (RTMCCs): http://www.cdc.gov/tb/education/rtmc/default.htm
- American Lung Association: www.lungusa.org/
- American Thoracic Society: www.thoracic.org

Additional Education and Training Resources

- Find TB Resources website: www.findtbresources.org
- TB Regional Training and Medical Consultation Centers product list: https://sntc.medicine.ufl.edu/rtmccproducts.aspx

Content Experts

Content experts included staff from the Centers for Disease Control and Prevention, Division of Tuberculosis Elimination.

For Additional Information

For additional information on TB, visit the CDC DTBE website at www.cdc.gov/tb. If you have questions on state-specific TB guidelines, please contact your state TB control office. A list of state TB control offices can be found on the CDC DTBE website at www.cdc.gov/tb/links/tboffices.htm

Chapter 1
Overview of Tuberculosis Epidemiology in the United States

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Chapter Objectives

After working through this chapter, you should be able to

- Discuss progress toward tuberculosis (TB) elimination in the United States;
- Identify TB disease trends in the United States; and
- List the racial and ethnic groups that are disproportionately affected by TB disease in the United States.

Progress Toward TB Elimination in the United States

In 1989, the Centers for Disease Control and Prevention (CDC) announced the goal of eliminating TB from the United States by the year 2010. A Strategic Plan for the Elimination of Tuberculosis in the United States was published in 1989 and reassessed in 1999 to identify the actions necessary to achieve elimination. The achievement of this goal was thwarted by the TB resurgence that occurred in the late 1980s and early 1990s. This resurgence was fueled by the following factors:

- The onset of the human immunodeficiency virus (HIV) epidemic;
- Increases in immigration of persons from countries where TB disease was common;
- TB transmission in congregate settings; and
- The development of multidrug-resistant (MDR) TB.

These factors occurred at a time when decades of cuts in funding had resulted in inadequate support for TB control and other public health efforts, and in the deterioration of TB control programs. As a result, federal, state, and local TB control officials had very few resources for TB control activities. Subsequently, the United States renewed its commitment to TB control in the 1990s and mobilized new resources. In 1993, the upward trend of new TB cases reversed, and the number of new cases has continued its decline up to and through 2011. This can be attributed to the increase in funds and resources which enabled TB programs to improve their control efforts to

- Promptly identify persons with TB disease;
- Start appropriate treatment for persons with TB disease; and
- Ensure patients complete treatment.

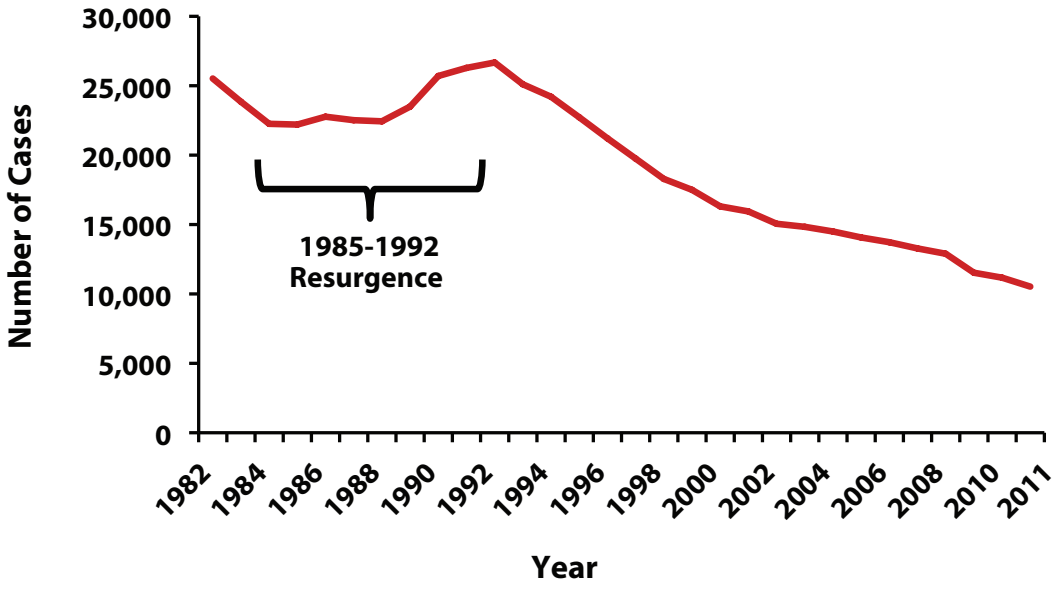
Despite unprecedented low rates of TB disease, elimination of TB faces some major barriers including

- TB disease in high-risk populations where it is difficult to detect, diagnose, and treat;
- Persistence and growth of the global TB epidemic; and
- Limitations of current control measures and the need for new tests and treatments, including an effective vaccine.

TB Disease Trends in the United States, 1982–2011

The resurgence of TB disease, which began in the mid-1980s, was marked by several years of increasing case counts until its peak in 1992. Case counts began decreasing in 1993, and 2011 marked the 19th year of decline in the total number of TB cases reported in the United States since the peak of the resurgence (Figure 1.1). From 1993 until 2002, the total number of TB cases decreased 5%–7% annually. Although rates continued to decline from 2003 through 2008, it was at a much slower rate. However, an unprecedented decline occurred in 2009, when the total number of TB cases decreased by more than 10% from 2008 to 2009. In 2011, a total of 10,528 TB cases were reported. This represents a decline of 5.8% from 2010 (Table 1.1).

Fig 1.1
Reported TB Cases*
United States, 1982–2011



*Updated as of June 25, 2012.

Table 1.1
TB Morbidity
United States, 2006–2011

Year	No.	Rate*
2006	13,727	4.6
2007	13,278	4.4
2008	12,895	4.2
2009	11,528	3.8
2010	11,171	3.6
2011	10,528	3.4

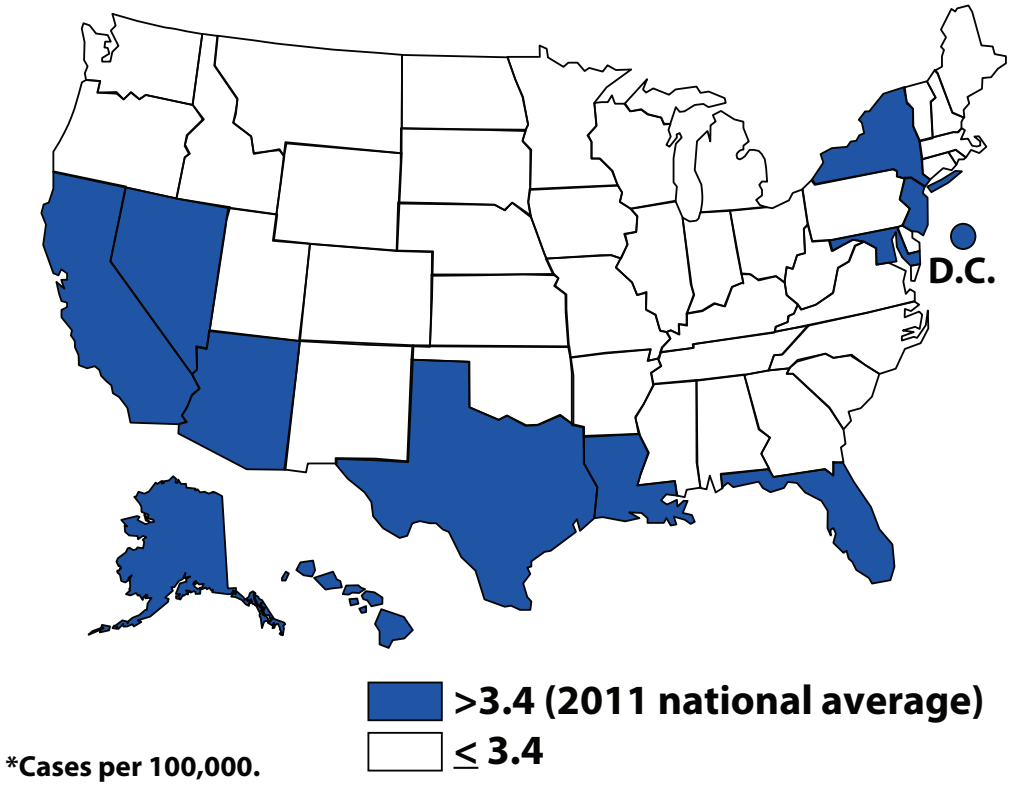
*Cases per 100,000, updated as of June 25, 2012

While national trends indicate that there has been a decline in the overall number of cases since 1993, cases continue to be reported. It is important to focus on local epidemiology to identify trends in individual states or regions.

While national trends indicate that there has been a decline in the overall number of cases since 1993, cases continue to be reported.

In 2011, a total of 38 states reported a rate less than or equal to 3.4 TB cases per 100,000, the 2011 national average. Twelve states and D.C. reported a rate above 3.4 TB cases per 100,000; these areas accounted for 67% of the national total in 2011 and have also experienced substantial overall decreases in cases and rates from 1992 through 2011 (Figure 1.2).

Figure 1.2
TB Case Rates*
United States, 2011



*Cases per 100,000.

TB Case Rates by Origin

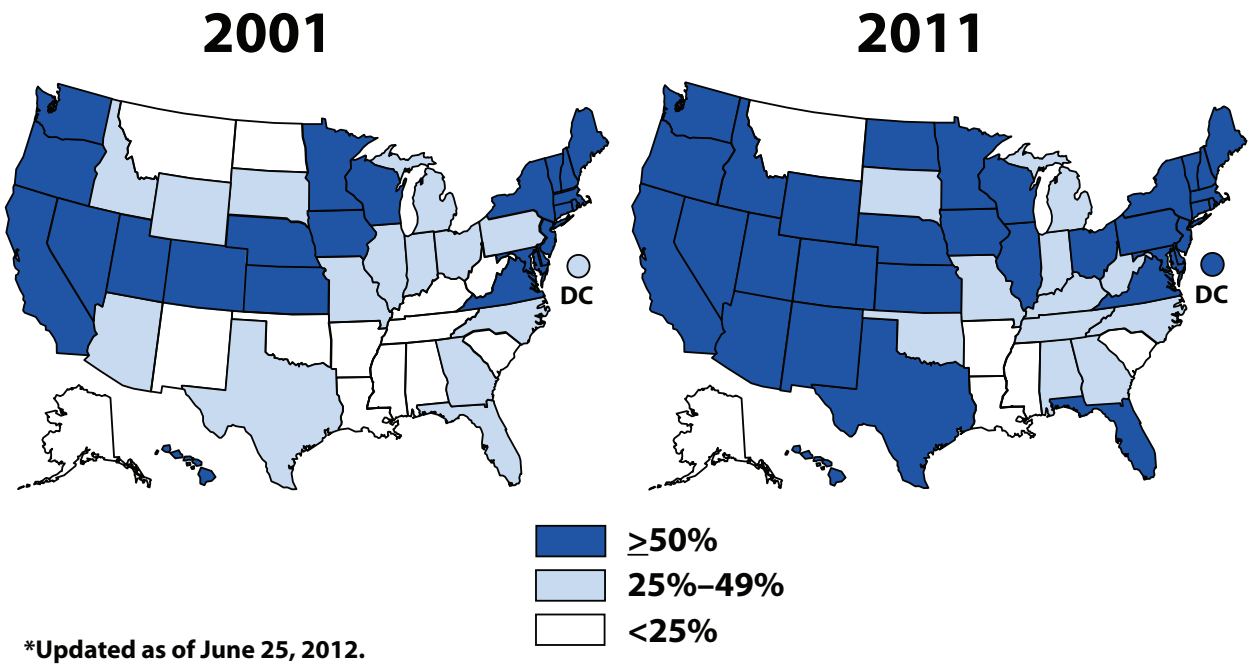
During 1993 to 2003, rates declined in both the U.S.-born and the foreign-born populations; however, the decline was substantially less among foreign-born populations. In 2002, for the first time, TB cases among foreign-born persons accounted for the majority (51.2%) of TB cases in the United States. Overall, the number of cases in foreign-born persons has remained virtually level with approximately 7,000–8,000 cases each year, until 2009 when the number dropped to 6,854. That decreasing trend continued in 2011 with the number of cases in foreign-born persons dropping to 6,510. The number of cases in U.S.-born persons decreased from more than 17,000 in 1993 to 3,981 in 2011.

In 2002, for the first time, TB cases among foreign-born persons accounted for the majority (51.2%) of TB cases in the United States.

Percentage of TB Cases among Foreign-Born Persons in the United States, 2001–2011

The percentage range of the total number of TB cases that occurred in foreign-born persons in each state is high¬lighted for 2001 and 2011 in side-by-side maps (Figure 1.3). The number of states with less than 25% of their TB cases among foreign-born persons decreased from 13 states in 2001 to 6 states in 2011. The number of states with 25%-49% of cases among foreign-born persons decreased from 14 states in 2001 to 11 states in 2011. However, the number of states that had 50% or more of their cases among foreign-born persons increased from 23 states in 2001 to 34 states in 2011.

Figure 1.3
Percentage of TB Cases Among Foreign-Born Persons
United States, 2001–2011*



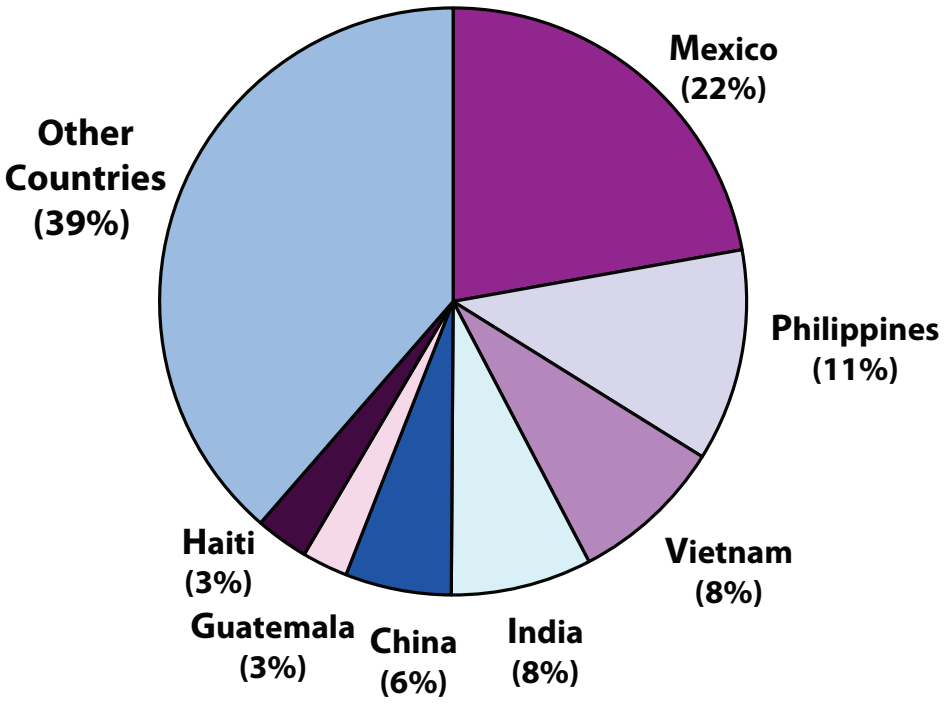
*Updated as of June 25, 2012.

The countries of birth of foreign-born persons reported with TB disease in the United States have remained relatively constant since 1986. Seven countries accounted for 61% of the total cases in foreign-born persons in 2011 (Table 1.2 and Figure 1.4).

Table 1.2
Countries of Birth of Foreign-Born Persons Reported with TB in the United States, 2011

Country	Percent of Total Foreign-Born Cases in the United States
Mexico	22%
Philippines	11%
Vietnam	8%
India	8%
China	6%
Guatemala	3%
Haiti	3%
Other Countries (135)	39%

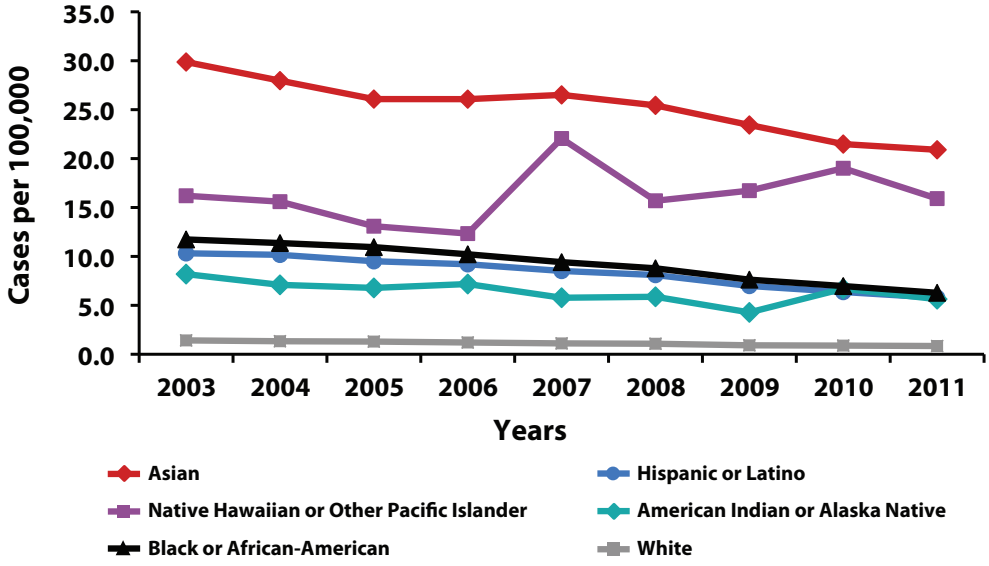
Figure 1.4
Countries of Birth of Foreign-Born Persons Reported with TB United States, 2011



Race and Ethnicity

Figure 1.5 shows the declining trend in TB rates by race/ethnicity during the years 2003–2011. Asians had the highest TB rates, which declined from 29.9 per 100,000 in 2003 to 20.9 in 2011, and had a percent decline over the time period of 30%. Rates also declined in the following racial/ethnic groups: among non-Hispanic blacks or African-Americans, from 11.7 in 2003 to 6.3 in 2011 (-46%); among Hispanics, from 10.3 to 5.8 (-44%); among American Indians and Alaska Natives, from 8.2 to 5.6 (-32%); and among non-Hispanic whites, from 1.4 to 0.8 (-43%). Rates decreased among Native Hawaiian or Other Pacific Islanders after two years of increase since 2008, from 16.2 in 2003 to 15.9 in 2011(-2%).

Figure 1.5
TB Case Rates by Race/Ethnicity*
United States, 2003–2011**



*All races are non-Hispanic
**Updated as of June 25, 2012.

Several important factors likely contribute to the disproportionate burden of TB in minorities, including the following:

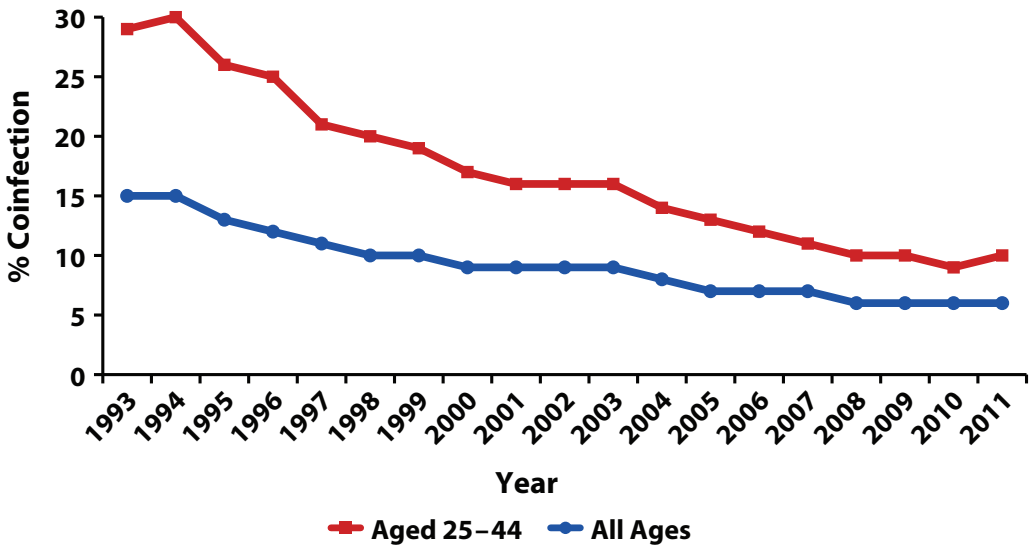
- Infection acquired in the country of origin in foreign-born minorities;
- Unequal distribution of TB risk factors contributing to
  - » An increased exposure to TB
  - » An increased risk of developing TB disease once infected with *M. tuberculosis* (e.g., HIV infection);
- Lower socioeconomic status and the effects of crowding

HIV-Infected Persons

HIV-infected persons are at high risk for developing TB disease after infection with *M. tuberculosis*. In the age group of 25–44 among persons reported with TB disease, the percentage of HIV coinfection declined from a high of 29% in 1993 to 10% in 2011. In all ages, the percentage of HIV coinfection decreased from 15% in 1993 to 6% in 2011.

Figure 1.6 provides minimum estimates of HIV coinfection among persons reported with TB from 1993 through 2011. Since the addition of the request for HIV status to the individual TB case report in 1993, incomplete reporting has provided a challenge to calculating reliable estimates. Results from the cross-matching of TB and AIDS registries have been used to supplement reported HIV test results.

Figure 1.6
Estimated HIV Coinfection in Persons Reported with TB
United States, 1993–2011*



*Updated as of June 25, 2012

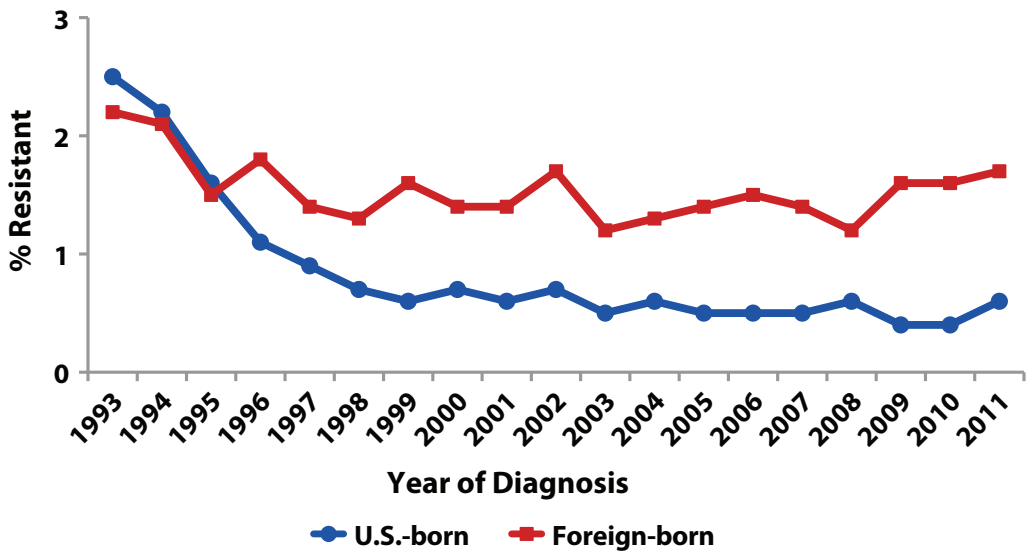
Note: Minimum estimates based on reported HIV-positive status among all TB cases in the age group.

HIV-infected persons are at high risk for developing TB disease after infection with *M. tuberculosis*.

Multidrug-Resistant TB

Multidrug-resistant TB (MDR TB) is caused by an organism that is resistant to at least isoniazid and rifampin, the two most potent TB drugs; it is a serious public health concern. Both U.S.-born and foreign-born persons had decreases in the number and percentage of cases of MDR TB, although the decline in U.S.-born persons has been greater (Figure 1.7). As a result, the percentage of all primary MDR TB cases reported and associated with being foreign born increased from approximately 25% of all MDR TB cases in 1993 to 83% in 2011.

Figure 1.7
Primary MDR TB in U.S.-Born vs. Foreign-Born Persons
United States, 1993– 2011*



*Updated as of June 25, 2012.

Note: Based on initial isolates from persons with no prior history of TB. MDR TB defined as resistance to at least isoniazid and rifampin.

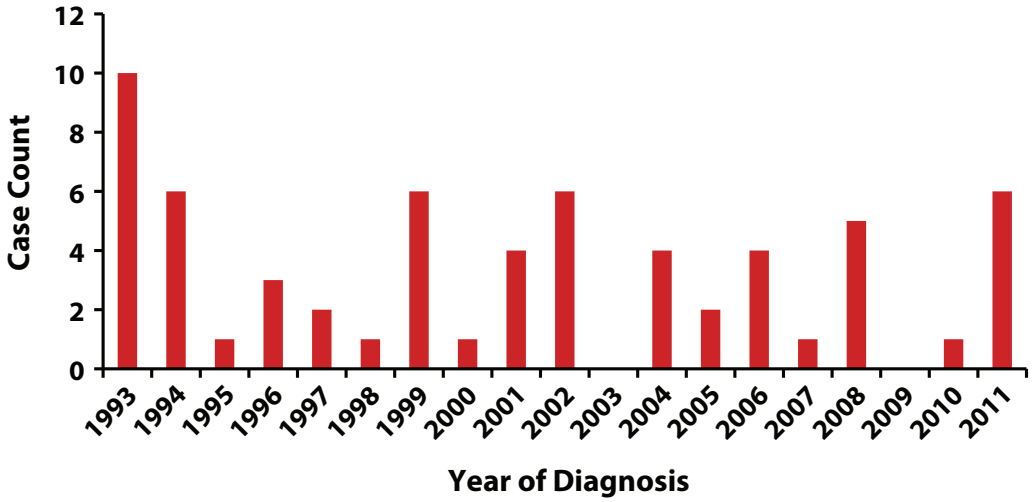
Primary MDR TB cases reported in foreign-born persons increased from approximately 25% of all MDR cases in 1993 to 83% in 2011.

Extensively Drug-Resistant TB

Extensively drug-resistant TB (XDR TB) is a rare type of MDR TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin). For 1993–2011, the annual numbers of reported XDR TB cases, as determined by the initial drug-susceptibility test (DST), are shown below (Figure 1.8). There is no apparent trend in the number of XDR TB cases over time in the United States. The greatest number of cases reported in a single year that met the XDR TB case definition was 10 in 1993. There were no cases reported in 2003 or 2009. One case of XDR TB was reported in 2010 and six cases in 2011.

There is no apparent trend in the number of XDR TB cases over time in the United States.

Figure 1.8
XDR TB Case Count Defined on Initial DST* by Year 1993–2011**



* Drug susceptibility test
** Updated as of June 25, 2012.

Note: Extensively drug-resistant TB (XDR TB) is defined as resistance to isoniazid and rifampin, plus resistance to any fluoroquinolone and at least one of three injectable second-line anti-TB drugs.

Identifying Groups at High Risk for TB

The decrease in TB cases and MDR TB is encouraging; however, the earlier resurgence of TB provides a valuable lesson. Every TB case is a potential outbreak. Health departments must be prepared to identify promptly and treat persons who have active TB disease, as well as identify and treat close contacts who may have become infected from persons with active TB disease. By understanding which groups are at higher risk for becoming infected with *M. tuberculosis*, health departments can better focus TB prevention and control efforts (Table 1.3).

Table 1.3
Persons at Higher Risk for Exposure to and/or Infection with *M. tuberculosis*

Description
• Close contacts of persons known or suspected to have TB disease
• Foreign-born persons from areas that have a high incidence of TB disease (e.g., Africa, Asia, Eastern Europe, Latin America, and Russia)
• Persons who visit areas with a high prevalence of TB disease, especially if visits are frequent or prolonged
• Residents and employees of high-risk congregate settings (e.g., correctional facilities, long-term care facilities, and homeless shelters)
• Health-care workers who serve clients who are at increased risk for TB disease
• Populations defined locally as having an increased incidence of latent *M. tuberculosis* infection or TB disease, possibly including medically underserved, low-income populations, or persons who abuse drugs or alcohol
• Infants, children, and adolescents exposed to adults who are at increased risk for latent tuberculosis infection or TB disease

Study Questions

1.1 In 2011, how many TB cases were reported from the 50 states and D.C.?
(circle the one best answer)

A. 5,466

B. 10,528

C. 21,553

1.2 Which of the following statements is true about TB case rates between 1993 and 2011?
(circle the one best answer)

A. Rates increased in both foreign-born populations and U.S.-born populations.

B. Rates decreased in both foreign-born populations and U.S.-born populations.

C. Rates remained level in both foreign-born populations and U.S.-born populations.

The following countries of birth of foreign-born persons accounted for 61% of the total number of TB cases in the United States in 2011. Match the country of birth with its percentage of total TB cases among foreign-born persons. (Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Country of Birth	Percent of Total TB Cases in Foreign-Born Persons in the United States, 2011 (Answers may be used more than once)
____ **1.3** China	**A.** 3%
____ **1.4** Guatemala	**B.** 6%
____ **1.5** Haiti	**C.** 8%
____ **1.6** India	**D.** 11%
____ **1.7** Mexico	**E.** 22%
____ **1.8** Philippines	
____ **1.9** Vietnam	

1.10 Which of the following statements about trends in TB rates by race/ethnicity in the United States, from 2003 to 2011, are true? (circle the one best answer)

A. Rates declined among Asians and Pacific Islanders from 29.9 per 100,000 in 2003 to 20.9 in 2011.

B. Rates declined by at least 22% among non-Hispanic blacks or African Americans, Hispanics, American Indians and Alaska Natives, and non-Hispanic whites from 2003 to 2011.

C. Rates increased among Hispanics, from 8.1 per 100,000 in 2003 to 19.9 in 2011.

D. A, B, and C are all correct.

E. Only A and B are correct.

1.11 Which of the following factors contribute to the disproportionate burden of TB disease in minorities? (circle the one best answer)

A. Infection acquired in the country of origin in foreign-born minorities.

B. Unequal distribution of TB risk factors (e.g., HIV), contributing to increased exposure to TB disease or to an increased risk of developing TB disease once infected with *M. tuberculosis*.

C. Lower socioeconomic status and the effects of crowding.

D. A, B, and C are all correct.

E. Only A and B are correct.

1.12 Which of the following statements about MDR TB and XDR TB in the United States are true? (circle the one best answer)

A. Primary MDR TB cases reported in foreign-born persons increased from approximately 25% among all MDR TB cases in 1993 to 83% in 2011.

B. There is no apparent trend in the number of XDR TB cases over time in the United States.

C. The annual number of cases of counted XDR TB cases during 1993–2011 was 160.

D. A, B, and C are correct.

E. Only A and B are correct.

1.13 Of the following persons, who is LEAST likely to be exposed to TB disease? (circle the one best answer)

A. Trang was born in Vietnam and recently immigrated to the United States.

B. Frank lives in a homeless shelter.

C. Joshua attends high school in Canton, Ohio.

D. Ellen is a nurse at the Texas State Penitentiary at Huntsville.

Chapter Summary

The resurgence of TB disease, which began in the mid-1980s, was marked by several years of increasing case counts until its peak in 1992. Case counts began decreasing in 1993, and 2011 marked the 19th year of decline in the total number of TB cases reported in the United States since the peak of the resurgence. From 1993 until 2002, the total number of TB cases decreased 5%–7% annually. Although rates continued to decline from 2003 through 2008, it was at a much slower rate. However, an unprecedented decline occurred in 2009, when the total number of TB cases decreased by more than 10% from 2008 to 2009. In 2011, a total of 10,528 TB cases were reported. This represents a decline of 5.8% from 2010.

HIV-infected persons are at high risk for developing TB disease after infection with *M. tuberculosis*. In the age group of 25–44 among persons reported with TB disease, the percentage of HIV coinfection declined from a high of 29% in 1993 to 10% in 2011. In all ages, the percentage of HIV coinfection decreased from 15% in 1993 to 6% in 2011.

MDR TB is caused by an organism that is resistant to at least isoniazid and rifampin, the two most potent TB drugs; it is a serious public health concern. Both U.S.-born and foreign-born persons had decreases in the number and percentage of cases of MDR TB, although the decline in U.S.-born persons has been greater. As a result, the percentage of all primary MDR TB cases reported and associated with being foreign-born increased from approximately 25% of all MDR TB cases in 1993 to 83% in 2011.

There is no apparent trend in the number of XDR TB cases over time in the United States. The greatest number of cases reported in a single year that met XDR TB case definition was 10 in 1993. There were no cases reported in 2003 or 2009. One case of XDR TB was reported in 2010 and six cases in 2011.

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Chapter 2
Transmission and Pathogenesis of Tuberculosis

Table of Contents

Chapter Objectives

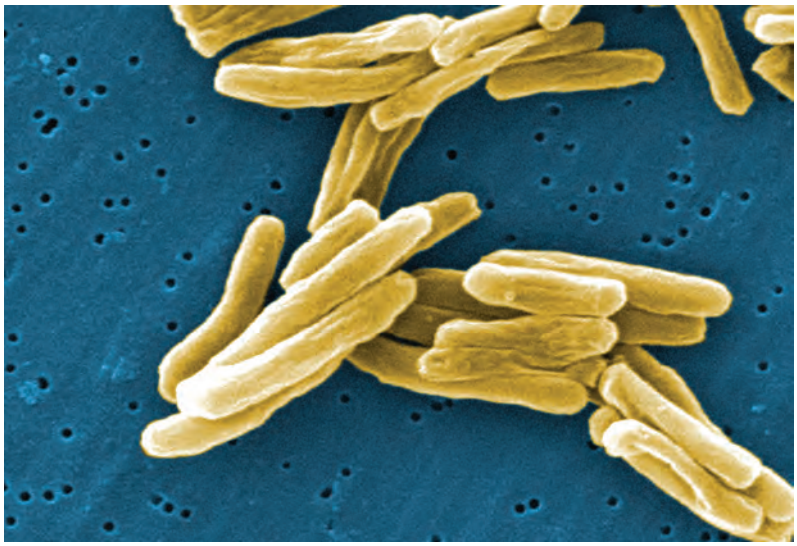
After working through this chapter, you should be able to

- Identify ways in which tuberculosis (TB) is spread;
- Describe the pathogenesis of TB;
- Identify conditions that increase the risk of TB infection progressing to TB disease;
- Define drug resistance; and
- Describe the TB classification system.

Introduction

TB is an airborne disease caused by the bacterium *Mycobacterium tuberculosis* (*M. tuberculosis*) (Figure 2.1). *M. tuberculosis* and seven very closely related mycobacterial species (*M. bovis, M. africanum, M. microti, M. caprae, M. pinnipedii, M. canetti* and *M. mungi*) together comprise what is known as the *M. tuberculosis* complex. Most, but not all, of these species have been found to cause disease in humans. In the United States, the majority of TB cases are caused by *M. tuberculosis*. *M. tuberculosis* organisms are also called tubercle bacilli.

Figure 2.1
Mycobacterium tuberculosis

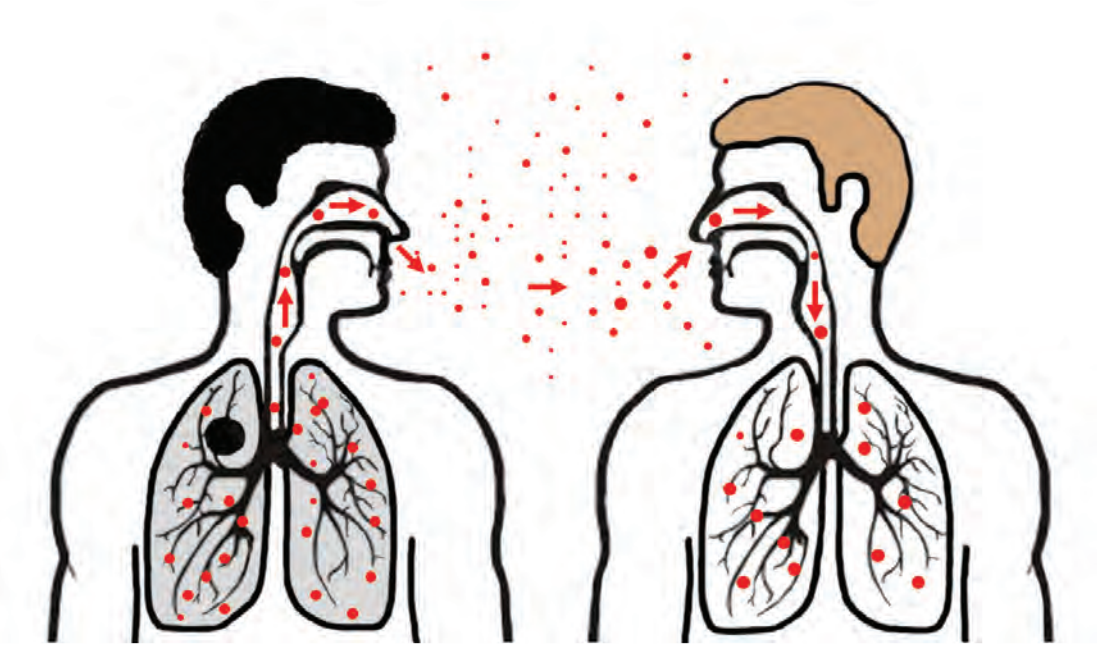


Transmission of TB

M. tuberculosis is carried in airborne particles, called droplet nuclei, of 1–5 microns in diameter. Infectious droplet nuclei are generated when persons who have pulmonary or laryngeal TB disease cough, sneeze, shout, or sing. Depending on the environment, these tiny particles can remain suspended in the air for several hours. *M. tuberculosis* is transmitted through the air, **not** by surface contact. Transmission occurs when a person inhales droplet nuclei containing *M. tuberculosis*, and the droplet nuclei traverse the mouth or nasal passages, upper respiratory tract, and bronchi to reach the alveoli of the lungs (Figure 2.2).

***M. tuberculosis* is carried in airborne particles, called droplet nuclei, of 1–5 microns in diameter. Infectious droplet nuclei are generated when persons who have pulmonary or laryngeal TB disease cough, sneeze, shout, or sing.**

Figure 2.2
Transmission of TB
TB is spread from person to person through the air. The dots in the air represent droplet nuclei containing tubercle bacilli.



Factors that Determine the Probability of *M. tuberculosis* Transmission

There are four factors that determine the probability of transmission of *M. tuberculosis* (Table 2.1).

Table 2.1
Factors that Determine the Probability of Transmission of *M. tuberculosis*

Factor	Description
Susceptibility	Susceptibility (immune status) of the exposed individual
Infectiousness	Infectiousness of the person with TB disease is directly related to the number of tubercle bacilli that he or she expels into the air. Persons who expel many tubercle bacilli are more infectious than patients who expel few or no bacilli (Table 2.2) (see Chapter 7, TB Infection Control)
Environment	Environmental factors that affect the concentration of *M. tuberculosis* organisms (Table 2.3)
Exposure	Proximity, frequency, and duration of exposure (Table 2.4)

Table 2.2
Characteristics of a Patient with TB Disease that Are Associated with Infectiousness

Factor	Description
Clinical	• Presence of cough, especially lasting 3 weeks or longer • Respiratory tract disease, especially with involvement of the larynx (highly infectious) • Failure to cover the mouth and nose when coughing • Inappropriate or inadequate treatment (drugs, duration)
Procedure	• Undergoing cough-inducing or aerosol-generating procedures (e.g., bronchoscopy, sputum induction, administration of aerosolized medications)
Radiographic and laboratory	• Cavitation on chest radiograph • Positive culture for *M. tuberculosis* • Positive AFB sputum smear result

The infectiousness of a person with TB disease is directly related to the number of tubercle bacilli that he or she expels into the air. Persons who expel many tubercle bacilli are more infectious than patients who expel few or no bacilli.

Table 2.3
Environmental Factors that Enhance the Probability that *M. tuberculosis* Will Be Transmitted

Factor	Description
Concentration of infectious droplet nuclei	The more droplet nuclei in the air, the more probable that *M. tuberculosis* will be transmitted
Space	Exposure in small, enclosed spaces
Ventilation	Inadequate local or general ventilation that results in insufficient dilution or removal of infectious droplet nuclei
Air circulation	Recirculation of air containing infectious droplet nuclei
Specimen handling	Improper specimen handling procedures that generate infectious droplet nuclei
Air Pressure	Positive air pressure in infectious patient's room that causes *M. tuberculosis* organisms to flow to other areas

Table 2.4
Proximity and Length of Exposure Factors that Can Affect Transmission of *M. tuberculosis*

Factor	Description
Duration of exposure to a person with infectious TB	The longer the duration of exposure, the higher the risk for transmission
Frequency of exposure to infectious person	The more frequent the exposure, the higher the risk for transmission
Physical proximity to infectious person	The closer the proximity, the higher the risk for transmission

Young children with pulmonary and laryngeal TB disease are less likely than adults to be infectious. This is because children generally do **not** produce sputum when they cough. However, transmission from children can occur. Therefore, children and adolescents with TB disease should be evaluated for infectiousness using the same criteria as adults. These criteria include presence of cough lasting 3 weeks or longer; cavitation on chest radiograph; or respiratory tract disease with involvement of lungs, airways, or larynx (see Chapter 3, Testing for Tuberculosis Infection and Disease).

Young children with pulmonary and laryngeal TB disease are less likely than adults to be infectious.

Study Questions

2.1 How is TB spread? (circle the one best answer)

A. From sharing eating utensils with an infected person.

B. From person to person through the air.

C. From insect bites.

D. From touching surfaces that are contaminated with *M. tuberculosis*.

2.2 The probability that *M. tuberculosis* will be transmitted depends on… (circle the one best answer)

A. Susceptibility (immune status) of the exposed individual.

B. Infectiousness of the person with TB.

C. Proximity, frequency, and duration of exposure.

D. Environmental factors that affect the concentration of *M. tuberculosis* organisms.

E. A, B, C, and D are correct.

Are the following statements about infectiousness true or false? (Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Statement about Infectiousness		True or False
____ **2.3**	The infectiousness of a person with TB disease is directly related to the number of tubercle bacilli that he or she expels into the air.	**A.** True **B.** False
____ **2.4**	Persons who expel few or no tubercle bacilli are just as infectious as those who expel many bacilli.	

2.5 Which of the following environmental factors do NOT increase the probability that *M. tuberculosis* will be transmitted? (circle the one best answer)

A. Exposure in small enclosed spaces.

B. Inadequate local or general ventilation that results in insufficient dilution or removal of infectious droplet nuclei.

C. Recirculation of air containing infectious droplet nuclei.

D. Improper specimen handling procedures that generate infectious droplet nuclei.

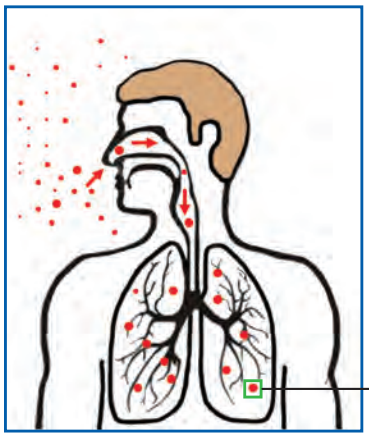
E. Negative pressure in an infectious TB patient's room.

Pathogenesis of TB

Infection occurs when a person inhales droplet nuclei containing tubercle bacilli that reach the alveoli of the lungs. These tubercle bacilli are ingested by alveolar macrophages; the majority of these bacilli are destroyed or inhibited. A small number may multiply intracellularly and are released when the macrophages die. If alive, these bacilli may spread by way of lymphatic channels or through the bloodstream to more distant tissues and organs (including areas of the body in which TB disease is most likely to develop: regional lymph nodes, apex of the lung, kidneys, brain, and bone). This process of dissemination primes the immune system for a systemic response. Further details about pathogenesis of latent tuberculosis infection (LTBI) and TB disease are described in Figure 2.3.

Figure 2.3
Pathogenesis of LTBI and TB Disease

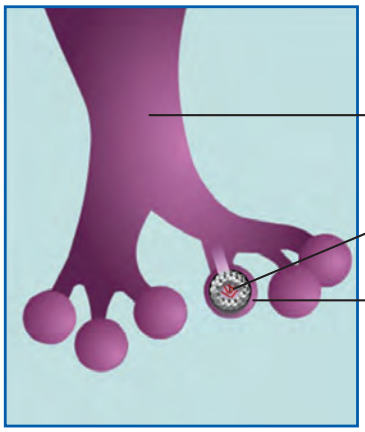
1.



Area of detail for boxes 2, 4, and 5

Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to the alveoli.

2.



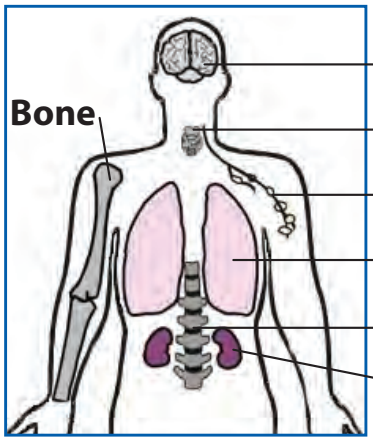
Bronchiole

Tubercle bacilli

Alveoli

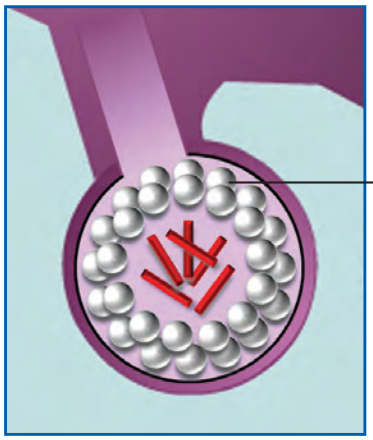
Tubercle bacilli multiply in the alveoli.

3.



A small number of tubercle bacilli enter the bloodstream and spread throughout the body. The tubercle bacilli may reach any part of the body, including areas where TB disease is more likely to develop (such as the brain, larynx, lymph node, lung, spine, bone, or kidney).

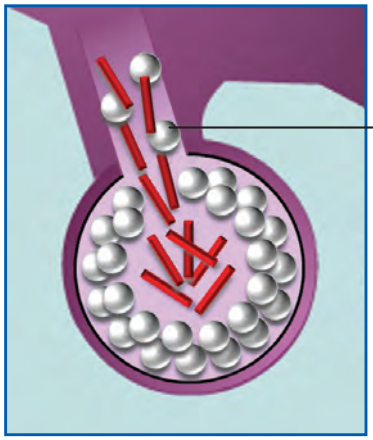
4.



Special immune cells form a barrier shell (in this example, bacilli are in the lungs)

Within 2 to 8 weeks, special immune cells called macrophages ingest and surround the tubercle bacilli. The cells form a barrier shell, called a granuloma, that keeps the bacilli contained and under control **(LTBI)**.

5.



Shell breaks down and tubercle bacilli escape and multiply

If the immune system **cannot** keep the tubercle bacilli under control, the bacilli begin to multiply rapidly (**TB disease**). This process can occur in different areas in the body, such as the lungs, kidneys, brain, or bone (see diagram in box 3).

Infection occurs when a person inhales droplet nuclei containing tubercle bacilli that reach the alveoli of the lungs.

Latent Tuberculosis Infection (LTBI)

Persons with LTBI have *M. tuberculosis* in their bodies, but do **not** have TB disease and **cannot** spread the infection to other people. A person with LTBI is **not** regarded as having a case of TB. The process of LTBI begins when extracellular bacilli are ingested by macrophages and presented to other white blood cells. This triggers the immune response in which white blood cells kill or encapsulate most of the bacilli, leading to the formation of a granuloma. At this point, LTBI has been established. LTBI may be detected by using the tuberculin skin test (TST) or an interferon-gamma release assay (IGRA) (see Chapter 3, Testing for Tuberculosis Disease and Infection). It can take 2 to 8 weeks after the initial TB infection for the body's immune system to be able to react to tuberculin and for the infection to be detected by the TST or IGRA. Within weeks after infection, the immune system is usually able to halt the multiplication of the tubercle bacilli, preventing further progression.

Persons with LTBI have *M. tuberculosis* in their bodies, but do not have TB disease and cannot spread the infection to other people.

TB Disease

In some people, the tubercle bacilli overcome the immune system and multiply, resulting in progression from LTBI to TB disease (Figure 2.4). Persons who have TB disease are usually infectious and may spread the bacteria to other people. The progression from LTBI to TB disease may occur at any time, from soon to many years later. Body fluid or tissue from the disease site should be collected for AFB smear and culture (see Chapter 5, Treatment for Latent Tuberculosis Infection). Positive culture for *M. tuberculosis* confirms the diagnosis of TB disease. Table 2.5 indicates the differences between LTBI and TB disease.

Persons who have TB disease may spread the bacteria to other people.

Figure 2.4
Progression of TB
People who are exposed to *M. tuberculosis* may or may **not** develop LTBI.
People with LTBI may or may **not** develop TB disease.

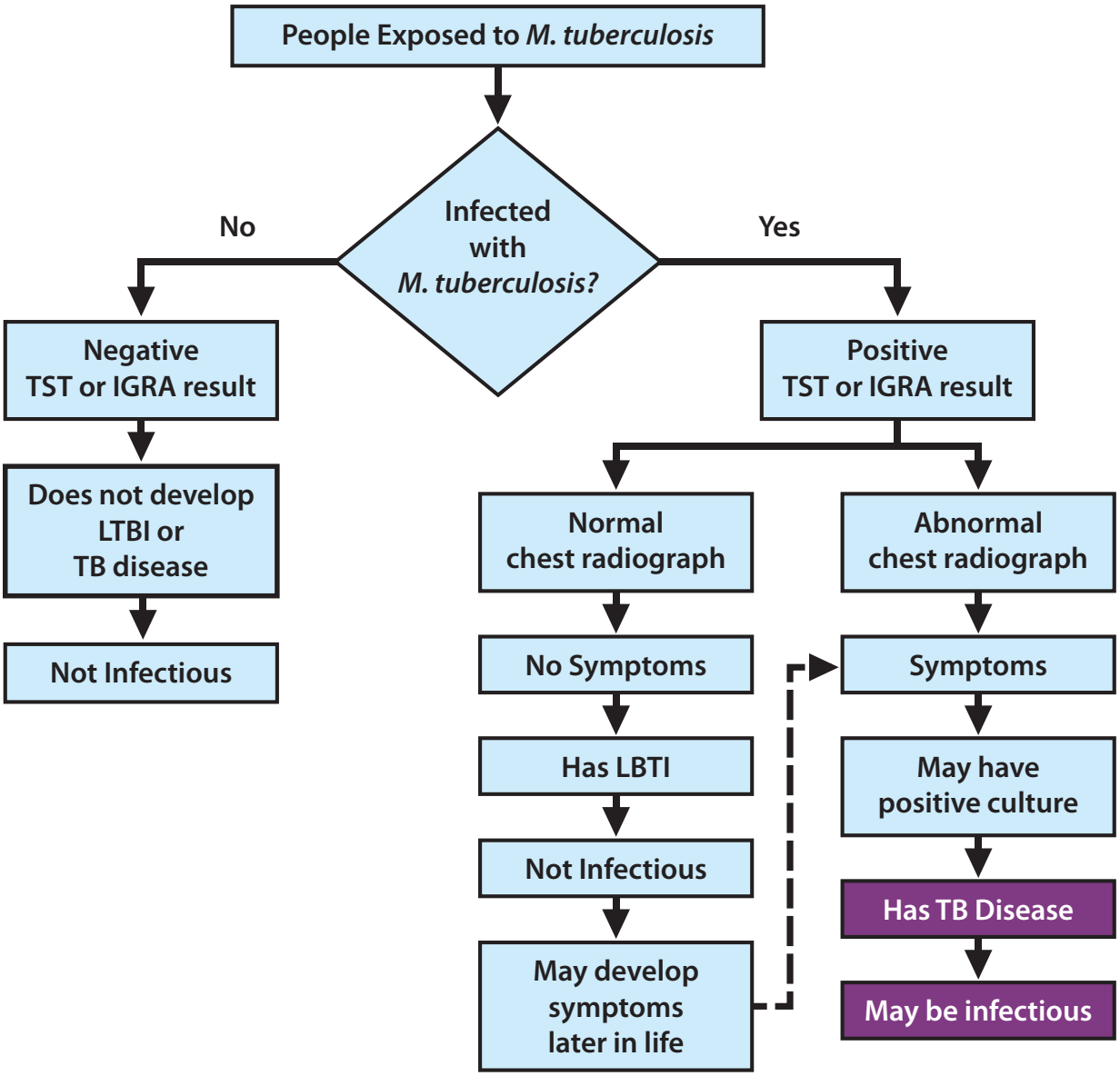


Table 2.5
LTBI vs. TB Disease

Person with LTBI (Infected)	Person with TB Disease (Infectious)
Has a small amount of TB bacteria in his/her body that are alive, but inactive	Has a large amount of active TB bacteria in his/her body
Cannot spread TB bacteria to others	May spread TB bacteria to others
Does **not** feel sick, but may become sick if the bacteria become active in his/her body	May feel sick and may have symptoms such as a cough, fever, and/or weight loss
Usually has a TB skin test or TB blood test reaction indicating TB infection	Usually has a TB skin test or TB blood test reaction indicating TB infection
Radiograph is typically normal	Radiograph may be abnormal
Sputum smears and cultures are negative	Sputum smears and cultures may be positive
Should consider treatment for LTBI to prevent TB disease	Needs treatment for TB disease
Does **not** require respiratory isolation	May require respiratory isolation
Not a TB case	A TB case

Risk of Developing TB Disease over a Lifetime

Without treatment, approximately 5% of persons who have been infected with *M. tuberculosis* will develop disease in the first year or 2 after infection, and another 5% will develop disease sometime later in life. Thus, without treatment, approximately 10% of persons with normal immune systems who are infected with *M. tuberculosis* will develop TB disease at some point in their lives.

Sites of TB Disease

TB disease can occur in pulmonary and extrapulmonary sites.

Pulmonary

TB disease most commonly affects the lungs; this is referred to as pulmonary TB. In 2011, 67% of TB cases in the United States were exclusively pulmonary. Patients with pulmonary TB usually have a cough and an abnormal chest radiograph, and may be infectious. Although the majority of TB cases are pulmonary, TB can occur in almost any anatomical site or as disseminated disease.

Extrapulmonary

Extrapulmonary TB disease occurs in places other than the lungs, including the larynx, the lymph nodes, the pleura, the brain, the kidneys, or the bones and joints. In HIV-infected persons, extrapulmonary TB disease is often accompanied by pulmonary TB. Persons with extrapulmonary TB disease usually are **not** infectious unless they have 1) pulmonary disease in addition to

extrapulmonary disease; 2) extrapulmonary disease located in the oral cavity or the larynx; or 3) extrapulmonary disease that includes an open abscess or lesion in which the concentration of organisms is high, especially if drainage from the abscess or lesion is extensive, or if drainage fluid is aerosolized. Persons with TB pleural effusions may have underlying pulmonary TB that is masked on chest radiograph because the effusion fluid compresses the lung. These patients should be considered infectious until pulmonary TB disease is excluded.

Miliary TB

Miliary TB occurs when tubercle bacilli enter the bloodstream and disseminate to all parts of the body, where they grow and cause disease in multiple sites. This condition is rare but serious. "Miliary" refers to the radiograph appearance of millet seeds scattered throughout the lung. It is most common in infants and children younger than 5 years of age, and in severely immunocompromised persons. Miliary TB may be detected in an individual organ, including the brain; in several organs; or throughout the whole body. The condition is characterized by a large amount of TB bacilli, although it may easily be missed, and is fatal if untreated. Up to 25% of patients with miliary TB may have meningeal involvement.

Central Nervous System

When TB occurs in the tissue surrounding the brain or spinal cord, it is called tuberculous meningitis. Tuberculous meningitis is often seen at the base of the brain on imaging studies. Symptoms include headache, decreased level of consciousness, and neck stiffness. The duration of illness before diagnosis is variable and relates in part to the presence or absence of other sites of involvement. In many cases, patients with meningitis have abnormalities on a chest radiograph consistent with old or current TB, and often have miliary TB.

Risk of LTBI Progressing to TB Disease

Anyone who has LTBI can develop TB disease, but some people are at higher risk than others (Table 2.6). HIV infection is the greatest risk factor for the development of TB disease in persons with LTBI, due to a weakened immune system. The risk of developing TB disease is 7% to 10% **each year** for persons who are infected with both *M. tuberculosis* and HIV and who are not receiving highly active treatment for HIV; it is 10% over a lifetime for persons infected only with *M. tuberculosis* (Figure 2.5). Children younger than 5 years of age are also at increased risk for progression of LTBI to TB disease.

Table 2.6
Persons at Increased Risk for Progression of LTBI to TB Disease

Persons at Increased Risk
• Persons infected with HIV; • Children younger than 5 years of age; • Persons who were recently infected with *M. tuberculosis* (within the past 2 years); • Persons with a history of untreated or inadequately treated TB disease, including persons with fibrotic changes on chest radiograph consistent with prior TB disease; • Persons who are receiving immunosuppressive therapy such as tumor necrosis factor-alpha (TNF) antagonists, systemic corticosteroids equivalent to/greater than 15 mg of prednisone per day, or immunosuppressive drug therapy following organ transplantation; • 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; • Persons who weigh less than 90% of their ideal body weight; • Cigarette smokers and persons who abuse drugs and/or alcohol; and • Populations defined locally as having an increased incidence of disease due to *M. tuberculosis*, including medically underserved, low-income populations.

Figure 2.5
Risk of Developing TB Disease

Risk Factor	Risk of Developing TB	Description
TB infection and no risk factors	 About 10% over a lifetime	For people with TB infection, **no risk factors**, and no treatment, the risk is about 5% in the first 2 years after infection and about 10% over a lifetime.
TB infection and diabetes	 About 30% over a lifetime	For people with TB infection and **diabetes**, and with no treatment, the risk is three times as high, or about 30% over a lifetime.
TB infection and HIV infection	 About 7% to 10% PER YEAR	For people with TB infection and **untreated HIV infection** and with no LTBI treatment, the risk is about 7% to 10% PER YEAR, a very high risk over a lifetime.

Anyone who has LTBI can develop TB disease, but some people are at higher risk than others. HIV infection is the highest risk factor for development of TB disease in persons with LTBI owing to weakening of the immune system.

Study Questions

2.6 Which statement about the difference between LTBI and TB disease is true?
(circle the one best answer)

A. Tubercle bacilli are in the body only with TB disease.

B. Persons with LTBI **cannot** spread TB bacteria to others.

C. Sputum smears and cultures are positive with LTBI but **NOT** with TB disease.

Which of the following patient characteristics indicate LTBI, TB disease, or both?
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Patient Characteristics	Type of TB (Answers May Be Used More Than Once)
____ **2.7** Has a positive TB skin test or TB blood test reaction.	**A.** LTBI
____ **2.8** May spread TB bacteria to others.	**B.** TB disease
____ **2.9** Has TB bacteria in his/her body.	**C.** Both LTBI and TB disease
____ **2.10** May require respiratory isolation.	
____ **2.11** Is **NOT** a case of TB.	

2.12 TB disease most commonly affects which part of the body?
(choose the one best answer)

A. Bone

B. Lungs

C. Kidneys

D. Brain

E. None of the above

The following persons have LTBI. Which persons have factors that put them either at an increased risk or NOT at an increased risk of progressing to TB disease?
(Choose the one best answer, and write the letter for the correct answer on the line next to the question number.)

Persons with LTBI	Risk of Progressing to TB Disease
____ **2.13** Susan has osteopenia.	**A.** Increased risk
____ **2.14** Andy has diabetes.	**B.** **Not** an increased risk
____ **2.15** Cindy is 3 years old.	

Case Study– Daniel

Daniel, a 30-year-old male, visits the Jackson County Health Department for a tuberculosis test because he is required to have one before he starts his new job at the Brice Nursing Home. He has a positive reaction to the test. He has no symptoms of TB and his chest x-ray findings are normal.

2.16 Should Daniel be considered a case of TB?
(circle the one best answer)

A. Yes, because he had a positive reaction to the tuberculosis test.

B. No, because he has TB infection, but no evidence of TB disease.

2.17 Should Daniel be considered infectious?
(circle the one best answer)

A. Yes, the test indicates that he has TB infection. Therefore he is infectious.

B. No, because he has TB infection, but not TB disease. Therefore he is not infectious.

Case Study– Lorena

Lorena, a 45-year-old female, is referred to the Galion County Health Department by her private physician because she was diagnosed with LTBI. She is obese, has high blood pressure, and has heart problems. She reports that she has injected illegal drugs in the past and also tested positive for HIV infection.

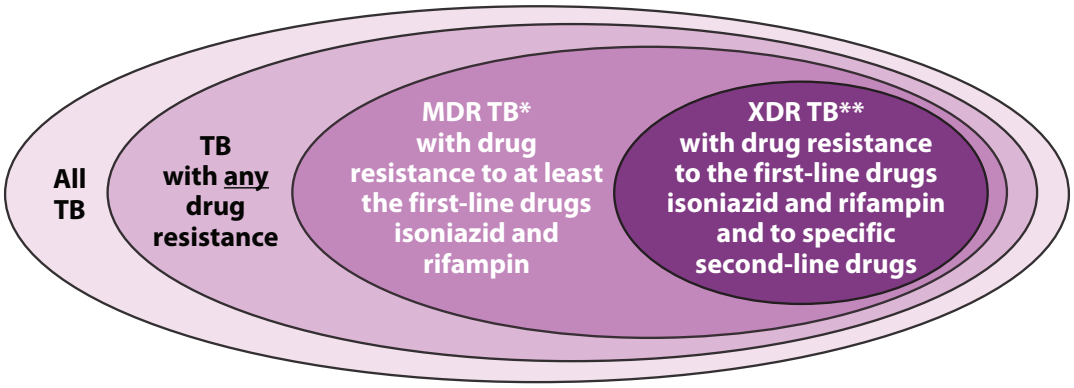
What conditions does Lorena have that increase the risk that she will develop TB disease? (Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Conditions of Persons with LTBI	Risk of Progressing to TB Disease
____ **2.18** Obesity	**A.** Increased risk
____ **2.19** High blood pressure	**B.** **Not** an increased risk
____ **2.20** Heart problems	
____ **2.21** Injection of illegal drugs	
____ **2.22** HIV	

Drug-Resistant TB (MDR and XDR)

Drug-resistant TB is caused by *M. tuberculosis* organisms that are resistant to the drugs normally used to treat the disease (Figure 2.6). Drug-resistant TB is transmitted in the same way as drug-susceptible TB, and is no more infectious than drug-susceptible TB. However, delay in the recognition of drug resistance or prolonged periods of infectiousness may facilitate increased transmission and further development of drug resistance.

Figure 2.6
Drug-Resistant Tuberculosis



* Often resistant to additional drugs

** Resistant to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin)

Drug-resistant TB is caused by *M. tuberculosis* organisms that are resistant to the drugs normally used to treat the disease. Drug-resistant TB is transmitted in the same way as drug-susceptible TB, and is no more infectious than drug-susceptible TB.

Multidrug-Resistant TB

Multidrug-resistant TB (MDR TB) is caused by organisms resistant to the most effective anti-TB drugs, isoniazid and rifampin. These drugs are considered first-line drugs and are used to treat most persons with TB disease (see Chapter 6, Treatment of Tuberculosis Disease).

Multidrug-resistant TB (MDR TB) is caused by organisms resistant to the most effective anti-TB drugs, isoniazid and rifampin.

Extensively Drug-Resistant TB

Extensively drug-resistant TB (XDR TB) is a relatively rare type of drug-resistant TB. XDR TB is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin). Because XDR TB is resistant to first-line and second-line drugs, patients are left with treatment options that are more toxic, more expensive, and much less effective.

Types of Drug-Resistant TB Disease

Drug-resistant TB disease can develop in two different ways, called **primary** and **secondary** resistance (Table 2.7). Primary resistance occurs in persons who are initially infected with resistant organisms. Secondary resistance, or acquired resistance, develops during TB therapy, either because the patient was treated with an inadequate regimen, did **not** take the prescribed regimen appropriately, or because of other conditions such as drug malabsorption or drug-drug interactions that led to low serum levels.

Circumstances in which an exposed person is at an increased risk of infection with drug-resistant TB include the following:

- Exposure to a person who has known drug-resistant TB disease;
- Exposure to a person with TB disease who has had prior treatment for TB (treatment failure or relapse) and whose susceptibility test results are **not** known;
- Exposure to a person with TB disease from an area in which there is a high prevalence of drug resistance, or travel to one of these areas (see the World Health Organization's "Tuberculosis: MDR-TB & XDR-TB: The 2008 Report" for a list countries with highest prevalence of drug resistance at www.who.int/tb/features_archive/drs_factsheet.pdf); or
- Exposure to a person who continue to have positive smear and cultures after 2 months of combination chemotherapy.

Table 2.7
Primary and Secondary MDR TB

Primary MDR TB (Infected with Drug-Resistant Organisms)	**Secondary MDR TB** (Acquired or Developed Drug Resistance)
Caused by person-to-person transmission of drug-resistant organisms	Develops during TB treatment
• Exposure to a person who » Has known drug-resistant TB » Had prior treatment for TB (treatment failure or relapse and whose susceptibility test results are **not** known) » Is from an area in which there is a high prevalence of drug resistance » Continues to have positive smears and cultures after 2 months of combination chemotherapy • Travel in areas with a high prevalence of drug-resistant TB disease	Develops because the patient • Was **not** treated with the appropriate treatment regimen **Or** • Did **not** follow the treatment regimen as prescribed » Took the drugs incorrectly » Took the drugs irregularly • Malabsorption • Drug-drug interactions causing low serum levels

Study Questions

2.23 Which of the following statements is true about drug-resistant TB disease?
(choose the one best answer)

A. Drug-resistant TB disease is transmitted in the same way as drug-susceptible TB disease.

B. Drug-resistant TB disease is **NO** more infectious than drug-susceptible TB disease.

C. Drug-resistant TB disease is easily treated with standard drug regimens.

D. A, B, and C are all correct.

E. Only A and B are correct.

2.24 Which of the following types of TB disease is caused by the organism *M. tuberculosis?*
(choose the one best answer.)

A. Drug-susceptible TB

B. MDR TB

C. XDR TB

D. A, B, and C are all correct.

E. Only A and B are correct.

What are the characteristics for each type of TB disease?
(Choose the one best answer, and write the letter for the correct answer on the line next to the question number.)

Characteristic	Type of TB
____ **2.25** Resistant to isoniazid and rifampin, plus any fluoroquinolone, and at least one of three injectable second-line drugs.	**A.** MDR TB **B.** XDR TB
____ **2.26** Resistant to at least the two first-line drugs, isoniazid and rifampin.	

What type of drug-resistant TB does each patient have?
(Choose the one best answer, and write the letter for the correct answer on the line next to the question number.)

Patient	Type of Drug-Resistant TB
____ **2.27** Sally is diagnosed with and treated for TB by her family physician. She is not placed on directly observed therapy DOT; thus she often forgets to take her anti-TB medicine and takes only part of her prescribed regimen. Because of inadequate treatment, she now has MDR TB.	**A.** Primary resistance **B.** Secondary "acquired" resistance
____ **2.28** Li, a 13-year-old boy, immigrates from China with his family. He gets MDR TB from his older brother.	

TB Classification System

The current clinical classification system for TB used in the United States is based on the pathogenesis of the disease (Table 2.8). It is intended mainly as an operational framework for public health programs. This classification system provides clinicians the opportunity to track the development of TB in their patients. Health-care providers should comply with state and local laws and regulations requiring the reporting of TB disease. All persons with Class 3 (clinically active) or Class 5 (TB suspected) TB should be reported promptly to the local or state health department. A patient should not have a Class 5 classification for more than 3 months.

Table 2.8
TB Classification System

Class	Type	Description
0	No TB exposure **Not** infected	• No history of TB exposure and no evidence of *M. tuberculosis* infection or disease • Negative reaction to TST or IGRA
1	TB exposure No evidence of infection	• History of exposure to *M. tuberculosis* • Negative reaction to TST or IGRA (given at least 8 to 10 weeks after exposure)
2	TB infection No TB disease	• Positive reaction to TST or IGRA • Negative bacteriological studies (smear and cultures) • No bacteriological or radiographic evidence of active TB disease
3	TB clinically active	• Positive culture for *M. tuberculosis* **OR** • Positive reaction to TST or IGRA, plus clinical, bacteriological, or radiographic evidence of current active TB
4	Previous TB disease (**not** clinically active)	• May have past medical history of TB disease • Abnormal but stable radiographic findings • Positive reaction to the TST or IGRA • Negative bacteriologic studies (smear and cultures) • No clinical or radiographic evidence of current active TB disease
5	TB suspected	• Signs and symptoms of active TB disease, but medical evaluation **not** complete

Study Questions

What is the TB classification for each of the following patients?
(Choose the one best answer, and write the letter for the correct answer on the line next to the question number.)

Patient	TB Classification
____ **2.29** Sonya has a positive reaction to a TST. There is no bacteriological or radiographic evidence of TB disease.	**A.** 0 No exposure Not infected
____ **2.30** Luke has signs and symptoms of TB disease, but his medical evaluation is **not** complete.	**B.** 1 TB exposure No evidence of infection
____ **2.31** Sergei has a past medical history of TB disease. His radiographic findings are abnormal, but stable. He has a positive reaction to an IGRA. Both smear and culture results are negative and there is no clinical or radiographic evidence of current TB disease.	**C.** 2 TB infection No TB disease
____ **2.32** Joseph has a history of exposure to *M. tuberculosis* and a negative TST result.	**D.** 3 TB, clinically active
____ **2.33** Louisa has no history of TB exposure and no evidence of *M. tuberculosis* infection or disease. She had a negative IGRA result.	**E.** 4 Previous TB disease (not clinically active)
____ **2.34** Rosella has a positive culture for *M. tuberculosis.*	**F.** 5 TB disease suspected

Chapter Summary

TB is an airborne disease caused by the bacterium *Mycobacterium tuberculosis* (*M. tuberculosis*). *M. tuberculosis* and seven very closely related mycobacterial species (*M. bovis*, *M. africanum*, *M. microti*, *M. caprae*, *M. pinnipedii*, *M. canetti* and *M. mungi*) together comprise what is known as the *M. tuberculosis* complex. Most, but not all, of these species have been found to cause disease in humans. In the United States, the majority of TB cases are caused by *M. tuberculosis*. *M. tuberculosis* organisms are also called tubercle bacilli.

M. tuberculosis is carried in airborne particles, called droplet nuclei, of 1–5 microns in diameter. Infectious droplet nuclei are generated when persons who have pulmonary or laryngeal TB disease cough, sneeze, shout, or sing. Depending on the environment, these tiny particles can remain suspended in the air for several hours. *M. tuberculosis* is transmitted through the air, **not** by surface contact. Transmission occurs when a person inhales droplet nuclei containing *M. tuberculosis*, and

the droplet nuclei traverse the mouth or nasal passages, upper respiratory tract, and bronchi to reach the alveoli of the lungs.

TB disease most commonly affects the lungs; this is referred to as pulmonary TB disease. In 2009, 71% of TB cases in the United States were exclusively pulmonary. Patients with pulmonary TB disease usually have a cough and an abnormal chest radiograph, and may be infectious. Although the majority of TB cases are pulmonary, TB can occur in almost any anatomical site or as disseminated disease.

Persons with LTBI have *M. tuberculosis* in their bodies, but do not have TB disease and **cannot** spread the infection to other people. A person with LTBI is **not** regarded as a case of TB disease. The process of LTBI begins when extracellular bacilli are ingested by macrophages and presented to other white blood cells. This triggers the immune response in which white blood cells kill or encapsulate most of the bacilli, leading to the formation of a granuloma. At this point, LTBI has been established. LTBI may be detected by using the TST or IGRA. It can take 2 to 8 weeks after the initial TB infection for the body's immune system to be able to react to tuberculin and for the infection to be detected by the TST or IGRA. Within weeks after infection, the immune system is usually able to halt the multiplication of the tubercle bacilli, preventing further progression.

In some people, the tubercle bacilli overcome the immune system and multiply, resulting in progression from LTBI to TB disease. Persons who have TB disease are usually infectious and may spread the bacteria to other people. The progression from LTBI to TB disease may occur soon or many years after infection. Body fluid or tissue from the disease site should be collected for AFB smear and culture. Positive culture for *M. tuberculosis* confirms the diagnosis of TB disease.

Drug-resistant TB disease can develop in two different ways, called **primary** and **secondary** resistance. Primary resistance occurs in persons who are initially exposed to and infected with resistant organisms. Secondary resistance, or acquired resistance, develops during TB therapy, either because the patient was treated with an inadequate regimen or did not take the prescribed regimen appropriately, or because of other conditions such as drug malabsorption or drug-drug interactions that led to low serum levels.

MDR TB is caused by organisms resistant to both isoniazid and rifampin, which are the two most effective anti-TB drugs. These drugs are considered first-line drugs and are used to treat most persons with TB disease.

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Chapter 3
Testing for Tuberculosis Infection and Disease

Table of Contents

Chapter Objectives

After working through this chapter, you should be able to

- Describe why high-risk groups should be tested for *M. tuberculosis* infection;
- Identify appropriate testing methods for *M. tuberculosis* infection;
- Identify special considerations when using tuberculin skin tests (TSTs); and
- Discuss general recommendations for the use of interferon-gamma release assays (IGRAs).

Introduction

Targeted testing is a TB control strategy that is used to identify, evaluate, and treat persons who are at high risk for latent tuberculosis infection (LTBI) or at high risk for developing TB disease once infected with *M. tuberculosis*. Identifying persons with LTBI is important to the goal of TB control and elimination because treatment of LTBI can prevent infected persons from developing TB disease and stop the further spread of TB. All testing activities should be accompanied by a plan for appropriate follow-up medical evaluation and treatment. Necessary medical evaluation and treatment resources need to be identified before testing activities begin.

Targeted testing is a TB control strategy that is used to identify, evaluate, and treat persons who are at high risk for latent tuberculosis infection (LTBI) or at high risk for developing TB disease once infected with *M. tuberculosis*.

Study Question

3.1 Why is targeted testing conducted? (circle the one best answer)

G. To identify, evaluate, and treat persons who are at high risk for latent tuberculosis infection.

H. To identify, evaluate, and treat persons who are at high risk for developing TB disease once infected with *M. tuberculosis*.

I. To identify the strain of TB bacteria that a patient may have so the correct treatment regimen can be provided.

J. A, B, and C are all correct.

K. Only A and B are correct.

Identifying High-Risk Groups for *M. tuberculosis* Testing

As part of their routine evaluation, health-care providers should identify and test persons who are at high risk for acquiring TB infection or at high risk of progressing to TB disease if infected. In some select settings, active case finding may be more appropriate than testing for *M. tuberculosis* infection. Flexibility is needed in defining high-risk groups for testing. The changing epidemiology of TB indicates that the risk for TB disease or LTBI among groups currently considered high risk may decrease over time, and groups currently **not** identified as being at risk may subsequently be considered high risk (see Chapter 1, Overview of Tuberculosis Epidemiology in the United States).

Evaluation of Persons with Positive TB Test Results

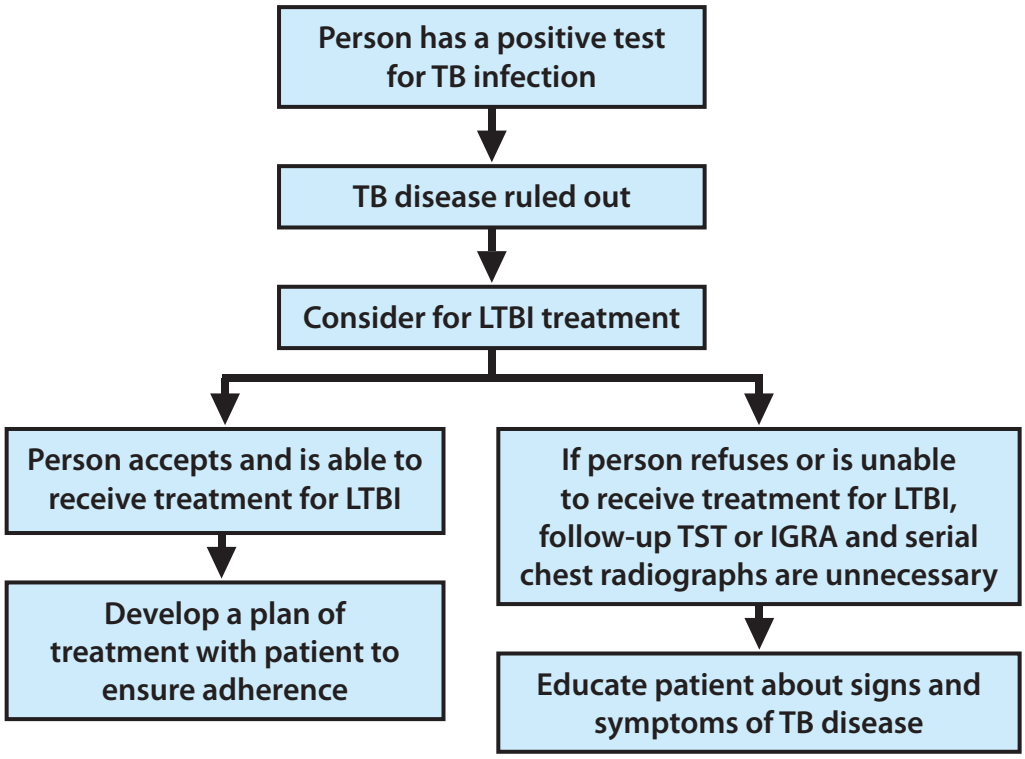
Health-care or other (e.g., correctional) facilities should consult with their local health department before starting a testing program, to ensure resources are available for the evaluation and treatment of

persons whose test results for LTBI or TB disease are positive. Persons with a positive test result for TB infection should be evaluated for TB disease and, if disease is ruled out, considered for treatment of LTBI (see Chapter 5, Treatment of Latent Tuberculosis Infection).

Health-care or other (e.g., correctional) facilities should consult with their local health department before starting a testing program to ensure there are resources available for the evaluation and treatment of persons whose test results for LTBI or TB disease are positive.

Follow-up TSTs or IGRAs and serial chest radiographs are unnecessary for persons who have a positive test result for TB infection and who have had TB disease ruled out or for persons who refuse or are unable to receive treatment for LTBI. These persons should be educated about the signs and symptoms of TB disease (Figure 3.1).

Figure 3.1
Evaluation of Persons with Positive TB Test Results



Study Question

3.2 Which of the following statements about evaluating persons with a positive TB test is true? (circle the one best answer)

A. Persons with a positive test for TB infection should be evaluated for TB disease and, if disease is ruled out, considered for treatment of LTBI.

B. If a person refuses or is unable to receive treatment for LTBI, follow-up TST or IGRA tests and serial chest radiographs are unnecessary.

C. All persons who have a positive test result for TB infection should receive LTBI treatment.

D. A, B, and C are all correct.

E. Only A and B are correct.

Testing Methods for TB Infection

Selection of the most suitable test(s) for detection of *M. tuberculosis* infection should be based on the reasons and the context for testing, test availability, and overall cost effectiveness of testing. Currently, there are two methods available for the detection of *M. tuberculosis* infection in the United States. The tests are:

- Mantoux tuberculin skin test (TST)
- Interferon-gamma release assays (IGRAs)
  - » QuantiFERON-TB Gold In-Tube test (QFT-GIT)
  - » T-SPOT.*TB* test

Currently, there are two methods available for the detection of *M. tuberculosis* infection in the United States. The tests are:
• Mantoux tuberculin skin test (TST)
• Interferon-gamma release assays (IGRAs)

These tests help clinicians differentiate infected from uninfected people. However, a negative reaction to any of the tests does **not** exclude the diagnosis of LTBI or TB disease. The decisions about medical or public health management should include epidemiological, historical, and other clinical information when using IGRA or TST results. Decisions should **not** be based on TST or IGRA results alone. Additional tests are needed to diagnose TB disease. A comparison of the TST and the IGRA is included in Table 3.1.

A negative reaction to a TST or IGRA does not exclude the diagnosis of LTBI or TB disease.

The decisions about medical or public health management should include epidemiological, historical, and other clinical information when using IGRA or TST results. Decisions should not be based on TST or IGRA results alone.

Table 3.1
TST vs IGRAs

TST	IGRA
Tuberculin is injected under the skin and produces a delayed-type hypersensitivity reaction if the person has been infected with *M. tuberculosis*	Blood is drawn for testing; test measures the immune response to the TB bacteria in whole blood
Requires two or more patient visits to conduct the test	Requires one patient visit to conduct the test
Results are available 48 to 72 hours later	Results can be available in 24 hours (depending on the batching of specimens by the laboratory and transport)
Can cause booster phenomenon	Does **not** cause booster phenomenon
Reading by HCW may be subjective	Laboratory test **not** affected by HCW perception or bias
BCG vaccination can cause false-positive result	BCG vaccination does **not** cause false-positive result and infection with most nontuberculous mycobacteria does **not** cause false-positive result
A negative reaction to the test does **not** exclude the diagnosis of LTBI or TB disease	A negative reaction to the test does **not** exclude the diagnosis of LTBI or TB disease

Mantoux Tuberculin Skin Test (TST)

The TST is used to determine if a person is infected with *M. tuberculosis*. In this test, a substance called purified protein derivative (PPD), which is derived from tuberculin, is injected under the skin. Typically PPD produces a T-cell mediated delayed-type hypersensitivity reaction if the person has been infected with *M. tuberculosis*. In most people who have TB infection, the immune system will recognize the PPD because it is extracted from the tubercle bacilli that caused the infection. It takes 2 to 8 weeks after initial infection with *M. tuberculosis* for the immune system to be able to react to PPD and for the infection to be detected by the TST.

The TST is used to determine if a person is infected with *M. tuberculosis*. In this test, a substance called PPD is injected under the skin.

It takes 2 to 8 weeks after initial infection with *M. tuberculosis* for the body's immune system to be able to react to PPD and for the infection to be detected by the TST.

In some people who are infected with *M. tuberculosis*, the ability to react to PPD may wane over the years. When these people receive a TST many years after infection, they may have an initial negative reaction. Subsequent TSTs may produce a positive reaction (see Boosted Reaction in this chapter).

Administering the TST

The TST is performed by intradermal injection of 0.1 ml of PPD containing 5 tuberculin units into the volar surface of the forearm. The injection should be made with a disposable 27-gauge tuberculin syringe, intradermally (just beneath the surface of the skin), with the needle bevel facing upward. This should produce a discrete, pale elevation of the skin (a wheal) 6 mm to 10 mm in diameter (Figure 3.2). Institutional guidelines regarding universal precautions for infection control (e.g., the use of gloves) should be followed (see Chapter 7, TB Infection Control).

The TST is performed by intradermal injection of 0.1 ml of PPD containing 5 tuberculin units into the volar surface of the forearm.

Reading the TST

The reaction to the TST should be assessed 48 to 72 hours after the injection by a health-care worker trained to read TST results. Reactions to PPD usually begin 5 to 6 hours after injection, reach a maximum at 48 to 72 hours, and subside over a period of a few days. However, positive reactions often persist for up to 1 week or longer. Health-care workers should **not** ask patients to read their own skin test.

The reaction to the TST should be assessed 48 to 72 hours after the injection by a health-care worker trained to read TST results.

The TST is read by palpating the site of injection to find an area of induration (firm swelling). The diameter of the indurated area should be measured across the forearm (Figure 3.3). Erythema (redness) should **not** be measured (Figure 3.4). Induration should be recorded in millimeters, even those classified as negative. If no induration is found, "0 mm" should be recorded.

The TST is read by palpating the site of injection to find an area of induration (firm swelling). The diameter of the indurated area should be measured across the forearm (Figure 3.3). Erythema (redness) should not be measured.

Figure 3.2
Administering the Mantoux TST

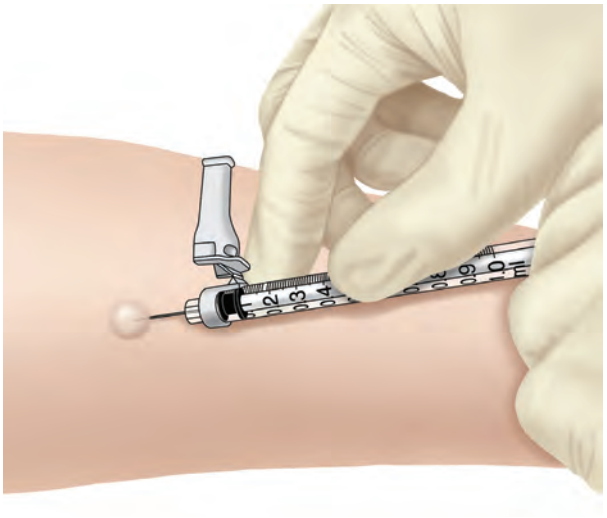


Figure 3.3
Reading the TST Correctly
Only the induration is being measured.
This is CORRECT.
The correct example below measures 10 mm.

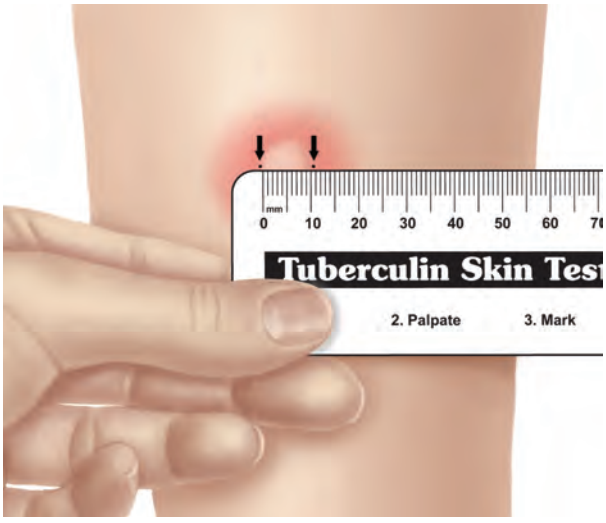
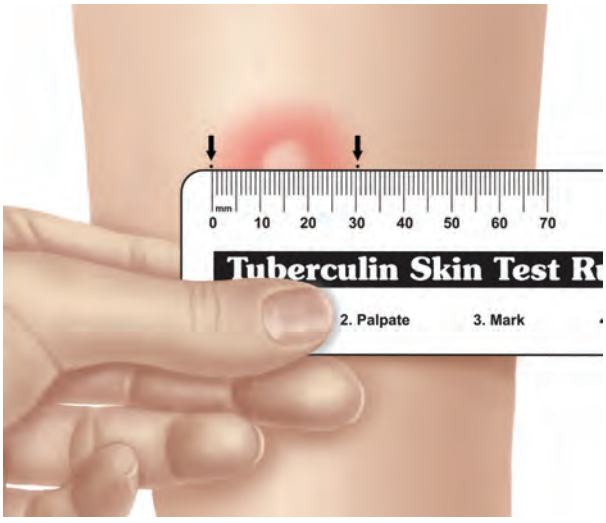


Figure 3.4
Reading the TST Incorrectly
The erythema is being measured.
This is INCORRECT.
The incorrect example below measures 30 mm.



Interpreting TST Reactions

Interpretation of TST reactions depends on the measurement (in millimeters) of induration and the person's risk of acquiring TB infection or the risk of progression to TB disease if infected (Table 3.2).

Induration of 5 or more millimeters is interpreted as a positive result in the following groups:

- HIV-infected persons;
- Recent contacts of persons with infectious TB disease;
- Persons with fibrotic changes on a chest radiograph consistent with prior TB; and
- Patients with organ transplants and other immunosuppressed patients (including patients receiving the equivalent of ≥ 15 mg/day of prednisone for ≥ 1 month).

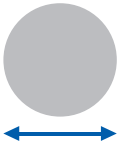
Induration of 10 millimeters or more is interpreted as a positive result in persons who do not meet the preceding criteria, but who have other risk factors for TB. These include the following:

- Recent arrivals to the United States (< 5 years) from high-prevalence areas (e.g., Africa, Asia, Eastern Europe, Latin America, and Russia);
- Injection drug users;
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, long-term care facilities, homeless shelters, and hospitals);
- Mycobacteriology laboratory personnel;
- Persons with medical conditions that increase the risk for progression to TB disease, including silicosis, diabetes mellitus, chronic renal failure, certain types of cancer (e.g., leukemia and lymphomas, or cancer of the head, neck, or lung), gastrectomy or jejunoileal bypass, and weight loss of at least 10% below ideal body weight;
- Children younger than 5 years of age; and
- Infants, children, and adolescents exposed to adults in high-risk categories.

An induration of 15 millimeters or greater is interpreted as a positive result in persons with no known risk factors for TB who, except for certain testing programs required by local law or regulation, would otherwise not be tested. Targeted testing programs should only be conducted among higher risk groups.

Interpretation of TST reactions depends on the measurement (in millimeters) of the induration and the person's risk of acquiring TB infection or the risk of progression to TB disease if infected.

Table 3.2
Interpreting the TST Reaction

		
5 or more millimeters	**10 or more millimeters**	**15 or more millimeters**
An induration of **5 or more millimeters** is considered positive for • HIV-infected persons • Recent contacts of persons with infectious TB • People who have fibrotic changes on a chest radiograph • Patients with organ transplants and other immunosuppressed patients (including patients taking a prolonged course of oral or intravenous corticosteroids or TNF-*α* antagonists)	An induration of **10 or more millimeters** is considered positive for • People who have come to the United States within the last 5 years from areas of the world where TB is common (for example, Asia, Africa, Eastern Europe, Russia, or Latin America) • Injection drug users • Mycobacteriology lab workers • People who live or work in high-risk congregate settings • People with certain medical conditions that place them at high risk for TB (silicosis, diabetes mellitus, severe kidney disease, certain types of cancer, and certain intestinal conditions) • Children younger than 5 years of age • Infants, children, and adolescents exposed to adults in high-risk categories	An induration of **15 or more millimeters** is considered positive for • People with no known risk factors for TB

TST False-Positive Reactions

The TST is a valuable tool, but it is **not** perfect. Several factors can lead to false-positive or false-negative skin test reactions (Table 3.3). Infection with nontuberculous mycobacteria can sometimes

cause a false-positive reaction to the TST. Another cause of a false-positive reaction is BCG (bacille Calmette-Guérin), a vaccine for TB disease that is rarely used in the United States. People who have been vaccinated with BCG may have a positive reaction to the TST even if they do **not** have TB infection (see BCG Vaccination in this chapter).

A false-positive reaction may also occur if an incorrect antigen is used or when the results are **not** measured or interpreted properly.

People who have been vaccinated with BCG may have a positive reaction to the TST even if they do not have TB infection.

TST False-Negative Reactions

Some people have a negative reaction to the TST even though they have been infected with *M. tuberculosis*. A false-negative reaction can be caused by many things (Table 3.3).

Some people have a negative reaction to the TST even though they have been infected with *M. tuberculosis*.

Anergy

A common cause of false-negative reactions is anergy. Anergy is the inability to react to a TST because of a weakened immune system. The absence of a reaction to a TST does **not** exclude a diagnosis of TB disease or infection with *M. tuberculosis*. Anergy may be caused by many factors, including advanced HIV infection, other acute or chronic bacterial, viral or fungal infections, sarcoidosis, poor nutrition, certain medications (e.g., TNF-alpha blockers or oral steroids), live virus vaccinations, TB disease itself, and other factors. HIV-infected persons may have a compromised ability to react to TST because of cutaneous anergy associated with progressive HIV immunosuppression; however, the usefulness of anergy testing in tuberculin-negative, HIV-infected persons who might benefit from treatment of LTBI has **not** been demonstrated.

Factors causing false-negative reactions may include, but are **not** limited to, the following:

- Concurrent viral infection (e.g., measles, mumps, chicken pox, HIV);
- Concurrent bacterial infection (e.g., typhoid fever, brucellosis, typhus, leprosy, pertussis);
- Concurrent fungal infection;
- Chronic renal failure;
- Low protein states (e.g., severe protein depletion, afibrinogenemia);
- Diseases affecting lymphoid organs (e.g., Hodgkin's disease, lymphoma, chronic leukemia, sarcoidosis);
- Immunosuppressive drugs (e.g., medical steroids);
- Children aged 6 months or less or elderly patients (i.e., immature or waning immunity);
- Stress (e.g., surgery, burns, mental illness, graft-versus-host reactions);

- Incorrect storage or handling of antigen or results that are **not** measured or interpreted properly;
- Vaccinations using live virus; or
- Recent TB infection.

Vaccinations

Vaccination with live viruses may interfere with TST reactivity and cause false-negative reactions; this includes measles, mumps, rubella, oral polio, varicella, yellow fever, BCG, and oral typhoid. For persons scheduled to receive TST and live virus vaccines, the testing should be done either on the same day as vaccination or at least 1 month after vaccination to minimize the potential for a false-negative TST reaction.

Infection occurs within 8 weeks of skin testing

False-negative TST reactions may occur if the TB infection occurred within 8 weeks of skin testing. For this reason, it is recommended that contacts of a person with infectious TB disease who have a negative reaction to the initial TST be retested at least 8 weeks after the last time they were in contact with the person who has infectious TB disease.

False-negative TST reactions may occur if the TB infection occurred within 8 weeks of skin testing.

Table 3.3
False-Positive and False-Negative Reactions to the TST

Type of Reaction	Possible Cause	People at Risk
False-positive	Nontuberculous mycobacteria (NTM)	People infected with NTM
	BCG vaccination	People vaccinated with BCG
	Administering of incorrect antigen	Any person being tested
	Incorrect interpretation of TST result	Any person being tested
False-negative	Anergy	HIV-infected people, other people with weakened immune systems, severe TB disease, and some viral illness (e.g., measles, mumps, and chicken pox) or bacterial infection (e.g., typhoid, etc.)
	Recent TB infection	People infected with *M. tuberculosis* within the past 8 weeks
	Concurrent viral infection	People injected with a live-virus vaccination
	Concurrent bacterial infection	People with typhoid fever, brucellosis, typhus, leprosy, pertussis
	Concurrent fungal infection	People with fungal infection
	Chronic renal failure	People with renal failure
	Low protein states	People with severe protein depletion or afibrinogenemia
	Diseases affecting lymphoid organs	People with Hodgkin's disease, lymphoma, chronic leukemia, sarcoidosis
	Immunosuppressive drugs	People taking medical steroids, TNF-alpha blockers or comparable drugs
	Very young or elderly persons	Newborns or elderly patients with immature or waning immunity
	Stress	People who have had surgery, burns, mental illness, graft-versus-host reactions
	Incorrect storage or handling of antigen, administering the TST, or results that are **not** measured or interpreted properly	Any person being tested

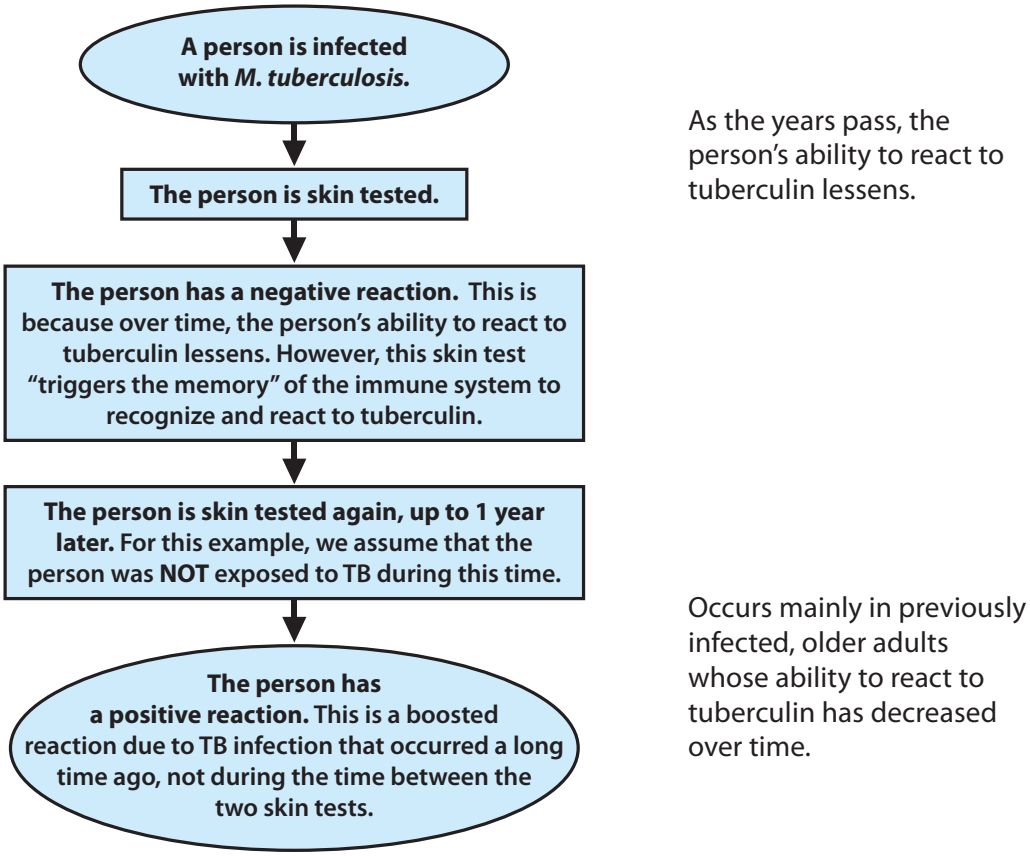
Special Considerations When Using TST

Boosted Reaction

The booster phenomenon occurs mainly in previously infected, older adults whose ability to react to tuberculin has waned over time (Figure 3.5). When these people are skin tested many years after they were infected with *M. tuberculosis*, they may have an initial negative reaction. However, if they are tested again within a year of the first test, they may have a positive reaction. This is because the first TST "triggered the memory" of the immune system, boosting its ability to react to the second TST. It may appear that these people were infected between the first and second tests (recent TB infection). The second, positive test reaction is actually a boosted reaction due to TB infection that occurred a long time ago. These people may still be considered for LTBI treatment if they fit into a high-risk category for progression to TB disease.

The booster phenomenon occurs mainly in previously infected, older adults whose ability to react to tuberculin has waned over time.

Figure 3.5
The TST Booster Phenomenon



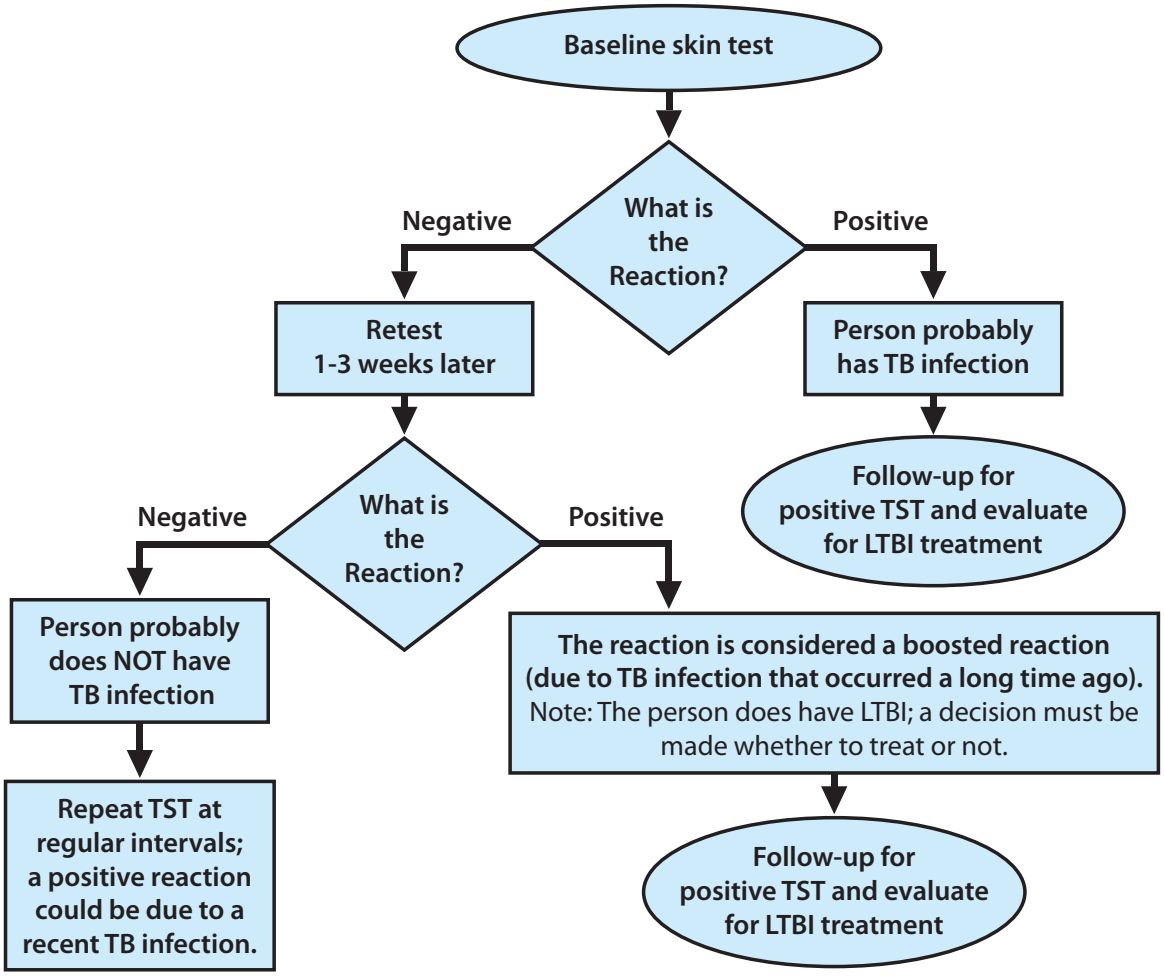
Two-step TST Testing

Two-step testing is a strategy used to reduce the likelihood that a boosted reaction will be misinterpreted as a recent infection (Figure 3.6). Two-step testing should be used for the initial skin testing of persons who will be retested periodically, such as health-care workers.

Two-step testing is a strategy used to reduce the likelihood that a boosted reaction will be misinterpreted as a recent infection.

If the reaction to the first test is classified as negative, a second test should be repeated 1 to 3 weeks later. A positive reaction to the second test probably represents a boosted reaction. On the basis of this second test result, the person should be classified as previously infected. This would **not** be considered a skin test conversion or a new TB infection; however, the patient may still be a candidate for LTBI treatment. If the second test result is also negative, the person should be classified as having a negative baseline TST result.

Figure 3.6
Two-Step TST Testing



Pregnant Women

TST is both safe and reliable throughout the course of pregnancy. Pregnant women should receive a TST if they have a specific risk factor for acquiring LTBI or for progression of LTBI to TB disease. No documented episodes of TST-related fetal harm have been reported since the test was developed, and no evidence exists that the TST has adverse effects on the pregnant mother.

TST is both safe and reliable throughout the course of pregnancy.

Occupational Exposure

Guidelines for interpreting TST reactions should also be applied to persons who may have occupational exposure to TB (e.g., health-care workers; staff of nursing homes, drug treatment centers, or correctional facilities). Thus, the appropriate cutoff for defining a positive reaction depends on the employee's individual risk factors for TB, including recent TB exposure and the prevalence of TB in the facility (based on facility risk assessment). In facilities where the risk of exposure is very low, 15 mm or greater induration may be an appropriate cut-off for employees with no other known risk factors.

Residents and employees of high-risk congregate facilities should be tested for TB with the two-step method upon employment or entry into the facility, and thereafter at intervals determined by the annual risk assessment in that facility (see Chapter 7, TB Infection Control).

Residents and employees of high-risk congregate facilities should be tested for TB with the two-step method upon employment or entry into the facility and thereafter at intervals determined by the annual risk assessment in that facility.

Study Questions

3.3 A negative reaction to a TST or IGRA does not exclude the diagnosis of LTBI or TB disease. (circle the one best answer)

A. True

B. False

3.4 After TB has been transmitted, how long does it take for the body's immune system to be able to react to tuberculin?
(circle the one best answer)

A. 48 to 72 hours

B. 7 to 10 days

C. 2 to 8 weeks

D. 6 months or more

What induration size is considered a positive TST reaction for the following people?
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Persons Who Received a TST		Size of Induration
____ **3.5**	Prieta lives in a homeless shelter in El Paso and has poor access to health care.	**A.** 5 or more millimeters **B.** 10 or more millimeters **C.** 15 or more millimeters
____ **3.6**	Gloria has no known risk factors for TB.	
____ **3.7**	Elwood has HIV infection.	

Match the factors associated with TST with the appropriate term.
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Factors Associated with TST	Terms
____ **3.8** Mainly occurs in previously infected, older adults whose ability to react to tuberculin has lessened over time.	**A.** False-positive skin test reaction
____ **3.9** May occur in people who have been vaccinated with BCG.	**B.** False-negative skin test reaction
____ **3.10** Should be used for initial skin testing of persons who will be retested periodically.	**C.** Anergy
____ **3.11** May occur in people who were recently infected with *M. tuberculosis.*	**D.** Boosted reaction
____ **3.12** Is the inability to react to a TST because of a weakened immune system.	**E.** Two-step testing

3.13 Is it safe for a pregnant woman to have a TST?
(choose the one best answer)

A. Yes

B. No

Case Study– Bret

Bret comes to the county health department for a TST. He believes that he has been exposed to TB, and he knows he is at high risk for TB disease because he is HIV infected. He is given a TST, and his reaction is read 48 hours later as 0 millimeters of induration.

3.14 Which of the following reasons is a possible interpretation for this result?
(circle the one best answer)

A. He may not have TB infection.

B. It may be less than 8 weeks since he was exposed to TB.

C. He may be anergic.

D. A, B, and C are all correct.

E. Only A and B are correct.

Interferon-Gamma Release Assays (IGRAs)

IGRAs detect the presence of *M. tuberculosis* infection by measuring the immune response to TB proteins in whole blood. IGRAs cannot differentiate between LTBI and active TB disease. As with the TST, additional tests are needed to diagnose or rule out TB disease. IGRAs may be used for surveillance purposes or to identify people who are likely to benefit from treatment, including people who are or will be at increased risk of progression to TB disease if infected with *M. tuberculosis*.

Two IGRAs are commercially available and approved by the U.S. Food and Drug Administration (FDA) as aids in diagnosing *M. tuberculosis* infection:

- QuantiFERON®-TB Gold In-Tube test (QFT-GIT); and
- T-Spot®.*TB* test.

IGRAs identify the presence of *M. tuberculosis* infection by measuring the immune response to the TB proteins in whole blood. IGRAs cannot differentiate between LTBI and active TB disease. As with the TST, additional tests are needed to diagnose or rule out TB disease.

IGRAs may be used for surveillance purposes or to identify people who are likely to benefit from treatment, including people who are or will be at increased risk of progression to TB disease if infected with *M. tuberculosis*.

General Recommendations for the Use of IGRAs

An IGRA may be used in place of (but **not** in addition to) a TST in all situations in which CDC recommends a TST as an aid in diagnosing *M. tuberculosis* infection, with the preferences and specific considerations noted below (Table 3.4).

- Preferred for testing persons from groups that historically have poor rates of return for TST reading.
- Preferred for testing persons who have received BCG (as a vaccine or for cancer therapy) (see BCG Vaccination in this chapter).
- Generally should not be used for testing children younger than 5 years of age unless used in conjunction with TST.
- May be used in place of TST to test recent contacts of persons with infectious TB disease with special considerations for follow-up testing:
  - » IGRAs offer the possibility of detecting *M. tuberculosis* infection with greater specificity than with a TST;
  - » Data on the ability of IGRAs to predict subsequent TB are limited;
  - » If IGRAs are to be used in contact investigations, negative results obtained prior to 8 weeks typically should be confirmed by repeating the test 8 to 10 weeks after the end of exposure;
  - » Use of the same test for repeat testing will minimize misclassification errors that occur due to test discordance.

- May be used in place of a TST for periodic screening that addresses occupational exposure to TB disease (e.g., surveillance programs for health-care workers).
- IGRAs do not boost subsequent test results and can be completed following a single patient visit.
- Routine testing with both a TST and an IGRA is **not** recommended; however, results from both tests may be useful in the following situations when the initial test is **negative**:
  - When the risk of infection, the risk of progression from infection to disease, and the risk of a poor outcome are high (e.g., HIV infection, children under 5 years of age who are exposed to persons with infectious TB); or
  - When there is clinical suspicion for TB disease (e.g., signs, symptoms, and/or radiographic evidence suggestive of TB disease) and confirmation of *M. tuberculosis* infection is desired.
- Routine testing with both a TST and an IGRA is **not** recommended; however, results from both tests may be useful in the following situations when the initial test is **positive**:
  - Additional evidence of infection is required to encourage compliance (e.g., foreign-born health-care workers who believe their positive TST is due to BCG); and
  - In healthy persons who have a low risk of both infection and progression from infection to TB disease.
- Repeating an IGRA or performing a TST may be useful when the initial IGRA result is indeterminate, borderline, or invalid, and a reason for testing persists.
- Each institution and TB control program should evaluate the availability, overall cost effectiveness, and benefits of the use of IGRAs.

An IGRA may be used in place of (but not in addition to) TST in all situations in which CDC recommends TST as an aid in diagnosing *M. tuberculosis* infection.

As with the TST, IGRAs generally should **not** be used for testing persons who have a low risk for both infection and disease attributable to *M. tuberculosis* (with exception of those who are likely to be at increased risk in the future) because screening such persons diverts resources from TB control activities of higher priority and increases the number of false-positive results.

Table 3.4
Recommendations for the Use of IGRAs

Category	Recommended	Not Recommended
Groups for use	• Preferred for groups that historically have poor rates of return for TST reading • Preferred for persons who have received BCG (as a vaccine or for cancer therapy)	• Children younger than 5 years of age unless it is used in conjunction with TST • Persons at low risk of infection • Persons at low risk of disease due to *M. tuberculosis* (except those who are likely to be at increased risk in the future)
In place of TST	• Recent contacts of persons with TB disease with special considerations for follow-up testing » If IGRAs are used in contact investigations, negative results obtained prior to 8 weeks typically should be confirmed by repeating the test 8 to 10 weeks after the end of exposure » Use of the same test for repeat testing will minimize misclassification errors that occur due to test discordance • Periodic screening that addresses occupational exposure to TB disease (e.g., surveillance programs for health workers)	
Testing with both TST and IGRA	Results from both tests may be useful when the initial test is **negative** • When the following risks are high » Risk of infection » Risk of progression from infection to disease » Risk of a poor outcome • When there is clinical suspicion for active TB and confirmation of *M. tuberculosis* infection is desired	Routine testing with both TST and IGRA

Category	Recommended	Not Recommended
Testing with both TST and IGRA	Results from both tests may be useful in the following situations when the initial test is **positive**: • Additional evidence of infection is required to encourage compliance (e.g., foreign-born health-care workers who believe their positive TST is due to BCG); and • In healthy persons who have a low risk of both infection and progression from infection to TB disease.	Routine testing with both TST and IGRA

Study Questions

Match the characteristic with the type of TB test.
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Characteristic	Type of TB Test
____ **3.15** Used to detect TB infection.	**A.** TST
____ **3.16** Blood is drawn for the test.	**B.** IGRA
____ **3.17** PPD is injected for the test.	**C.** Both TST and IGRA
____ **3.18** Requires two or more patient visits to conduct test.	
____ **3.19** Requires one patient visit to conduct test.	
____ **3.20** Results need to be read in 48–72 hours.	
____ **3.21** Results can be available in 24 hours.	
____ **3.22** BCG vaccination can cause false-positive result.	
____ **3.23** BCG vaccination does **not** cause false-positive result.	

BCG Vaccination

The bacille Calmette-Guérin (BCG) vaccine is a live, attenuated (weakened) vaccine derived from a strain of *Mycobacterium bovis* that was developed over several years by Calmette and Guérin at the Pasteur Institute in Lille, France. An early version of BCG was first administered to humans in 1921. Since that time, many different strains have been derived and used throughout the world. BCG vaccination is **not** generally recommended in the United States because of the low risk of infection with *M. tuberculosis*, the variable efficacy of the BCG vaccine against pulmonary TB, the low risk of severe disseminated TB disease in young children in the United States, and the vaccine's interference with the ability to determine TST reactivity. Many highly TB-prevalent countries vaccinate infants with BCG as part of their TB control effort to prevent children from contracting severe disseminated TB or TB meningitis.

BCG vaccination is not generally recommended in the United States because of the low risk of infection with *M. tuberculosis*, the variable efficacy of the BCG vaccine against pulmonary TB, the low risk of severe disseminated TB disease in young children in the United States and the vaccine's interference with the ability to determine TST reactivity.

Recommendations for the Use of BCG Vaccination in the United States

The BCG vaccine may be considered in limited circumstances for selected persons who meet specific criteria. The use of the BCG vaccine should be undertaken only after consultation with local health departments and experts in the management of TB.

Recent BCG vaccination may cause a subsequent false positive reaction to the TST. Thus, it may complicate decisions to prescribe treatment for LTBI for BCG-vaccinated persons who have a positive TST result. In such cases, an IGRA would be the test of choice for LTBI diagnosis.

Recent BCG vaccination may cause a subsequent false positive reaction to the TST. Thus, it may complicate decisions to prescribe treatment for LTBI for BCG-vaccinated persons who have a positive TST result.

Infants and Children

In the United States, BCG vaccination should only be considered for those children who have a negative TST or IGRA result and who are continually exposed to, and cannot be separated from, adults who:

- Are untreated or ineffectively treated for TB disease (if the child cannot be given long-term treatment for infection); or
- Have TB disease caused by strains resistant to isoniazid and rifampin.

The BCG vaccination is **contraindicated** in children infected with HIV.

BCG vaccination is contraindicated in children infected with HIV.

Health-Care Workers

BCG vaccination of health-care workers should be considered on an individual basis in settings in which:

- A high percentage of TB patients are infected with *M. tuberculosis* strains resistant to both isoniazid and rifampin;
- Transmission of such drug-resistant *M. tuberculosis* strains to health-care workers and subsequent infection are likely; and
- Comprehensive TB infection control precautions have been implemented and have **not** been successful.

BCG vaccination should **not** be required for employment or for assignment of health-care workers in specific work areas. Health-care workers considered for BCG vaccination should be counseled regarding the risks and benefits associated with both BCG vaccination and treatment of LTBI. BCG vaccination is **contraindicated** in health-care workers who are infected with HIV.

Contraindications to BCG Vaccination

BCG is contraindicated in persons who have an impaired immune system from the following:

- HIV infection;
- Congenital immunodeficiency;
- Leukemia;
- Lymphoma;
- Generalized malignancy;
- High-dose steroid therapy;
- Alkylation agents;
- Antimetabolites; or
- Radiation therapy.

It is also prudent to avoid giving BCG vaccination to pregnant women, although no harmful effects of BCG on the fetus have been observed.

BCG vaccination should not be given to pregnant women.

Interpretation of TB Testing Results in BCG-Vaccinated Persons

The TST or IGRA is **not** contraindicated for persons who have been vaccinated with BCG. The TST or IGRA results are used to support decisions about the diagnosis of infection with *M. tuberculosis*. TST in persons vaccinated with BCG should be interpreted using the same criteria for those **not** BCG vaccinated. The booster phenomenon may occur among persons who have had a prior BCG vaccination.

The TST or IGRA is not contraindicated for persons who have been vaccinated with BCG. The TST or IGRA results are used to support decisions about the diagnosis of infection with *M. tuberculosis*.

TST in persons vaccinated with BCG should be interpreted using the same criteria for those not BCG vaccinated. The booster phenomenon may occur among persons who have had a prior BCG vaccination.

Study Questions

3.24 Which of the following statements about recommendations for using BCG in the United States is true?
(choose the one best answer)

A. Should **NOT** be given to pregnant women.

B. Should be used for children infected with HIV.

C. Should be required for employment of all health-care workers.

D. A, B, and C are all correct.

E. Only A and B are correct.

Case Study–Anshuman

Anshuman recently immigrated from India. He is given a TST that results in an induration of 14 millimeters. 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.

Are the following statements about how to interpret Anshuman's results true or false? (Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Statement	True or False
____ **3.25** He has a positive reaction to the TST.	**A.** True
____ **3.26** He is a contact of a person with pulmonary TB.	**B.** False
____ **3.27** There is no reliable way to distinguish a positive TST reaction caused by BCG or from a true TB infection.	
____ **3.28** Because he was vaccinated with BCG there is no need to evaluate him further.	
____ **3.29** He should be further evaluated for LTBI or TB disease.	

Which of the following factors make it more likely that Anshuman's positive reaction is due to TB infection? (Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Factor	Yes or No
____ **3.30** He is from an area of the world where TB is common, so he was probably exposed to TB in his native country.	**A.** Yes, a factor
____ **3.31** His wife has had pulmonary TB, which further increases the probability that he has been exposed to TB.	**B.** No, not a factor
____ **3.32** He had BCG as a child, not as an adult.	

Chapter Summary

Targeted testing is a TB control strategy that is used to identify, evaluate, and treat persons who are at high risk for LTBI or at high risk for developing TB disease once infected with *M. tuberculosis*. Identifying persons with LTBI is important to the goal of TB control and elimination because treatment of LTBI can prevent infected persons from developing TB disease and stop the further spread of TB. All testing activities should be accompanied by a plan for appropriate follow-up medical evaluation and treatment. Necessary medical evaluation and treatment resources need to be identified before testing activities begin.

As part of their routine evaluation, health-care providers should identify and test persons who are at high risk for acquiring TB infection or at high risk for progressing to TB disease if infected. In some select settings, active case finding may be more appropriate than testing for *M. tuberculosis* infection. Flexibility is needed in defining high-risk groups for testing. The changing epidemiology of TB indicates that the risk for TB disease or LTBI among groups currently considered high risk may decrease over time, and groups currently **not** identified as being at risk may subsequently be considered high risk.

Selection of the most suitable test(s) for detection of *M. tuberculosis* infection should be based on the reasons and the context for testing, test availability, and overall cost effectiveness of testing. Currently, there are two methods available for the detection of *M. tuberculosis* infection in the United States. The tests are:

- Mantoux tuberculin skin test (TST)
- Interferon-gamma release assays (IGRAs)
  - » QuantiFERON-TB Gold In-Tube test (QFT-GIT)
  - » T-Spot®.*TB* test

The TST is used to determine if a person is infected with *M. tuberculosis*. In this test, a substance called purified protein derivative (PPD), which is derived from tuberculin, is injected under the skin. Typically PPD produces a T-cell mediated delayed-type hypersensitivity reaction if the person has been infected with *M. tuberculosis*. In most people who have TB infection, the immune system will recognize the PPD because it is extracted from the tubercle bacilli that caused the infection. It takes 2 to 8 weeks after initial infection with *M. tuberculosis* for the body's immune system to be able to react to PPD and for the infection to be detected by the TST.

The booster phenomenon occurs mainly in previously infected, older adults whose ability to react to tuberculin has waned over time. When these people are skin tested many years after they were infected with *M. tuberculosis*, they may have an initial negative reaction. However, if they are tested again within a year of the first test, they may have a positive reaction. This is because the first TST "triggered the memory" of the immune system, boosting its ability to react to the second TST. It may appear that these people were infected between the first and second tests (recent TB infection). The second, positive test reaction is actually a boosted reaction due to TB infection that occurred a long time ago. These people may still be considered for LTBI treatment if they fit into a high-risk category for progression to TB disease.

IGRAs identify the presence of *M. tuberculosis* infection by measuring the immune response to the TB proteins in whole blood. These tests cannot differentiate between LTBI and active TB disease. As with the TST, additional tests are needed to diagnose or rule out TB disease. IGRAs may be used for surveillance purposes or to identify people who are likely to benefit from treatment, including people who are or will be at increased risk of progression to TB disease if infected with *M. tuberculosis*.

The bacille Calmette-Guérin (BCG) vaccine is a live, attenuated (weakened) vaccine derived from a strain of *Mycobacterium bovis* that was developed by Calmette and Guérin at the Pasteur Institute in Lille, France. An early version of BCG was first administered to humans in 1921. Since that time, many different strains have been derived and used throughout the world. BCG vaccination is **not** generally recommended in the United States because of the low risk of infection with *M. tuberculosis*, the variable efficacy of the BCG vaccine against pulmonary TB, the low risk of severe disseminated TB disease in young children in the United States, and the vaccine's interference with the ability to determine TST reactivity. Many highly TB-prevalent countries vaccinate infants with BCG as part of their TB control effort to prevent children from contracting severe disseminated TB or TB meningitis.

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Chapter 4
Diagnosis of Tuberculosis Disease

Table of Contents

Chapter Objectives

After working through this chapter, you should be able to

- Describe the five components of a TB medical evaluation;
- Identify the major components of TB diagnostic microbiology;
- List at least five symptoms of pulmonary TB disease;
- Explain the purpose and significance of acid-fast bacilli (AFB);
- Explain the purpose and significance of the culture; and
- Explain the purpose and significance of genotyping.

Introduction

Tuberculosis (TB) is not as common as it was many years ago in the United States; consequently, clinicians do not always consider the possibility of TB disease when evaluating patients who have symptoms. As a result, the diagnosis of TB disease may be delayed or even overlooked, and the patient may remain ill and possibly infectious for a prolonged period.

Not all persons with TB disease have symptoms; however, most persons with TB disease have one or more symptoms that lead them to seek medical care. All persons with symptoms of TB disease, or either a positive tuberculin skin test (TST) or an interferon-gamma release assay (IGRA) indicative of *M. tuberculosis* infection, should be medically evaluated to exclude TB disease.

Not all persons with TB disease have symptoms; however, most persons with TB disease have one or more symptoms that lead them to seek medical care.

All persons with symptoms of TB disease, or either a positive TST or IGRA indicative of *M. tuberculosis* infection, should be medically evaluated to exclude TB disease.

Study Question

4.1 All persons with symptoms of TB disease, or a positive TST or IGRA result indicating *M. tuberculosis* infection, should be medically evaluated to exclude TB disease.
(choose the one best answer)

C. True

D. False

Medical Evaluation

A complete medical evaluation for TB disease includes the following five components:

1. Medical history
2. Physical examination
3. Test for *M. tuberculosis* infection
4. Chest radiograph
5. Bacteriologic examination of clinical specimens.

1. Medical History

When conducting a medical history, the clinician should ask if any symptoms of TB disease are present; if so, for how long, and if there has been known exposure to a person with infectious TB disease. Equally important is obtaining information on whether or not the person has been diagnosed in the past with latent tuberculosis infection (LTBI) or TB disease. Clinicians may also contact the local health department for information on whether a patient has a past history of TB infection or disease. If the previous treatment regimen for TB disease was inadequate or if the patient did **not** adhere to therapy, TB disease may recur and possibly be drug-resistant. It is important to consider demographic factors (e.g., country of origin, age, ethnicity, occupation, or racial group) that may increase the patient's risk for being exposed to TB infection (see Chapter 2, Transmission and Pathogenesis of Tuberculosis). Clinicians should determine if the patient has underlying medical conditions, especially human immunodeficiency virus (HIV) infection or diabetes, that increase the risk for progression to TB disease in those latently infected with *M. tuberculosis*.

Clinicians should determine if the patient has underlying medical conditions, especially HIV infection and diabetes, that increase the risk for progression to TB disease in those latently infected with *M. tuberculosis*.

As discussed in Chapter 2, Transmission and Pathogenesis of Tuberculosis, TB disease most commonly affects the lungs and is referred to as pulmonary TB disease. Pulmonary TB disease usually causes one or more of the symptoms indicated in Table 4.1.

TB disease most commonly affects the lungs and is referred to as pulmonary TB disease.

Extrapulmonary TB disease may cause symptoms related to the part of the body that is affected (Table 4.1). For example, TB of the spine may cause back pain; TB of the kidney may cause blood in the urine; TB meningitis may cause headache or confusion. Extrapulmonary TB disease should be considered in the differential diagnosis of ill persons who have systemic symptoms and who are at high risk for TB disease.

Both pulmonary and extrapulmonary TB disease symptoms can be caused by other diseases; however, they should prompt the clinician to consider TB disease.

Both pulmonary and extrapulmonary TB disease symptoms can be caused by other diseases; however, they should prompt the clinician to consider TB disease.

Table 4.1
Symptoms of Pulmonary and Extrapulmonary TB Disease

Symptoms of Pulmonary TB Disease (TB disease usually causes one or more of the symptoms)	**Symptoms of Possible Extrapulmonary TB Disease** (Depends on the part of the body that is affected by the disease)
• Cough (especially if lasting for 3 weeks or longer) with or without sputum production • Coughing up blood (hemoptysis) • Chest pain • Loss of appetite • Unexplained weight loss • Night sweats • Fever • Fatigue	• TB of the kidney may cause blood in the urine • TB meningitis may cause headache or confusion • TB of the spine may cause back pain • TB of the larynx can cause hoarseness • Loss of appetite • Unexplained weight loss • Night sweats • Fever • Fatigue

Study Questions

Match the patient symptoms with the type of TB.
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Patient Symptoms	Type of TB
____ **4.2** Regina has back pain and blood in her urine, unexplained weight loss, fever, fatigue, loss of appetite.	**A.** Pulmonary TB **B.** Extrapulmonary TB
____ **4.3** Maria has a cough, loss of appetite, and unexplained weight loss. She has also been coughing up blood.	

2. Physical Examination

A physical examination is an essential part of the evaluation of any patient. It cannot be used to confirm or rule out TB disease, but it can provide valuable information about the patient's overall condition, inform the method of diagnosis, and reveal other factors that may affect TB disease treatment, if diagnosed.

A physical examination is an essential part of the evaluation of any patient. It cannot be used to confirm or rule out TB disease, but it can provide valuable information about the patient's overall condition, inform the method of diagnosis, and reveal other factors that may affect TB disease treatment, if diagnosed.

Study Question

4.4 A physical examination can be used to confirm and rule out TB disease.
(circle the one best answer)

A. True

B. False

3. Test for *M. tuberculosis* Infection

Selection of the most suitable tests for detection of *M. tuberculosis* infection should be based on the reasons and the context for testing, test availability, and overall cost effectiveness of testing. Currently, there are two methods available for the detection of *M. tuberculosis* infection in the United States. The tests are:

- Mantoux tuberculin skin test (TST) (Figure 4.1); and
- Interferon-gamma release assays (IGRAs)*
  - » QuantiFERON-TB Gold In-Tube test (QFT-GIT) (Figure 4.2);
  - » T-SPOT®.*TB* test (Figure 4.3).

*See Chapter 3, Testing for Tuberculosis Infection and Control

Figure 4.1
Mantoux Tuberculin Skin Test

Figure 4.2
QuantiFERON-TB Gold In-Tube Test (QFT-GIT)

Figure 4.3
T-SPOT®.*TB* Test

These tests help clinicians differentiate people infected with *M. tuberculosis* from those uninfected. However, a negative reaction to any of the tests does **not** exclude the diagnosis of TB disease or LTBI (see Chapter 3, Testing for Tuberculosis Infection and Disease).

TST and QFT tests help clinicians differentiate people infected with *M. tuberculosis* from those uninfected. However, a negative reaction to any of the tests does NOT exclude the diagnosis of TB disease or LTBI.

Study Question

4.5 A negative reaction for a TST or IGRA test excludes a person from having TB disease. (choose the one best answer)

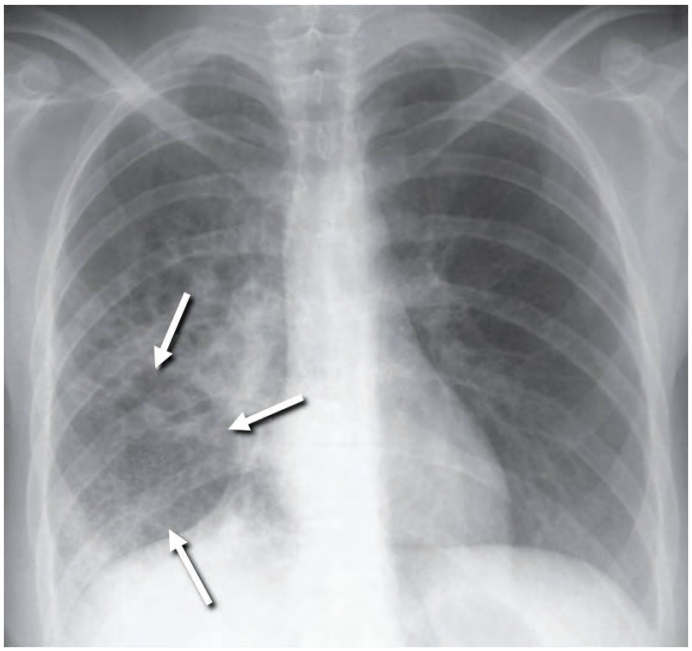
A. True

B. False

4. Chest Radiograph

With pulmonary TB being the most common form of disease, the chest radiograph is useful for diagnosis of TB disease. Chest abnormalities can suggest pulmonary TB disease (Figure 4.4). A posterior-anterior radiograph of the chest is the standard view used for the detection of TB-related chest abnormalities. In some cases, especially in children, a lateral view may be helpful.

Figure 4.4
Chest Radiograph with Lower Lobe Cavity



In some instances, a computerized tomography (CT) scan may provide additional information. A CT scan provides more detailed images of parts of the body that cannot easily be seen on a standard chest radiograph; however, CT scans can be substantially more expensive.

In pulmonary TB disease, radiographic 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 HIV-infected and other immunosuppressed persons. Radiographic abnormalities in children tend to be minimal with a greater likelihood of lymphadenopathy, more easily diagnosed on the lateral film.

Mixed nodular and fibrotic lesions may contain slowly multiplying tubercle bacilli and have the potential for progression to TB disease. Persons who have lesions consistent with findings of "old" TB disease on a chest radiograph and have a positive TST reaction or positive IGRA result should be considered high-priority candidates for treatment of LTBI (see Chapter 5, Treatment for Latent Tuberculosis Infection), but only after TB disease is excluded by obtaining three specimens for AFB smear and culture because "old" TB cannot be differentiated from active TB disease based on radiographic appearance alone. Conversely, fully calcified, discrete, nodular lesions without fibrosis likely represent granulomas and pose a lower risk for future progression to TB disease.

In HIV-infected persons, pulmonary TB disease may present with atypical findings or with no lesions seen on the chest radiograph. The radiographic appearance of pulmonary TB disease in persons infected with HIV might be typical; however, cavitary disease is less common among such patients. More common chest radiograph findings for HIV-infected persons include infiltrates in any lung zone, mediastinal or hilar adenopathy, or, occasionally, a normal chest radiograph. Typical cavitary lesions are usually observed in patients with higher CD4 counts, and more atypical patterns are observed in patients with lower CD4 counts because cavitation is thought to occur as a result of the immune response to TB organisms. In HIV-infected persons, almost any abnormality on a chest radiograph may be indicative of TB disease. In patients with symptoms and signs of TB disease, a negative chest radiograph result does **not** exclude TB disease.

Abnormalities seen on chest radiographs may be suggestive of, but are never diagnostic of, TB disease. Chest radiographs may be used to exclude pulmonary TB disease in an HIV-negative person who has a positive TST reaction or IGRA and who has no symptoms or signs of TB disease.

Abnormalities seen on chest radiographs may be suggestive of, but are never diagnostic of, TB disease. Chest radiographs may be used to exclude pulmonary TB disease in a person with a normal immune system who has a positive TST reaction or IGRA and who has no symptoms or signs of TB disease.

Study Question

4.6 Chest radiographs may be used to exclude pulmonary TB disease in an HIV-negative person who has a positive TST reaction or IGRA and who has no symptoms or signs of TB disease. (choose the one best answer)

A. True

B. False

5. Bacteriologic Examination of Clinical Specimens

Examinations of clinical specimens (e.g., sputum, urine, or cerebrospinal fluid) are of critical diagnostic importance. The specimens should be examined and cultured in a laboratory that specializes in testing for *M. tuberculosis*. The bacteriologic examination has five parts:

- Specimen collection, processing, and review
- AFB smear classification and results
- Direct detection of *M. tuberculosis* in clinical specimen using nucleic acid amplification (NAA)
- Specimen culturing and identification
- Drug-susceptibility testing

Specimen Collection, Processing, and Review

For diagnostic purposes, all persons suspected of having TB disease at any site should have sputum specimens collected for an AFB smear and culture, even those without respiratory symptoms. At least three consecutive sputum specimens are needed, each collected in 8- to 24-hour intervals, with at least one being an early morning specimen. If possible, specimens should be obtained in an airborne infection isolation (AII) room or other isolated, well-ventilated area (e.g., outdoors) (Figure 4.5).

For diagnostic purposes, all persons suspected of having TB disease at any site should have sputum collected for TB culture. At least three consecutive sputum specimens are needed, each collected in 8- to 24-hour intervals, with at least one being an early morning specimen.

Figure 4.5
TB Patient Coughing Up Sputum

A TB patient has coughed up sputum and is spitting it into a sterile container. The patient is sitting in a special sputum collection booth that, if properly ventilated, prevents the spread of tubercle bacilli.

For diagnostic purposes, all persons suspected of having TB disease should have sputum collected for AFB smear and culture.

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 (see Chapter 7, TB Infection Control).

During specimen collection, patients produce an aerosol that may be hazardous to health-care workers or other patients in close proximity.

Specimen Collection Methods for Pulmonary TB Disease

There are four specimen collection methods for pulmonary TB disease (Table 4.2):

- Coughing
- Induced sputum
- Bronchoscopy
- Gastric aspiration

Coughing– Coughing is the most commonly used method of sputum collection. Coughing should be supervised to ensure that sputum is collected correctly. A health-care worker wearing the recommended personal protective equipment should coach and directly supervise the patient when sputum is collected (Figure 4.6). 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. Unsupervised patients are less likely to provide an adequate specimen, especially the first time.

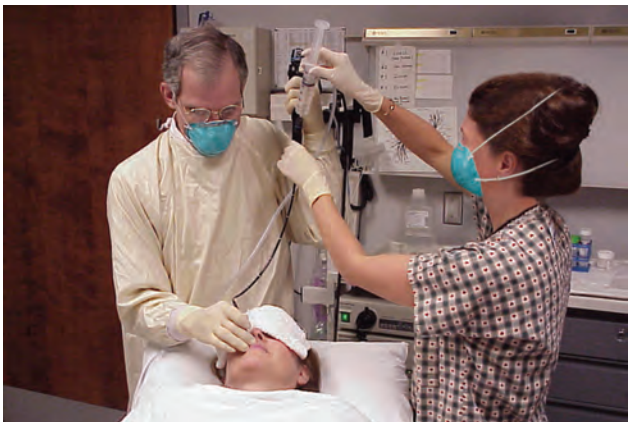
Patients should be informed that sputum is the material brought up from the lungs, and that mucus from the nose or throat and saliva are not good specimens.

Figure 4.6
Patient Coughing Up Sputum

Sputum Induction– For patients unable to cough up sputum, deep sputum-producing coughing may be induced by inhalation of an aerosol of warm, sterile, hypertonic saline (3%–5%). Because induced sputum is very watery and resembles saliva, it should be labeled "induced" to ensure that the laboratory staff workers do **not** discard it.

Bronchoscopy– A bronchoscopy is a medical procedure that allows visualization of the inside of a person's airways. The airways are called the bronchial tubes or bronchi. Bronchoscopy might be needed for specimen collection, especially if previous results have been nondiagnostic and doubt exists as to the diagnosis. At other times, bronchoscopy is considered because TB is among several other diagnoses being considered. If possible, examine three spontaneous or induced sputum to exclude a diagnosis of TB disease before bronchoscopy. If possible, avoid bronchoscopy on patients with suspected or confirmed TB disease or postpone the procedure until the patient is determined to be noninfectious, by confirmation of the three negative AFB sputum smear results (Figure 4.7). Bronchial washings, brushings, and biopsy specimens may be obtained, depending on the bronchoscopy findings. Sputum collected after a bronchoscopy may also be useful for a diagnosis. A bronchoscopy should never be substituted for sputum collection, but rather used as an additional diagnostic procedure.

Figure 4.7
Performing a Bronchoscopy



Whenever feasible, bronchoscopy should be performed in a room that meets the ventilation requirements for an airborne infection isolation (AII) room. Health-care workers should wear N95 respirators while present during a bronchoscopy procedure on a patient with suspected or confirmed infectious TB disease (see Chapter 7, TB Infection Control).

Gastric Aspiration– Gastric aspiration is a procedure sometimes used to obtain a specimen for culture when a patient cannot cough up adequate sputum. A tube is inserted through the mouth or nose and into the stomach to recover sputum that was coughed into the throat and then swallowed. This procedure is particularly useful for diagnosis in children, who are often unable to cough up sputum (Figure 4.8). Gastric aspiration often requires hospitalization and should be done in the morning before the patient gets out of bed or eats, as it is the optimal time to collect swallowed respiratory secretions from the stomach. Specimens obtained by gastric aspiration should be transported to the lab immediately for neutralization or neutralized immediately at the site of collection.

Figure 4.8
Performing a Gastric Aspiration

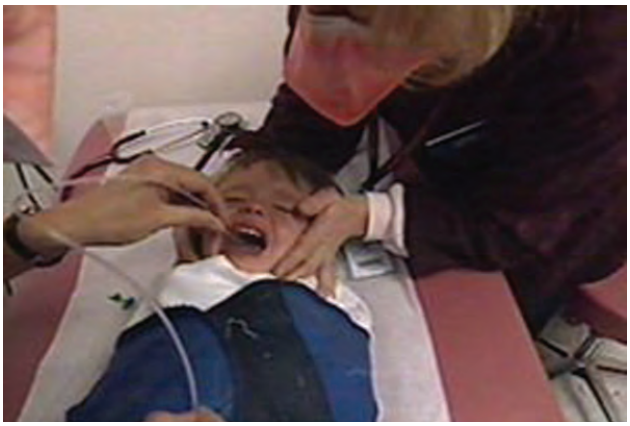


Table 4.2
Methods of Obtaining a Sputum Specimen

Method	Description	Advantage	Disadvantage
Spontaneous sputum sample	Patient coughs up sputum into a sterile container	• Inexpensive • Easy to do	• Patient may **not** be able to cough up sputum without assistance or may spit up saliva instead of sputum • Health-care worker has to coach and supervise the patient when collecting sputum
Sputum induction	Patient inhales a saline mist which can cause a deep cough	• Easy to do • Use to obtain sputum when coughing sputum is not productive	• Specimens may be watery and may be confused with saliva (should be labeled "induced specimen") • Requires special equipment • May cause bronchospasm
Bronchoscopy	Bronchoscope is passed through the mouth or nose directly into the diseased portion of the lung, and sputum or lung tissue is removed	Use to obtain sputum when coughing or inducing sputum is not productive or other diagnoses are being considered	• Most expensive and invasive procedure • Requires special equipment • Must be done by a specialist in a hospital or clinic • Requires anesthesia
Gastric washing	Tube is inserted through the patient's mouth or nose and passed into the stomach to get a sample of gastric secretions that contain sputum that has been coughed into the throat and then swallowed	Use to obtain samples in children, who do **not** produce sputum when they cough	• Must be done as soon as patient wakes up in the morning; patient may be required to stay in hospital • Can be uncomfortable for the patient

Specimen Collection Methods for Extrapulmonary TB

TB disease can occur in almost any anatomical site; thus, 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 (Figures 4.9 and 4.10). Procedures for the expeditious and recommended handling of the specimen must be in place or assured before the specialist performs an invasive procedure to obtain the specimen. Especially important is rapid transportation to the laboratory according to the laboratory's instructions. It is important to note that the portion of the specimen placed in formalin for histologic examination cannot be used for culture.

TB disease can occur in almost any anatomical site; thus, 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.

Figure 4.9
Clinical Specimen Used for Examination When Extrapulmonary TB Disease Is Suspected

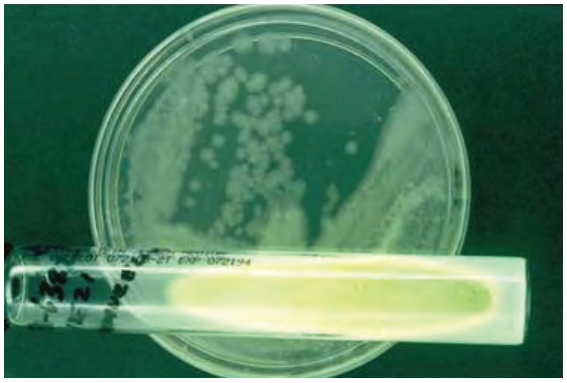


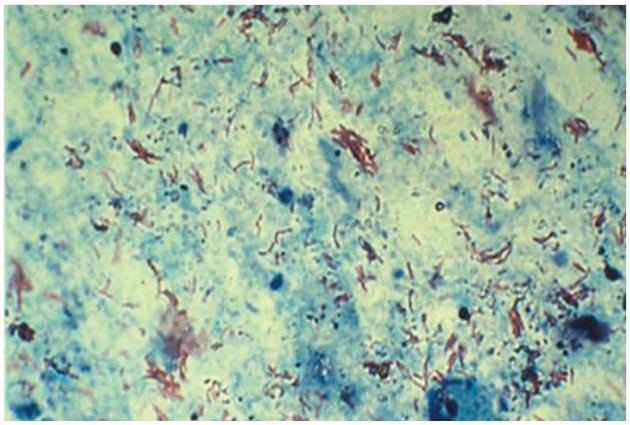
Figure 4.10
Collection Bottles Used for Collecting Specimens When Extrapulmonary TB Disease Is Suspected

AFB Smear Classification and Results

Detection of acid-fast bacilli in stained and acid-washed smears examined microscopically may provide the initial bacteriologic evidence of the presence of mycobacteria in a clinical specimen (Figure 4.11). Smear microscopy is the quickest and easiest procedure that can be performed.

Detection of acid-fast bacilli in stained and acid-washed smears examined microscopically may provide the first bacteriologic evidence of the presence of mycobacteria in a clinical specimen.

Figure 4.11
Acid-Fast Bacilli Stained in Smear
Tubercle bacilli are shown in red



There are two procedures commonly used for acid-fast staining:

- Carbolfuchsin methods which include the Ziehl-Neelsen and Kinyoun methods (direct microscopy)
- Fluorochrome procedure using auramine-O or auramine-rhodamine dyes (fluorescent microscopy).

Studies have shown that there must be 5,000 to 10,000 bacilli per milliliter of specimen to allow the detection of bacteria in stained smears. In contrast, 10 to 100 bacilli are needed for a positive culture. Smear examination is a quick procedure; results should be available within 24 hours of specimen collection when specimens are delivered to the laboratory promptly. However, smear examination permits only the presumptive diagnosis of TB disease because the acid-fast bacilli in a smear may be acid-fast organisms other than *M. tuberculosis*. Also, many TB patients have negative AFB smears with a subsequent positive culture. Negative smears do **not** exclude TB disease (Table 4.3).

Many TB patients have negative AFB smears with a subsequent positive culture. Negative smears do not exclude TB disease.

When acid-fast bacilli are seen in a smear, they are counted. There is a system for reporting the number of acid-fast bacilli that are seen at a certain magnification. According to the number of acid-fast bacilli seen, the smears are classified as 4+, 3+, 2+, or 1+. The greater the number, the more infectious the patient (Table 4.3).

Table 4.3
Smear Classification Results

Smear Result (Number of AFB observed at 1000X magnification)	Smear Interpretation	Infectiousness of Patient
4+ (>9/field)	Strongly positive	Probably very infectious
3+ (1-9/field)	Strongly positive	Probably very infectious
2+ (1-9/10 fields)	Moderately positive	Probably infectious
1+ (1-9/100 fields)	Moderately positive	Probably infectious
+/- (1-2/300 fields)*	Weakly positive†	Probably infectious
No acid-fast bacilli seen	Negative	Probably not infectious**

* There are variations on labeling for this result, and include listing the number of AFB counted.

† Laboratories may report these smear results as "doubtful" or "inconclusive" based on CDC guidelines.

** The criteria for determining whether a patient may be considered noninfectious are discussed in Chapter 7 on TB Infection Control.

Direct Detection of *M. tuberculosis* in Clinical Specimen Using Nucleic Acid Amplification (NAA)

NAA tests are used to amplify DNA and RNA segments to rapidly identify the microorganisms in a specimen. NAA testing can reliably detect *M. tuberculosis* bacteria in specimens in hours as compared to 1 week or more for culture (Figure 4.12). Possible benefits of using NAA tests include

- Earlier laboratory confirmation of TB disease;
- Earlier treatment initiation;
- Improved patient outcomes;
- Interruption of transmission by early diagnosis, respiratory isolation and appropriate treatment;
- Earlier, more efficient use of respiratory isolation;
- Earlier initiation of contact investigation; and
- More effective public health interventions.

NAA tests are used to amplify DNA and RNA segments to rapidly identify the microorganisms in a specimen.

CDC recommends that NAA testing be performed on at least one respiratory specimen from each patient with signs and symptoms of pulmonary TB for whom a diagnosis of TB is being considered but has not yet been established, and for whom the test result would alter case management or TB control activities, such as contact investigations.

Figure 4.12
Nucleic Acid Amplification (NAA) Test

Clinicians should interpret all laboratory results in the context of the clinical situation. A single negative NAA test result should not be used as a definitive result to exclude TB disease, especially when the clinical suspicion of TB disease is moderate to high. Rather, the negative NAA test result should be used as additional information in making clinical decisions, to expedite testing for an alternative diagnosis, or to prevent unnecessary TB disease treatment.

Culture remains the gold standard for laboratory confirmation of TB disease, and growing bacteria are required to perform drug-susceptibility testing and genotyping. In accordance with current recommendations, sufficient numbers and portions of specimens should always be reserved for culture. Nonetheless, NAA testing should become standard practice for patients suspected of having TB, and all clinicians and public health TB programs should have access to NAA testing for TB to shorten the time to diagnosis.

Culture remains the gold standard for laboratory confirmation of TB disease, and growing bacteria are required to perform drug-susceptibility testing and genotyping.

Specimen Culture and Identification

Positive cultures for *M. tuberculosis* confirm the diagnosis of TB disease; however, in the absence of a positive culture, TB disease may also be diagnosed on the basis of clinical signs and symptoms alone. Culture examinations should be done on all diagnostic specimens, regardless of AFB smear or NAA results. The commercially available broth culture systems (e.g., BACTEC, MGIT, VersaTREK, MBBACT) allow detection of most mycobacterial growth in 4 to 14 days compared to 3 to 6 weeks for solid media (Figure 4.13). Laboratories performing TB cultures should routinely use a broth-based system (Table 4.4).

Positive cultures for *M. tuberculosis* confirm the diagnosis of TB disease; however, in the absence of a positive culture, TB disease may also be diagnosed on the basis of clinical signs and symptoms alone.

Culture examinations should be done on all diagnostic specimens, regardless of AFB smear or NAA results.

Figure 4.13
Colonies of *M. tuberculosis* Grown in Culture

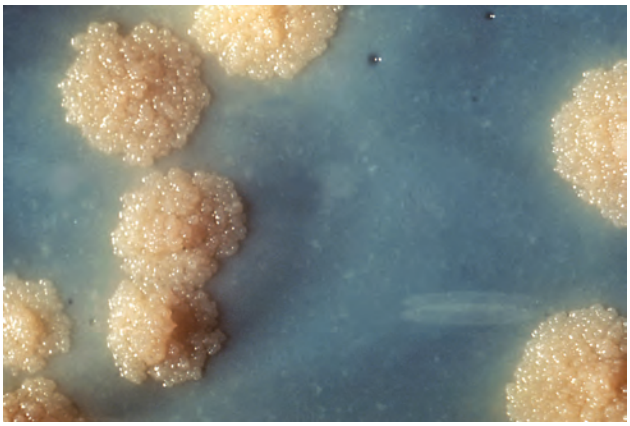


Table 4.4
Differences Between Sputum Smears and Cultures

Feature	Smears	Cultures
Equipment needed	• Microscope • Glass slides • Special dyes	• Incubators • Safety cabinet • Culture plates or tubes • Culture media, biochemicals for tests
Time needed to make report	• 1 day	• 4 days to 12 weeks (depending on method used and how quickly the organism grows)
Basis of procedure	• Looking for acid-fast bacilli on slide under microscope	• Growth and identification of tubercle bacilli or other mycobacteria on culture media in incubator
Significance of a negative report	• Patient is probably **not** infectious • Does **not** rule out TB disease (culture may be positive)	• No live tubercle bacilli found in specimen • Does **not** rule out TB disease (live tubercle bacilli may be in other specimens and/or body sites)
Significance of a positive report	• Patient is more likely to be infectious (if acid-fast bacilli are tubercle bacilli) • Acid-fast bacilli could be nontuberculous mycobacteria	• Confirms diagnosis of TB disease

Follow-up Bacteriologic Examination

Follow-up bacteriologic examinations are important for assessing the patient's infectiousness and response to therapy. Specimens should be obtained at monthly intervals until two consecutive specimens sent for culture are reported as negative. Culture conversion is the most important objective measure of response to treatment. Conversion is documented by the first negative culture in a series of previously positive cultures. In addition, all subsequent culture results must remain negative.

Specimens should be obtained at monthly intervals until two consecutive specimens sent for culture are reported as negative.

Reporting Results

Laboratories should report initial positive smears, positive *M. tuberculosis* cultures, and positive NAA results within 24 hours by telephone or fax to the primary health-care provider and health department. Out-of-state laboratories who receive referral specimens must contact the health-care provider and health department in the patient's state of origin. Follow-up results may be reported by mail. It is the responsibility of the primary health-care provider to report all suspected or confirmed cases of TB disease promptly to the state or local health department unless state laws indicate otherwise. Prompt reporting to health authorities ensures that the person with TB disease can be adequately treated, interrupting the potential for ongoing transmission. It also ensures that contact investigations can be initiated quickly to find contacts of the patient who may have LTBI or TB disease.

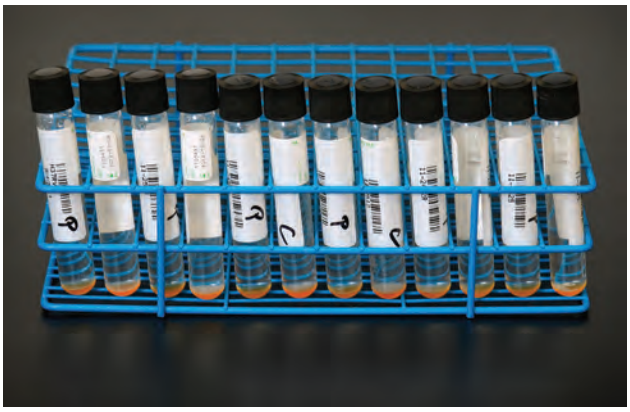
Laboratories should report initial positive smears, positive *M. tuberculosis* cultures, and positive NAA results within 24 hours by telephone or fax to the primary health-care provider and health department.

Drug-Susceptibility Testing

For all patients, the initial *M. tuberculosis* isolate should be tested for resistance to the first-line anti-TB drugs: isoniazid, rifampin, ethambutol, and pyrazinamide (Figure 4.14). The results of drug-susceptibility tests should direct clinicians to choose the appropriate drugs for treating each patient. Patients with TB disease who are treated with drugs to which their strain of TB is resistant may **not** be successfully cured. In fact, their strain of TB may become resistant to additional drugs.

For all patients, the initial *M. tuberculosis* isolate should be tested for resistance to the first-line anti-TB drugs: isoniazid, rifampin, ethambutol, and pyrazinamide.

Figure 4.14
Drug-Susceptibility Testing



Rapid, broth-based systems should be used to identify drug resistance as early as possible in order to ensure appropriate treatment. Susceptibility results from laboratories should be promptly forwarded to the physician and health department. Drug-susceptibility tests should be repeated for patients who do **not** respond as expected or who have positive culture results despite 3 months of adequate treatment.

Second-line drug susceptibility testing should be done only in reference laboratories and generally be limited to specimens from patients who have the following characteristics:

- Prior TB disease treatment;
- Contact with a patient with known anti-TB drug resistance;
- Demonstrated resistance to first-line anti-TB drugs; or
- Positive cultures after more than 3 months of treatment.

A patient is diagnosed with multidrug-resistant TB (MDR TB) disease if the organisms are resistant to at least isoniazid and rifampin, the two most potent first-line anti-TB drugs. A patient is diagnosed with extensively drug-resistant TB (XDR TB) disease if the TB isolate is resistant to isoniazid and rifampin, any fluoroquinolone, and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).

A patient is diagnosed with multidrug-resistant TB (MDR TB) disease if the organisms are resistant to at least isoniazid and rifampin, the two most potent first-line anti-TB drugs.

A patient is diagnosed with extensively drug-resistant TB (XDR TB) disease if the isolate is resistant to isoniazid and rifampin, any fluoroquinolone, and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).

Molecular Detection of Drug Resistance

The drug resistance of clinical isolates as determined by conventional methods (e.g, broth-based and agar proportion) is due to the presence of mutations in specific *M. tuberculosis* genes. These mutations often are single base pair changes in the DNA sequence of the bacteria. There are a variety of commercial assays and laboratory developed tests that can detect mutations associated with drug resistance. The assays are done on patient specimens or isolates from patient specimens.

- Line-probe assays use polymerase chain reaction (PCR) to amplify the region of a gene known to be associated with resistance. The amplified product is labeled and specifically joins to probes on a nitrocellulose strip. Mutations are detected by the lack of binding to probes with the normal sequence or by binding to probes specific for commonly occurring mutations.
- PCR amplification of genes known to be associated with drug resistance can be followed by DNA sequencing that can detect mutations.
- Real-time PCR with fluorescing probes that specifically join to the target can do so in one step, a technique sometimes called "molecular beacons."

All of these assays allow rapid detection of drug resistance through the identification of genetic mutations associated with resistance and provide **preliminary** guidance on effective therapy. Molecular detection of drug resistance should be considered for patients with the following characteristics:

- High risk of rifampin resistance, including MDR TB (e.g., previously treated TB, contact with someone with MDR TB, or being foreign born from a high-risk country);
- First-line drug susceptibility results are available and show resistance to rifampin;
- Infectiousness poses a risk to vulnerable contacts (e.g., daycare workers, nurses, and infants); and
- Contraindications to essential first-line medications (e.g., rifampin allergy).

A limitation of molecular testing for drug resistance is that the clinical relevance of some mutations remains unknown. Further, not all biological mechanisms of resistance are known. As a result, if no mutations are detected by the molecular assay, resistance cannot be ruled out. **Therefore, it is essential that conventional growth-based drug-susceptibility tests are done and used in conjunction with molecular results.**

It is essential that conventional growth-based drug-susceptibility tests are done and used in conjunction with molecular results.

Study Questions

Indicate which of the following activities is a component of a complete medical evaluation for TB. (Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Activity	Yes or No
____ **4.7** Medical history	**A.** Yes, is a component of a complete medical evaluation for TB
____ **4.8** Physical examination	**B.** No, is **not** a component of a complete medical evaluation for TB
____ **4.9** Test for *M. tuberculosis* infection	
____ **4.10** Chest radiograph	
____ **4.11** Bone density testing	
____ **4.12** Bacteriological examination of clinical specimens	

Match the specimen collection method with how to use it.
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Use of Specimen Collection Method	Method
____ **4.13** Use only if there is a suspicion of TB disease and there are three negative sputum smears or induced sputum AFB results.	**A.** Coughing
____ **4.14** Best way to obtain specimens from children who cannot produce sputum.	**B.** Sputum induction
____ **4.15** Use for extrapulmonary TB disease.	**C.** Bronchoscopy
____ **4.16** Use for patients unable to cough up sputum to encourage deep coughing.	**D.** Gastric aspiration
____ **4.17** Most common method for collecting sputum.	**E.** Biopsy

4.18 What do laboratory personnel look for in a sputum smear?
(choose the one best answer)

A. White-blood cells

B. Fast-moving bacilli

C. Drug-resistant bacilli

D. Acid-fast bacilli

Case Study– Chin

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

4.19 Does this rule out the diagnosis of pulmonary TB disease for Chin?
(circle the one best answer)

A. **Yes**, because his sputum smears are negative for acid-fast bacilli. Even though he has symptoms of TB disease and a cavity on his chest radiograph, his sputum smears have to be positive for acid-fast bacilli to indicate a diagnosis of pulmonary TB disease.

B. **No**, because he has symptoms of TB disease and his abnormal chest x-ray suggest that he does have pulmonary TB disease. Also, *M. tuberculosis* may grow in the cultures even though there are no acid-fast bacilli on the smear.

Which of the following statements about nucleic acid amplification (NAA) tests and cultures are true or false? (Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Statements about NAA and Cultures	True or False
____ **4.20** NAA tests are used to amplify DNA and RNA segments to rapidly identify the microorganisms in a specimen.	**A.** True **B.** False
____ **4.21** Culture is required for growing bacteria for drug-susceptibility testing and genotyping.	
____ **4.22** Culture is the gold standard for laboratory confirmation of TB disease.	
____ **4.23** A single negative NAA test result should be used as a definitive result to exclude TB disease.	
____ **4.24** Cultures should be done on all diagnostic specimens, regardless of AFB smear or NAA results.	

4.25 During patient follow-up, how often should specimens be obtained? (circle the one best answer)

A. At monthly intervals until one specimen sent for culture is reported as negative.

B. At monthly intervals until three consecutive specimens sent for culture are reported as negative.

C. At monthly intervals until two consecutive specimens sent for culture are reported as negative.

Are the following statements about drug-susceptibility testing true or false?
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Statements about Drug-Susceptibility Testing	True or False
____ **4.26** For all patients, the initial *M. tuberculosis* isolate should be tested for resistance to the first-line anti-TB drugs.	**A.** True **B.** False
____ **4.27** For all patients, the initial *M. tuberculosis* isolate should be tested for resistance to the second-line anti-TB drugs.	
____ **4.28** Drug-susceptibility tests should be repeated for patients who do not respond as expected.	
____ **4.29** Drug-susceptibility tests should be repeated for patients who have positive culture results despite 3 months of adequate therapy.	

Case Study–Lea

Lea 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+.

4.30 What do these results tell you about Lea's diagnosis and her infectiousness?
(circle the one best answer)

A. Because the smears are positive, clinicians should suspect that Lea has TB disease.

B. She is probably very infectious.

C. It is possible that the acid-fast bacilli are mycobacteria other than tubercle bacilli. Therefore, diagnosis of TB disease cannot be proven until further results are available.

D. A, B, and C are all correct.

E. Only A and B are correct.

Case Study– Francis

In the health clinic you see Francis, a new patient. She 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.

4.31 What parts of Francis' medical history lead you to suspect TB disease?
(circle the one best answer)

A. Her symptoms of TB disease (weight loss, fever, and a persistent cough).

B. The fact that she has been treated for TB disease in the past.

C. Her history of injecting illegal drugs (heroin).

D. A, B, and C are all correct.

E. Only A and C are correct.

4.32 What diagnostic tests should be done on Francis?
(circle the one best answer)

A. Sputum specimen collection for smear and culture.

B. Drug-susceptibility testing if culture is positive.

C. Chest radiograph because she has symptoms of pulmonary TB disease.

D. A, B, and C are all correct.

E. Only A and B are correct.

Genotyping

TB genotyping is a laboratory-based approach used to analyze the genetic material (i.e., DNA) of *M. tuberculosis*. The total genetic content is referred to as the genome. Specific sections of the *M. tuberculosis* genome form distinct genetic patterns that help distinguish different strains of *M. tuberculosis*. *M. tuberculosis* genotyping is based on polymorphisms in the number and genomic location of mycobacterial repetitive elements. *M. tuberculosis* isolates with identical genotypes suggest that there may have been recent TB transmission among the persons from whom they were isolated. The main purpose of genotyping is to add to TB controllers' understanding of TB transmission in their community.

TB genotyping is a laboratory-based approach used to analyze the genetic material (i.e., DNA) of *M. tuberculosis*.

M. tuberculosis isolates with identical genotypes are often indicative of recent TB transmission among the persons from whom they were isolated.

When coupled with traditional epidemiologic investigations, analyses of the genotype of *M. tuberculosis* strains have confirmed suspected transmission and detected unsuspected transmission of *M. tuberculosis*. These analyses have also identified risk factors for recent infection with rapid progression to disease, demonstrated re-infection with different strains, identified weaknesses in conventional contact investigations, documented the existence of laboratory cross-contamination, and identified outbreaks of TB that were not previously recognized (Table 4.5). Genotyping has become an increasingly useful tool for studying the pathogenesis, epidemiology, and transmission of TB infection and disease.

Table 4.5
Use of Genotyping Analyses

How Genotyping Has Been Used
• Confirmed suspected transmission and detected unsuspected transmission of *M. tuberculosis*, when coupled with traditional epidemiologic investigations
• Identified risk factors for recent infection with rapid progression to disease
• Demonstrated re-infection with different strains
• Identified weaknesses in conventional contact investigations
• Documented the existence of laboratory cross-contamination
• Identified outbreaks of TB that were not previously recognized

Study Question

4.33 What is the main purpose of genotyping?
(choose the one best answer)

A. To amplify DNA and RNA segments to rapidly identify the microorganisms in a specimen.

B. To add to TB controllers' understanding of TB transmission in their community.

C. To determine drug susceptibility of TB strains.

D. A, B, and C are all correct.

E. Only A and B are correct.

Chapter Summary

TB is **not** as common as it was many years ago in the United States; consequently, clinicians do **not** always consider the possibility of TB disease when evaluating patients who have symptoms. As a result, the diagnosis of TB disease may be delayed or even overlooked, and the patient may remain ill and possibly infectious for a prolonged period.

Not all persons with TB disease have symptoms; however, most persons with TB disease have one or more symptoms that lead them to seek medical care. All persons with symptoms of TB disease, and either a positive TST or IGRA indicative of *M. tuberculosis* infection, should be medically evaluated.

A complete medical evaluation for TB disease includes the following five components:

1. Medical history
2. Physical examination
3. Test for *M. tuberculosis* infection
4. Chest radiograph
5. Bacteriologic examination of clinical specimens

1. Medical History

When conducting a medical history, the clinician should ask if any symptoms of TB disease are present; if so, for how long, and if there has been known exposure to a person with infectious TB disease. Equally important is obtaining information on whether or not the person has been diagnosed in the past with LTBI or TB disease.

TB disease most commonly affects the lungs and is referred to as pulmonary TB disease. Symptoms include:

- Cough (especially if lasting for 3 weeks or longer) with or without sputum collection
- Coughing up blood (hemoptysis)
- Chest pain
- Loss of appetite
- Unexplained weight loss
- Night sweats
- Fever
- Fatigue

Extrapulmonary TB disease may cause symptoms related to the part of the body that is affected. For example, TB of the spine may cause back pain; TB of the kidney may cause blood in the urine; TB meningitis may cause headache or confusion. Extrapulmonary TB disease should be considered in the differential diagnosis of ill persons who have systemic symptoms and who are at high risk for TB disease.

Both pulmonary and extrapulmonary TB disease symptoms can be caused by other diseases; however, they should prompt the clinician to consider TB disease.

2. Physical Examination

A physical examination is an essential part of the evaluation of any patient. It **cannot** be used to confirm or rule out TB disease, but it can provide valuable information about the patient's overall condition, inform the method of diagnosis, and reveal other factors that may affect TB disease treatment, if diagnosed.

3. Test for *M. tuberculosis* Infection

Selection of the most suitable tests for detection of *M. tuberculosis* infection should be based on the reasons and the context for testing, test availability, and overall cost effectiveness of testing. Currently, there are two methods available for the detection of *M. tuberculosis* infection in the United States. The tests are:

- Mantoux tuberculin skin test (TST); and
- Interferon-gamma release assays (IGRAs)
  - » QuantiFERON-TB Gold In-Tube test (QFT-GIT)
  - » T-SPOT®.*TB* test.

These tests may help clinicians differentiate people infected with *M. tuberculosis* from those uninfected. However, a negative reaction to any of the tests does **not** exclude the diagnosis of TB disease or LTBI.

4. Chest Radiograph

With pulmonary TB being the most common form of disease, the chest radiograph is useful for diagnosis of TB disease. Chest abnormalities can suggest pulmonary TB disease. A posterior-anterior radiograph of the chest is the standard view used for the detection of chest abnormalities. In some cases, especially in children, a lateral view may be helpful.

Abnormalities seen on chest radiographs may be suggestive of, but are never diagnostic of, TB disease. Chest radiographs may be used to exclude TB disease in an HIV-negative person who has a positive TST reaction or IGRA and who has no symptoms or signs of TB disease.

5. Bacteriologic Examination of Clinical Specimens

Examinations of clinical specimens (for example, sputum or urine) are of critical diagnostic importance. The specimens should be examined and cultured in a laboratory that specializes in testing for *M. tuberculosis*. The bacteriologic examination has five parts:

- Specimen collection, processing, and review;
- AFB smear classification and results;
- Direct detection of *M. tuberculosis* in clinical specimen (NAA);
- Specimen culturing and identification; and
- Drug-susceptibility testing.

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Chapter 5
Treatment for Latent Tuberculosis Infection

Table of Contents

Chapter Objectives

After working through this chapter, you should be able to

- List the high-risk groups who should be given priority for latent tuberculosis infection (LTBI) treatment;
- Describe LTBI treatment regimens;
- Describe LTBI treatment regimens for specific situations; and
- Identify components of patient monitoring at baseline and during the treatment of LTBI.

Introduction

It is currently estimated that more than 11 million people in the United States have latent tuberculosis (TB) infection, which is about 4 percent of the total population. While not everyone with latent TB infection (LTBI) will develop TB disease, about 5 to 10 percent of infected people will develop TB disease if not treated. This equates to approximately 550,000 to 1,100,000 people who will develop TB at some point in their life, unless they receive adequate treatment for LTBI.

Treatment of LTBI is essential to controlling and eliminating TB disease in the United States. It substantially reduces the risk that persons infected with *M. tuberculosis* will progress to TB disease. Certain groups are at high risk of developing TB disease once infected. Targeted testing programs should be designed to identify persons who are at high risk for TB disease and who would benefit from treatment of LTBI. Targeted testing should be undertaken only if resources are identified and available to ensure full evaluation and treatment. There are two methods available for the detection of *M. tuberculosis* infection in the United States, the Mantoux tuberculin skin test (TST) and interferon-gamma release assays (IGRAs) (see Chapter 3, Testing for Tuberculosis Infection and Disease).

Targeted testing programs should be designed to identify persons who are at high risk for TB disease and who would benefit from treatment of LTBI.

Study Question

5.1 Which statement about the purpose of LTBI treatment is true?
(choose the one best answer)

F. It is given to people who have LTBI to prevent them from testing positive on a subsequent TST.

G. It is given to people who have LTBI to prevent the progression to TB disease.

H. It is given to people who have TB disease to prevent the disease from getting worse.

I. It is given to people who have TB disease to prevent them from becoming infectious.

Candidates for the Treatment of LTBI

Persons with Positive IGRA Result, or TST Reaction ≥5 mm

Persons in the following high-risk groups should be given treatment for LTBI if they have either a positive IGRA result **or** if their reaction to the TST is ≥5 mm (Table 5.1):

- HIV-infected persons;
- Recent contacts of persons with infectious TB disease;
- Persons with fibrotic changes on chest radiograph consistent with prior TB disease (once TB disease is excluded); and
- Patients with organ transplants, and other immunosuppressed patients (including patients receiving the equivalent of 15 mg/day of prednisone for >1 month).

Persons with Positive IGRA Result, or TST Reaction ≥10 mm

Persons in the following high-risk groups should be considered for treatment of LTBI if they have either a positive IGRA result **or** if their reaction to the TST is ≥10 mm (Table 5.1):

- Recent arrivals to the United States (<5 years) from high-prevalence areas (e.g., Africa, Asia, Eastern Europe, Latin America, and Russia);
- Injection drug users;
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, and hospitals);
- Mycobacteriology laboratory personnel;
- Persons with medical conditions that increase the risk for progression to TB disease, i.e., silicosis, diabetes mellitus, chronic renal failure, certain types of cancer (e.g., leukemia and lymphomas, or cancer of the head, neck, or lung), gastrectomy or jejunoileal bypass, and weight loss of at least 10% from ideal body weight;
- Children younger than 5 years of age; and
- Infants, children, and adolescents exposed to adults in high-risk categories (see Chapter 3, Testing for Tuberculosis Disease and Infection).

Table 5.1
High-Priority Candidates for LTBI Treatment Using IGRA or TST*

Groups Who Should Be Given High Priority for LTBI Treatment	
People who have a positive IGRA result or a TST reaction of 5 or more millimeters	**People who have a positive IGRA result or a TST reaction of 10 or more millimeters**
• HIV-infected persons** • Recent contacts of persons with infectious TB disease** • Persons with fibrotic changes on chest radiograph consistent with prior TB disease • Patients with organ transplants and other immunosuppressed patients (including patients receiving the equivalent of 15 mg/day of prednisone for ≥1 month)	• Recent arrivals to the United States (<5 years) from high-prevalence areas (e.g., Asia, Africa, Eastern Europe, Russia, or Latin America) • Injection drug users • Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, hospitals, or other health-care facilities) • Mycobacteriology laboratory personnel • Persons with medical conditions that increase the risk for progression to TB disease, including silicosis, diabetes mellitus, chronic renal failure, certain types of cancer (e.g., leukemia and lymphomas, or cancer of the head, neck or lung), gastrectomy or jejunoileal bypass, and weight loss of at least 10% below body weight; • Children younger than 5 years of age; or children and adolescents exposed to adults in high-risk categories

* See Chapter 3, Testing for Tuberculosis Infection and Disease for information on interpreting a TST or IGRA result

** In certain circumstances, people in these categories may be given LTBI treatment even if they do **not** have a positive TST or IGRA result (see the Special Considerations for LTBI Treatment section in this Chapter).

Persons with No Known Risk Factors Who Have Positive IGRA Result, or TST Reaction ≥15 mm

People without any risk factors generally should **not** be tested for TB infection. Testing should be targeted to groups at high risk for LTBI and TB disease (see Chapter 3, Testing for Tuberculosis Infection and Disease). However, if a person without any risk factors is tested and has a positive IGRA result or TST reaction that is ≥15 mm, he or she should be evaluated for LTBI treatment once TB disease is excluded.

People without any risk factors generally should not be tested for TB infection.

Close Contacts Who Have a Negative IGRA or TST Result

Some contacts who have a negative IGRA or TST result should be evaluated for treatment of LTBI after TB disease has been ruled out. These contacts include:

- Children less than 5 years of age
- Immunosuppressed persons
- Those at risk for rapid progression to TB disease once infected (see Chapter 3, Testing for Tuberculosis Infection and Disease)

Any contact who is to be treated for LTBI should have a chest radiograph to exclude pulmonary TB disease before starting treatment.

Any contact who is to be treated for LTBI should have a chest radiograph to exclude pulmonary TB disease before starting treatment.

Close contacts who have a negative IGRA or TST result should be retested 8 to 10 weeks after they were last exposed to infectious TB disease. This is due to the fact that it can take 2 to 8 weeks after TB infection for the body's immune system to react to tuberculin and for the infection to be detected.

Close contacts who have a negative IGRA or TST result should be retested 8 to 10 weeks after they were last exposed to infectious TB disease.

HIV-Infected Contacts

Contacts known or suspected to be HIV infected or who have other serious immunocompromising conditions should be started on treatment for LTBI regardless of their IGRA or TST result after TB disease has been excluded. Treatment of LTBI may be discontinued if the TST or IGRA result is negative on the second test given 8 to 10 weeks after the last exposure and if the person is no longer exposed to infectious TB disease. However, because HIV-infected and other immunocompromised persons may be anergic and not be able to manifest a positive TST or IGRA result if infected, in some cases medical providers may decide to prescribe a complete course of LTBI treatment even if the second TST or IGRA result is negative, particularly if the exposure to TB is substantial (e.g., prolonged, frequent exposure to very infectious TB patient).

Contacts known or suspected to be HIV infected or who have other serious immunocompromising conditions should be started on treatment for LTBI regardless of their IGRA or TST result after TB disease has been excluded.

Infants and Young Children

Because of their age, infants and young children with LTBI are known to have been infected recently, and thus are at a high risk of their infection progressing to TB disease (Table 5.2). Infants and young children are also more likely than older children and adults to develop life-threatening forms of TB disease, especially meningeal and disseminated disease, because they do **not** have fully developed immune systems.

Because of their age, infants and young children with LTBI are known to have been infected recently, and thus are at a high risk of their infection progressing to TB disease.

Infants and young children are more likely than older children and adults to develop life-threatening forms of TB disease.

Window Prophylaxis

Children less than 5 years of age who are close contacts to an adult with infectious TB should receive treatment for LTBI even if the TST result is negative and once TB disease is excluded by chest radiograph and symptom review; this is called "window" prophylaxis. Also, infected infants may be anergic as late as 6 months of age. A second TST should be administered 8 to 10 weeks after the last exposure to infectious TB disease. Window prophylaxis can be discontinued if all of the following conditions are met:

- The infant is at least 6 months of age
- The second TST result is also negative
- The second TST was performed at least 8 weeks after the child was last exposed to an adult with infectious TB disease

Children less than 5 years of age who are close contacts to an adult with infectious TB should receive treatment for LTBI even if the TST result is negative once TB disease is excluded by chest radiograph and symptom review.

Table 5.2
LTBI in Children

Infants and Young Children with LTBI	Treating Children Less than 5 Years of Age Who Are Close Contacts
• Are known to have been infected recently (because of their age) • Are more likely than older children and adults to develop life-threatening forms of TB disease (e.g., disseminated TB, TB meningitis)	• Should provide LTBI treatment even if initial TST result is negative once TB disease is excluded (infected infants may be anergic as late as 6 months of age)
	• Administer a second TST 8 to 10 weeks after the last exposure to infectious TB disease
	• Discontinue window prophylaxis if all of the following conditions are met: » Infant is at least 6 months of age » Second TST result is also negative » Second TST was performed at least 8 weeks after the child was last exposed to infectious TB disease

Study Questions

Match the patient with the TST reaction size that makes them a candidate for LTBI.
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Patients	TST Reaction that Makes Them a Candidate for LTBI
____ **5.2** Peter is an injection drug user.	**A.** ≥5 mm of induration
____ **5.3** Louis is HIV positive.	**B.** ≥10 mm of induration
____ **5.4** Katrina, a 4-year-old, is a recent arrival from Mexico.	**C.** ≥15 mm of induration
____ **5.5** Edith is a resident at the DeLand Nursing Home.	
____ **5.6** Ann lives with her brother Joel, who has infectious TB disease.	
____ **5.7** Richard is the recipient of a heart transplant.	
____ **5.8** Sherry is a bank teller and has no known risk factors for TB.	
____ **5.9** Ginny is a nurse in the Dade County Correctional Facility.	
____ **5.10** Joe is diabetic.	

5.11 The following close contacts to someone with infectious TB disease have a negative IGRA result. Which patient(s) should be evaluated for treatment of LTBI?
(choose the one best answer)

A. Bernard is being treated for leukemia.

B. Sophia is 6 years old.

C. Kathy works in a bakery.

D. A, B, and C are all correct.

E. Only A and B are correct.

5.12 When should close contacts who have a negative IGRA or TST result be retested?
(choose the one best answer)

A. 4 to 6 weeks after they were last exposed to infectious TB disease.

B. 8 to 10 weeks after they were last exposed to infectious TB disease.

C. It is **not** necessary to retest them.

5.13 Which of the following statements is true about infants and young children with LTBI?
(choose the one best answer)

A. Because of their age, they are known to have been infected recently.

B. They are at high risk of their infection progressing to TB disease.

C. They are less likely than older children and adults to develop life-threatening forms of TB disease.

D. A, B, and C are all correct.

E. Only A and B are correct.

LTBI Treatment Regimens

There are several treatment regimens available for the treatment of LTBI. Providers should choose the appropriate regimen based on

- Drug-susceptibility results of the presumed source case (if known);
- Coexisting medical illnesses; and
- Potential for drug-drug interactions (Table 5.3).

For persons who are at especially high risk for TB disease and are either suspected of nonadherence or are given an intermittent dosing regimen, directly observed therapy (DOT) for LTBI should be considered (for more information on DOT, see Chapter 6, Treatment of Tuberculosis Disease). This method of treatment is especially appropriate if the person in need of LTBI treatment lives with a household member who is on DOT for TB disease, or lives in an institution or facility where treatment for LTBI can be observed by a staff member. It is necessary to exclude TB disease before starting LTBI treatment.

For persons who are at especially high risk for TB disease and are either suspected of nonadherence or are given an intermittent dosing regimen, directly observed therapy (DOT) for LTBI should be considered.

Isoniazid (INH) Dosage

When INH alone is given to persons with TB disease, drug resistance may develop. For this reason, persons suspected of having TB disease should receive the recommended multidrug regimen for treatment of TB disease rather than INH monotherapy until the diagnosis is confirmed or excluded.

There are two options for treatment with INH (Table 5.3):

- 9-month regimen
- 6-month regimen

INH is normally used alone for treatment of LTBI in a single daily dose of 300 mg in adults and 10–20 mg/kg body weight in children, not to exceed 300 mg per dose. INH can be given two times a week at a dosage of 20–40 mg/kg by DOT for LTBI for children, or 900 mg for adults.

The 9-month regimen is preferred because it is more efficacious. Treatment for LTBI for 6 months rather than 9 months may be more cost-effective and result in greater adherence by patients; therefore, local programs may prefer to implement the 6-month regimen rather than the 9-month regimen. Every effort should be made to ensure that patients adhere to LTBI treatment for at least 6 months.

When INH alone is given to persons with TB disease, drug resistance may develop. For this reason, persons suspected of having TB disease should receive the recommended multidrug regimen for treatment of disease rather than INH monotherapy until the diagnosis is confirmed or excluded.

9-Month INH Regimen

A 9-month INH regimen is considered optimal treatment. In order to be considered adequate treatment, the patient must receive a minimum of 270 doses administered within 12 months. The preferred regimen for children 2 to 11 years of age is 9 months of daily INH. Patients may be treated with a twice-weekly regimen as an alternative as long as they are undergoing DOT. In a twice-weekly regimen, 76 doses administered within 12 months is considered adequate therapy.

6-Month INH Regimen

A 6-month INH regimen also provides substantial protection against developing TB disease, but it is less protective than the 9-month regimen. In order to be considered adequate treatment, the patient must receive a minimum of 180 doses administered within 9 months. Patients may be treated with a twice-weekly regimen given by DOT as an alternative regimen. In the twice-weekly regimen, 52 doses administered within 9 months is considered adequate therapy. This regimen is not recommended for children, or immunosuppressed persons, or those with evidence of previous TB on chest radiograph.

Isoniazid (INH) and Rifapentine (RPT) Regimen

3-Month INH-RPT Regimen (12-Dose Regimen)

The 12-dose regimen is a combination of INH and RPT given in 12 once-weekly doses under DOT. Because missed doses, altered dosing intervals or amounts, or incomplete treatment could jeopardize the 12-dose regimen efficacy or safety, DOT is strongly recommended for this regimen. Patients using the 12-dose regimen should undergo monthly clinical monitoring, including inquiries about side effects and a physical assessment for signs of adverse effects.

The 12-dose regimen

- Is recommended as an equal option to 9 months of daily INH, but does **not** replace other recommended treatment options for LTBI (Table 5.3)
- Is recommended for treating LTBI in
  - » Otherwise healthy people, 12 years of age or older and who were recently in contact with infectious TB, or who had tuberculin skin test or positive blood test for TB infection conversions.
- Can be considered for specific groups when it offers practical advantages, such as completion of treatment within a limited timeframe.

The 12-dose regimen is **not** recommended for children younger than 2 years, HIV-infected patients taking antiretroviral therapy (ART), patients with presumed INH or RIF-resistant *M. tuberculosis*, pregnant women, or women expecting to become pregnant within the treatment period.

The dosage for a combination 12-dose regimen of INH and RPT is:

Isoniazid (INH)

- 15 mg/kg rounded up to the nearest 50 or 100 mg with a 900 mg maximum.

Rifapentine (RPT)

- 10.0–14.0 kg 300 mg
- 14.1–25.0 kg 450 mg
- 25.1–32.0 kg 600 mg
- 32.1–49.9 kg 750 mg
- ≥ 50.0 kg 900 mg maximum.

INH is formulated as 100 mg and 300 mg tablets. RPT is formulated as 150 mg tablets packed in blister packs that should be kept sealed until usage. New formulations with larger dosage per tablet and fixed-dose INH-RPT combinations are in development.

The 12-dose regimen is recommended as an equal option to 9 months of daily INH, but does not replace other recommended treatment options for LTBI.

Table 5.3
Drug Regimens for the Treatment of LTBI*

Drug	Duration	Interval	Minimum Doses	Comments
INH	9 months	Daily	270	• The preferred regimen is daily treatment for 9 months • Recommended regimen for people with HIV, for children, and for people with chest radiograph findings suggestive of previous TB disease • DOT **must** be used with twice-weekly dosing
		Twice weekly	76	
	6 months	Daily	180	• **Not** recommended for people with HIV, for children, or for people with chest radiograph findings suggestive of previous TB disease • DOT **must** be used with twice-weekly dosing
		Twice weekly	52	
INH and RPT	3 months	Once weekly	12	• Recommended as an equal alternative to 9 months of daily INH for otherwise healthy patients aged ≥12 years who were recently in contact with infectious TB, or who had tuberculin skin test or a positive blood test for TB infection conversions • The 12-dose regimen can be considered for other groups when it offers practical advantages, such as completion within a limited timeframe • DOT is strongly recommended • **Not** recommended for children younger than 2 years, HIV-infected patients taking ART, patients with presumed INH or RIF-resistant *M. tuberculosis*, pregnant women, or women expecting to become pregnant within the treatment period

* For more detailed information on LTBI treatment, please refer to Targeted tuberculin testing and treatment of latent TB infection. *MMWR* 2000; 49 (No. RR-6).
http://www.cdc.gov/tb/publications/reportsarticles/mmwr/mmwr_updates.htm

* Adverse event data and revised American Thoracic Society/CDC recommendations against the use of rifampin and pyrazinamide for treatment of latent tuberculosis infection. *MMWR* 2003; 52 (31).
http://www.cdc.gov/MMWR/preview/MMWRhtml/mm5231a4.htm

* Recommendations for use of an isoniazid-rifapentine regimen with direct observation to treat latent *Mycobacterium tuberculosis* infection. MMWR 2011; 60 (48).
http://www.cdc.gov/mmwr/preview/mmwrhtml/mm6048a3.htm?s_cid=mm6048a3_w

Table 5.4
Adverse Drug Reactions to INH

Adverse Reaction	Comments
Peripheral neuropathy	• Uncommon at doses of 5 mg/kg • Those at risk may also be given pyridoxine (vitamin B_6) » Persons at high risk for neuropathy (e.g., diabetes, uremia, alcoholism, malnutrition, HIV infection) » Pregnant women » Persons with a seizure disorder » Patients who develop signs and symptoms of peripheral neuropathy
Fatal hepatitis	• Pregnant women are at increased risk • Postpartum women are at increased risk, especially during the initial 3-month postpartum period
Elevated liver enzymes	• 10% to 20% of persons taking INH will have some mild elevation of liver enzymes. These tend to resolve even if INH is continued. • Discontinue INH if the following occurs: » Measurements exceed 3 times the normal limit with symptoms present » Measurements exceed 5 times the upper limit of normal in an asymptomatic individual • Provide close clinical and laboratory monitoring if there are any signs or symptoms of hepatotoxicity or liver function test elevations less than the levels listed above

Rifampin (RIF) Regimen

For persons who **cannot** tolerate INH or have been exposed to INH-resistant TB, an alternative treatment regimen is 4 months of RIF. In order to be considered adequate treatment, the patient must receive a minimum of 120 doses administered within 6 months. RIF should not be used in HIV-infected persons being treated with some combinations of ART. In some situations where RIF **cannot** be used because of interactions with ART, another drug, rifabutin, may be used.

For persons who cannot tolerate INH or have been exposed to INH-resistant TB, an alternative treatment regimen is 4 months of RIF.

RIF should not be used in HIV-infected persons being treated with some combinations of ART.

Adverse Drug Reactions

Patients on treatment for LTBI should be instructed to report any signs and symptoms of adverse drug reactions to their health care provider, including

- Unexplained anorexia, nausea or vomiting, dark urine*, or icterus
- Persistent paresthesia of hands and feet
- Persistent weakness, fatigue, fever, or abdominal tenderness
- Easy bruising or bleeding

Peripheral neuropathy is associated with the use of INH, but is uncommon at doses of 5 mg/kg (Table 5.4). Persons with risk factors for neuropathy (e.g., diabetes, uremia, alcoholism, malnutrition, HIV infection), pregnant women, and persons with seizure disorder may be given pyridoxine (vitamin B6) 10–50 mg/day with INH, as this may prevent neuropathy. Patients who develop signs and symptoms of peripheral neuropathy may also be started on vitamin B6.

About 10% to 20% of persons taking INH will have some mild, asymptomatic elevation of liver enzymes (ALT, AST). These abnormalities tend to resolve even if INH is continued. For this reason, routine monitoring of liver enzymes is not recommended for all patients receiving INH. In persons who experience symptoms consistent with liver injury, liver enzymes should be measured to evaluate for hepatotoxicity. If any of the liver enzymes exceed three times the normal limit with symptoms present, it is generally recommended that INH be withheld. For liver enzyme elevations less than three times the upper limit of normal in symptomatic patients, at minimum close clinical and laboratory monitoring should be instituted if treatment is to be continued. Additional information on monitoring patients on LTBI treatment is provided later in this chapter.

About 10% to 20% of persons taking INH will have some mild, asymptomatic elevation of liver enzymes.

Some evidence suggests that pregnant women are at increased risk for fatal hepatitis associated with INH. This risk may also increase during the immediate postpartum period. These persons should be closely monitored for adverse reactions throughout the course of treatment.

Recommendation Against the Use of RIF/Pyrazinamide (PZA) Treatment Regimen

Recommendations for the use of a daily or a twice-weekly, 2-month regimen of RIF with PZA for LTBI treatment have changed due to associated severe liver injury. Based on the high rates of hospitalization and death from liver injury in patients treated with RIF and PZA for LTBI treatment, the American Thoracic Society (ATS) and CDC now recommend that this regimen not be offered to persons with LTBI. Alternative regimens are recommended for the treatment of LTBI (Table 5.1). RIF and PZA should continue to be administered in multidrug regimens for the treatment of persons with TB disease.

RIF and PZA should not be offered to persons with LTBI.

RIF and PZA should continue to be administered in multidrug regimens for the treatment of persons with TB disease.

Study Questions

5.14 What should an appropriate LTBI treatment regimen be based on?
(choose the one best answer)

A. Drug-susceptibility results of the source case (if known).

B. Coexisting medical illnesses.

C. Potential for drug-drug interactions.

D. A, B, and C are all correct.

E. Only A and B are correct.

5.15 Which of the following is a recommended LTBI treatment regimen?
(choose the one best answer)

A. INH given daily (270 doses) for 9 months.

B. INH and RPT given once weekly (12 doses) for 3 months.

C. INH and RIF given daily (270 doses of each drug) for 9 months.

D. A, B, and C are all correct.

E. Only A and B are correct.

5.16 Which of the following is an adverse reaction to INH?
(choose the one best answer)

A. Peripheral neuropathy

B. Fatal hepatitis

C. Elevated liver enzymes

D. A, B, and C are all correct.

E. Only A and B are correct.

5.17 Which of the following statements about the use of the RIF/PZA drug combination for treating LTBI is true? (circle the one best answer)

A. Can be used for both HIV-negative and HIV-infected patients who cannot tolerate INH.

B. Not recommended for LTBI treatment based on high rates of hospitalization and death from liver injury.

C. Is the recommended drug for treating pregnant women.

D. A, B, and C are all correct.

E. Only A and B are correct.

5.18 What LTBI treatment regimen may be recommended for people with a positive TST or IGRA result who have been exposed to INH-resistant TB disease?
(circle the one best answer)

A. RIF, at a minimum of 120 doses for 4 months.

B. RIF, at a minimum of 180 doses for 6 months.

C. RIF, at a minimum of 270 doses for 9 months.

LTBI Treatment Regimens for Specific Situations

HIV-Infected Persons

LTBI treatment of HIV-infected persons should be provided in consultation with an expert in the management of HIV and TB.

LTBI treatment of HIV-infected persons should be done in consultation with an expert in the management of HIV and TB.

INH

A 9-month regimen of daily INH is considered the optimal treatment for HIV-infected adults with LTBI. To be considered adequate therapy, the patient must receive a minimum of 270 doses of INH administered within 12 months. HIV-infected children should receive 9 months of INH treatment for LTBI. To be considered adequate therapy for HIV-infected persons, twice-weekly regimens of INH must be administered by DOT and consist of at least 76 doses administered within 12 months.

In HIV-infected persons, INH may be administered together with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or non-nucleoside reverse transcriptase inhibitors (NNRTIs). Children and adolescents who are HIV infected and/or have nutritional deficiencies should receive pyridoxine (vitamin B_6) supplementation.

INH-RPT (12-dose Regimen)

HIV-infected persons who are receiving ART should **not** take the 12-dose regimen of INH-RPT because the drug interactions have not been studied. However, HIV-infected persons who are otherwise healthy and are not receiving ART can be considered for the 12-dose regimen.

RIF

For HIV-infected patients who cannot tolerate INH or have been exposed to INH-resistant TB, an alternative treatment regimen is 4 months of RIF. To be considered adequate treatment, the patient must receive a minimum of 120 doses of RIF administered within 6 months. RIF should not be used in HIV-infected persons being treated with some combinations of ART. In some situations where RIF cannot be used because of interactions with ART, another drug, rifabutin, may be used.

Most protease inhibitors and delavirdine should not be administered together with RIF. Rifabutin with appropriate dose adjustments can be used with protease inhibitors and NNRTIs (except delavirdine). For more information, please see Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/default.htm.

Persons with Fibrotic Lesions

Persons who have a chest radiograph suggestive of old fibrotic lesions thought to represent previous TB disease should be treated for LTBI if they have the following:

- A positive IGRA result, or TST reaction (induration) of 5 mm or more;
- No symptoms of infectious TB disease; and
- No history of treatment for TB disease.

These persons should be evaluated with three sputum specimens for AFB smear and culture and only treated for LTBI once these specimens are negative by culture. Acceptable regimen options are described in Table 5.5.

Persons with evidence suggestive of healed, primary TB disease (i.e., calcified solitary pulmonary nodules, calcified hilar lymph nodes, and apical pleural capping) are **not** at increased risk for TB disease. Their risk for developing TB disease and the need for treatment of LTBI should be determined by consideration of other risk factors.

Persons with evidence suggestive of healed, primary TB disease (i.e., calcified solitary pulmonary nodules, calcified hilar lymph nodes, and apical pleural capping) are not at increased risk for TB disease.

Table 5.5
Drug Regimens for the Treatment of LTBI for Persons with Fibrotic Lesions

Drug	Duration	Interval	Minimum Doses	Comments
INH*	9 months	Daily	270	Provide LTBI treatment for patients who have a chest radiograph suggestive of old fibrotic lesions thought to represent previous TB disease and • A positive IGRA result or a TST reaction (induration of 5 mm or more) • No symptoms of infectious TB disease • No history of treatment for TB disease • Three negative sputum smears and cultures
		Twice weekly	76	
RIF	4 months	Daily	120	

* Preferred.

Contacts of Persons with Multidrug-Resistant TB

If a person is a contact of a patient with multidrug-resistant (MDR) TB, the risk of progressing to MDR TB disease should be considered before recommending treatment for LTBI. For persons likely to have been infected with a strain of *M. tuberculosis* resistant to both INH and RIF, alternative LTBI treatment regimens should be considered. The treatment of drug-resistant LTBI should be prescribed **in consultation with an MDR TB expert**.

If a person is a contact of a patient with multidrug-resistant (MDR) TB, the risk of progressing to MDR TB disease should be considered before recommending treatment for LTBI.

Pregnancy and Breast-feeding

INH administered either daily or twice weekly is the preferred regimen for the treatment of LTBI in pregnant women. Pregnant women taking INH should also take pyridoxine (vitamin B6) supplementation to ameliorate the side effects of the drug (Table 5.6). For pregnant women who are intolerant of INH or likely to be infected with an INH-resistant strain of *M. tuberculosis*, consultation with a TB expert is recommended.

The 12-dose regimen of INH-RPT is **not** recommended for pregnant women or women expecting to become pregnant during the treatment period because its safety in pregnancy has not yet been studied.

The 12-dose regimen of INH-RPT is not recommended for pregnant women or women expecting to become pregnant during the treatment period because its safety in pregnancy has not yet been studied.

For women who are at high risk for progression from LTBI to TB disease, especially those who are HIV infected or diabetic, LTBI treatment should **not** be delayed on the basis of pregnancy alone, even during the first trimester. TB disease must be excluded through symptom review (to see an example, go to: http://health.state.ga.us/pdfs/tb/TB.Symp.Screen.09.Eng.pdf) and chest radiograph prior to initiation of LTBI treatment. For these women, careful clinical monitoring and/or lab monitoring should be conducted.

For women who are at high risk for the progression of LTBI to TB disease, especially those who are HIV infected or diabetic, LTBI treatment should not be delayed on the basis of pregnancy alone, even during the first trimester.

Breast-feeding is not contraindicated when a mother is being treated for LTBI. The amount of INH in the mother's breast milk is inadequate to either harm or benefit an infant. Breast-fed infants of mothers who take INH should receive supplemental pyridoxine (vitamin B_6).

Table 5.6
Drug Regimens for the Treatment of LTBI for Pregnancy and Breast-Feeding

Drug	Duration	Interval	Minimum Doses	Comments
INH	9 months	Daily	270	• **Do not** delay initiation of therapy based on pregnancy alone, even during the first trimester for women who are at high risk for progression from LTBI to TB disease, especially those who are HIV infected or diabetic • Breast-feeding is **not** contraindicated when a mother is being treated for LTBI • The amount of INH provided in the mother's breast milk is inadequate to either harm or benefit an infant. • Breast-feeding infants whose mothers are taking INH should receive supplemental pyridoxine (vitamin B_6)
		Twice weekly	76	

Study Questions

Case Study– Jesse

Jesse has fibrotic lesions representative of previous TB disease, a TST reaction of 5 mm, and no history of treatment for TB disease.

5.19 How should Jesse be evaluated?
(choose the one best answer)

A. With a CT scan to determine the extent of lesions

B. With three sputum specimens for AFB smear and culture

C. With a bronchoscopy to obtain specimen samples

D. A, B, and C are all correct.

E. Only A and B are correct.

5.20 Once TB disease is ruled out, what should Jesse's LTBI treatment regimen include?
(choose the one best answer)

A. 3 months of INH or 1 month of RIF

B. 6 months of INH or 2 months of RIF

C. 9 months of INH or 4 months of RIF

5.21 Which of the following statements about pregnancy and breast-feeding is true?
(choose the one best answer)

A. The preferred regimen for the treatment of LTBI in pregnant women is INH taken daily or twice weekly, with pyridoxine supplement.

B. For pregnant women who are HIV infected, initiation of therapy should **not** be delayed on the basis of pregnancy alone even during the trimester.

C. Breast-feeding is contraindicated when a mother is being treated for LTBI.

D. A, B, and C are all correct.

E. Only A and B are correct.

Patient Monitoring

Patient Medical Evaluation and Monitoring for LTBI Treatment

The components of patient monitoring for LTBI treatment include:

- Medical evaluation prior to LTBI treatment
- Baseline laboratory testing
- Monthly medical evaluation
- Routine laboratory monitoring
- Treatment follow-up

Medical Evaluation Prior to LTBI Treatment

Before treatment for LTBI is started, clinicians should conduct a medical history to:

- Exclude the possibility of TB disease, including symptom review;
- Determine if there is a history of prior treatment for LTBI or TB disease;
- Determine if there are any co-existing medical conditions that are a contraindication to LTBI treatment or are associated with an increased risk of adverse effects from treatment;
- Obtain information about current and previous drug therapy, including any previous or current adverse reactions to drugs considered for treatment of LTBI; and
- Recommend HIV testing for all TB and LTBI patients after the patient is notified that testing will be performed, unless the patient declines (opt-out screening).

In addition, conducting a medical history provides an opportunity to establish rapport with the patient and to highlight important aspects of treatment, such as:

- Benefits of treatment;
- Importance of adherence to the treatment regimen;
- Possible adverse side effects of the regimen; and
- Establishment of an optimal follow-up plan.

A chest radiograph should be performed; LTBI treatment should only be prescribed if the radiograph is normal, without evidence of any findings consistent with TB disease. If there are any abnormalities consistent with TB disease or if the patient is symptomatic, the patient should have three sputum specimens collected for AFB smear and culture, and only be given treatment for LTBI once all three cultures are negative.

A chest radiograph should be performed; LTBI treatment should only be prescribed if the radiograph is normal, without evidence of any findings consistent with TB disease.

Baseline Laboratory Testing

Baseline laboratory testing is **not** routinely indicated for all patients at the start of treatment for LTBI. Baseline hepatic measurements of serum AST (SGOT) or ALT (SGPT) and bilirubin are indicated for patients whose initial evaluation suggests a liver disorder. Baseline testing is also indicated for

- Patients with HIV infection;
- Women who are pregnant or in the immediate postpartum period (within 3 months after delivery); or
- Persons with a history of chronic liver disease (e.g., hepatitis B or C, alcoholic hepatitis or cirrhosis), persons who use alcohol regularly, and others who are at risk of chronic liver disease.

Baseline laboratory testing is **not** routinely indicated in older persons. However, testing may be considered on an individual basis, particularly for patients who are taking other medications for chronic medical conditions. Active hepatitis and end-stage liver disease are relative contraindications to the use of INH or RIF for treatment of LTBI. Use of these drugs in such patients must be undertaken with caution. Patients with baseline abnormal liver function tests should be monitored at regular intervals with clinical and laboratory evaluation.

Patients with baseline abnormal liver function tests should be monitored at regular intervals with clinical and laboratory evaluation.

Baseline laboratory testing is not routinely indicated in older persons. However, testing may be considered on an individual basis, particularly for patients who are taking other medications for chronic medical conditions.

Monthly Evaluation

At least once a month, the patient should be evaluated for

- Adherence to the prescribed regimen;
- Signs and symptoms of TB disease; and
- Signs and symptoms of adverse effects, especially hepatitis (i.e., jaundice, loss of appetite, fatigue, and/or muscle and joint aches).

Routine Laboratory Monitoring

Routine laboratory monitoring during treatment of LTBI is recommended only for those whose baseline liver function tests are abnormal and for other persons with a risk of hepatic disease. Clinicians should order laboratory testing, such as liver function studies, for patients with symptoms compatible with hepatotoxicity, to evaluate possible adverse reactions that occur during the treatment regimen. If any of the liver enzymes exceed three times the normal limit with symptoms present or five times the upper limit of normal in an asymptomatic individual, it is generally recommended that INH be withheld. For liver enzyme elevations less than three times the upper limit of normal in

symptomatic patients, at minimum close clinical and laboratory monitoring should be instituted if treatment is to be continued.

Treatment Follow-Up

Patients should receive documentation of TST or IGRA results, medication taken, treatment duration, and treatment completion dates. They should be told to present this documentation when they are required to be tested for TB. Patients should also be re-educated about the signs and symptoms of TB disease and advised to seek medical attention if these occur. They should be advised that treatment greatly reduces the risk of progression to disease, but does not entirely eliminate it.

Patients should be advised that treatment greatly reduces the risk of progression to disease but does not entirely eliminate it.

Study Questions

5.22 Why should patients receive a medical evaluation before starting treatment for LTBI?
(choose the one best answer)

A. To exclude the possibility of TB disease

B. To determine if there is a history of prior treatment for LTBI or TB disease

C. To determine existing medical conditions

D. A, B, and C are all correct.

E. Only A and B are correct.

Case Study– Edgar, Louise, and Samantha

Edgar was admitted to the hospital last week and diagnosed with infectious TB disease. He lives with his wife, Louise, and 1-year-old daughter Samantha. You visit their home to give both Louise and Samantha a TST. Neither one has symptoms of TB disease. You return 2 days later to read the results. You find that Louise has 14 mm of induration, but Samantha has no induration.

5.23 Why should Louise, Edgar's wife, be evaluated for LTBI treatment?
(choose the one best answer)

A. She is a close contact of someone with infectious TB disease.

B. She has a positive skin test reaction of greater than 5 mm.

C. She has an infant daughter.

D. A, B, and C are all correct.

E. Only A and B are correct.

5.24 After Louise is evaluated, when should she receive LTBI treatment?
(choose the one best answer)

A. After TB disease is ruled out.

B. After it has been determined that she has never been treated for TB infection or disease.

C. After any medical problems that may complicate therapy have been ruled out.

D. A, B, and C are all correct.

E. Only A and B are correct.

5.25 Should Samantha, Edgar's daughter, receive LTBI treatment?
(choose the one best answer)

A. Yes, she should start LTBI treatment after TB disease has been excluded because she is a close contact of a person with infectious TB disease and she is less than 4 years old.

B. No, because she had a negative TST.

5.26 Baseline laboratory testing is routinely indicated for which of the following patients?
(choose the one best answer)

A. HIV-infected persons

B. Pregnant women

C. Teenagers

D. A, B, and C are all correct.

E. Only A and B are correct.

5.27 Loretta is receiving LTBI treatment and is evaluated each month by her public health nurse. What should she be evaluated for?
(choose the one best answer)

A. Adherence to the prescribed regimen

B. Signs and symptoms of TB disease

C. Signs and symptoms of adverse effects, especially hepatitis

D. A, B, and C are all correct.

E. Only A and B are correct.

5.28 Routine laboratory monitoring is recommended for which of the following patients with LTBI? (circle the one best answer)

A. Persons whose baseline liver function tests are abnormal

B. Persons with a risk of hepatic disease

C. All patients receiving LTBI

D. A, B, and C are all correct.

E. Only A and B are correct.

Chapter Summary

Treatment of LTBI is essential to controlling and eliminating TB disease in the United States. It substantially reduces the risk that persons infected with *M. tuberculosis* will progress to TB disease. Certain groups are at high risk of developing TB disease once infected. Targeted testing programs should be designed to identify persons who are at high risk for TB disease and who would benefit from treatment of LTBI. Targeted testing should be undertaken only if resources are identified and available to ensure full evaluation and treatment. There are two methods available for the detection of *M. tuberculosis* infection in the United States, the TST and IGRAs.

Persons in the following high-risk groups should be given treatment for LTBI if they have either a positive IGRA result **or** if their reaction to the tuberculin skin test is ≥5 mm:

- HIV-infected persons;
- Recent contacts of persons with infectious TB disease;
- Persons with fibrotic changes on chest radiograph consistent with prior TB disease (once TB disease is excluded); and
- Patients with organ transplants, and other immunosuppressed patients (including patients receiving the equivalent of 15 mg/day of prednisone for ≥1 month).

Persons in the following high-risk groups should be considered for treatment of LTBI if they have either a positive IGRA result **or** if their reaction to the TST is ≥10 mm:

- Recent arrivals to the United States (<5 years) from high-prevalence areas (e.g. Africa, Asia, Eastern Europe, Latin America, and Russia);
- Injection drug users;
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, nursing homes, homeless shelters, and hospitals);
- Mycobacteriology laboratory personnel;
- Persons with medical conditions that increase the risk for progression to TB disease, i.e., silicosis, diabetes mellitus, chronic renal failure, certain types of cancer (e.g., leukemia and lymphomas, or cancer of the head, neck, or lung), gastrectomy or jejunoileal bypass, and weight loss of at least 10% from ideal body weight;

- Children younger than 5 years of age; and
- Infants, children, and adolescents exposed to adults in high-risk categories.

People without any risk factors generally should **not** be tested for TB infection. Testing should be targeted to groups at high risk for LTBI and TB disease. However, if a person without any risk factors is tested and has a positive IGRA result or TST reaction that is ≥15 mm, he or she should be evaluated for LTBI treatment once TB disease is excluded.

There are several treatment regimens available for the treatment of LTBI. Providers should choose the appropriate regimen based on the susceptibility results of the presumed source case (if known), coexisting medical illnesses, and the potential for drug-drug interactions.

INH Regimens

When INH alone is given to persons with TB disease, resistance may develop. For this reason, persons suspected of having TB disease should receive the recommended multidrug regimen for treatment of TB disease rather than INH monotherapy until the diagnosis is confirmed or excluded.

There are two options for treatment with INH:

- 9-month regimen
- 6-month regimen

INH is normally used alone for treatment of LTBI in a single daily dose of 300 mg in adults and 10–20 mg/kg body weight in children, not to exceed 300 mg per dose. INH can be given two times a week at a dosage of 20–40 mg/kg by DOT for LTBI for children, or 900 mg for adults.

The 9-month regimen is the preferred because it is more efficacious. Treatment for LTBI for 6 months rather than 9 months may be more cost-effective and result in greater adherence by patients; therefore, local programs may prefer to implement the 6-month regimen rather than the 9-month regimen. Every effort should be made to ensure that patients adhere to treatment for LTBI infection for at least 6 months.

9-Month INH Regimen

A 9-month INH regimen is considered optimal treatment. In order to be considered adequate treatment, the patient must receive a minimum of 270 doses administered within 12 months. The preferred regimen for children 2 to 11 years of age is 9 months of daily INH. Patients may be treated with a twice-weekly regimen as an alternative as long as they are undergoing DOT. In a twice-weekly regimen, 76 doses administered within 12 months is considered adequate therapy.

6-Month INH Regimen

A 6-month INH regimen also provides substantial protection against developing TB disease, but it is less protective than the 9-month regimen. In order to be considered adequate treatment, the patient must receive a minimum of 180 doses administered within 9 months. Patients may be treated with a twice-weekly regimen given as DOT as an alternative. In a twice-weekly regimen, 52 doses administered within 9 months is considered adequate therapy. This regimen is not recommended for children, or immunosuppressed persons, or those with evidence of previous TB on chest radiograph.

3-Month INH-RPT Regimen (12-Dose Regimen)

The 12-dose regimen is a combination of INH and RPT given in 12 once-weekly doses under DOT. Because missed doses, altered dosing intervals or amounts, or incomplete treatment could jeopardize the 12-dose regimen efficacy or safety, DOT is strongly recommended for this regimen. Patients using the 12-dose regimen should undergo monthly clinical monitoring, including inquiries about side effects and a physical assessment for signs of adverse effects.

The 12-dose regimen does **not** replace other recommended treatment options for LTBI, but can be considered an equal option to the standard INH 9-month daily regimen for treating LTBI in otherwise healthy people, 12 years of age or older, who were recently in contact with infectious TB, or who had tuberculin skin test or blood test for TB infection conversions.

The dosage for a combination 12-dose regimen of INH and RPT is:

Isoniazid (INH)

- 15 mg/kg rounded up to the nearest 50 or 100 mg, with a 900 mg maximum.

Rifapentine (RPT)

- 10.0–14.0 kg 300 mg
- 14.1–25.0 kg 450 mg
- 25.1–32.0 kg 600 mg
- 32.1–49.9 kg 750 mg
- ≥ 50.0 kg 900 mg maximum.

INH is formulated as 100 mg and 300 mg tablets. RPT is formulated as 150 mg tablets packaged in blister packs that should be kept sealed until usage. New formulations with larger dosage per tablet and fixed-dose INH-RPT combinations are in development.

For persons who are at especially high risk for TB disease and are either suspected of nonadherence or given an intermittent dosing regimen, DOT for LTBI should be considered. This method of treatment is especially appropriate if the person in need of LTBI treatment lives with a household member who is on DOT for TB disease, or lives in an institution or facility where treatment for TB infection can be observed by a staff member. It is necessary to exclude TB disease before starting LTBI treatment.

Baseline laboratory testing is **not** routinely indicated for all patients at the start of treatment for LTBI. Baseline hepatic measurements of serum AST (SGOT) or ALT (SGPT) and bilirubin are indicated for patients whose initial evaluation suggests a liver disorder. Baseline testing is also indicated for:

- Patients with HIV infection;
- Women who are pregnant or in the immediate postpartum period (within 3 months of delivery); or
- Persons with a history of chronic liver disease (e.g., hepatitis B or C, alcoholic hepatitis or cirrhosis), persons who use alcohol regularly, and others who are at risk of chronic liver disease.

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Chapter 6
Treatment of Tuberculosis Disease

Table of Contents

Chapter Objectives

After working through this chapter, you should be able to

- Describe tuberculosis (TB) disease treatment adherence strategies;
- Identify anti-TB drugs;
- Describe treatment regimens for TB disease;
- Describe patient monitoring; and
- List common adverse drug reactions to TB medications.

Introduction

The major goals of treatment for TB disease are to

- Cure the individual patient;
- Minimize risk of death and disability; and
- Reduce transmission of *M. tuberculosis* to other persons.

To ensure that these goals are met, TB disease must be treated for at least 6 months and in some cases even longer. Most of the bacteria are killed during the first 8 weeks of treatment; however, there are persistent organisms that require longer treatment. If treatment is **not** continued for a long enough duration, the surviving bacteria may cause the patient to become ill and infectious again, potentially with drug-resistant disease.

There are several options for daily and intermittent therapy, but the goal of treatment for TB disease should be to provide the safest and most effective therapy in the shortest period of time. Given adequate treatment, almost all patients will recover and be cured.

Regimens for the treatment of TB disease must contain multiple drugs to which the bacteria are susceptible. The standard of care for initiating treatment of TB disease is four-drug therapy. Treatment with a single drug can lead to the development of a bacterial population resistant to that drug. Likewise, the addition of a single drug to a failing anti-TB regimen can lead to additional resistance. When two or more drugs to which in vitro susceptibility has been demonstrated are given together, each helps prevent the emergence of tubercle bacilli resistant to the others.

The standard of care for initiating treatment of TB disease is four-drug therapy. Treatment with a single drug can lead to the development of a bacterial population resistant to that drug.

Study Questions

6.1 The major goals for treatment of TB disease include which of the following?

A. Curing the individual patient

B. Minimizing risk of death and disability

C. Reducing transmission of *M. tuberculosis* to other persons

D. A, B, and C are all correct.

E. Only A and B are correct.

Are the following statements about TB treatment true or false?
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Statements		True or False
____ **6.2**	Most of the TB bacteria are killed during the first 8 weeks of treatment. However, some persistent organisms require longer treatment.	**A.** True **B.** False
____ **6.3**	Regimens for the treatment of TB disease need to only contain one drug to which the bacteria are susceptible.	
____ **6.4**	Treatment that is **not** continued for a long enough time allows the surviving bacteria to cause the patient to become ill and infectious again.	
____ **6.5**	Treatment with a single drug cannot lead to the development of a bacterial population resistant to that drug.	
____ **6.6**	When two or more drugs to which in vitro susceptibility has been demonstrated are given together, each helps prevent the emergence of tubercle bacilli resistant to the other drugs(s).	
____ **6.7**	Given adequate treatment, almost all patients will recover and be cured.	

Treatment and Monitoring Plan

For each patient with newly diagnosed TB disease, a specific treatment and monitoring plan should be developed in collaboration with the local TB control program within 1 week of the presumptive diagnosis. This plan should include:

- Description of the TB treatment regimen;
- Methods of assessing and ensuring adherence to the TB treatment regimen;
- Methods to monitor for adverse reactions; and
- Methods for evaluating treatment response.

Study Question

6.8 Which of the following should NOT be included in a treatment and monitoring plan? (choose the one best answer)

A. Description of the TB treatment regimen

B. Methods of assessing and ensuring adherence to the TB treatment regimen

C. Methods to monitor for adverse reactions

D. Methods to prevent a patient returning to work when noninfectious

E. Methods for evaluating treatment response

Adherence Strategies

To treat TB disease and prevent acquired drug resistance, clinicians must ensure that their patients with TB disease follow the recommended course of treatment. However, ensuring that patients adhere to treatment can be difficult because patients are often unable or reluctant to take multiple medications for several months. Nonadherence to treatment is a major problem in TB control. Inadequate treatment can lead to

- Treatment failure;
- Relapse;
- Ongoing transmission; and
- Development of drug resistance.

Responsibility for successful treatment is assigned to the health-care provider, **not** the patient. Health-care professionals should consult their health department's TB control program to ensure their TB patients are able to adhere to a prescribed treatment regimen. The TB control program should assist the health-care professional in evaluating patient barriers to adherence and recommend directly observed therapy (DOT) and the use of incentives and enablers that may assist the patient in completing the recommended therapy.

Inadequate treatment can lead to treatment failure, relapse, ongoing transmission, and the development of drug resistance.

Responsibility for successful treatment is assigned to the health-care provider, not the patient.

If these efforts are unsuccessful, the TB control program should take more restrictive action. The TB program should consider court-ordered DOT or, if all other measures fail, the involuntary isolation of a patient who is unwilling or unable to complete treatment. This is necessary to protect the general public from patients who are infectious, at risk of becoming infectious, or at risk for developing drug-resistant TB disease. A patient may be involuntarily isolated, but the patient **cannot** be forced to swallow anti-TB drugs. Involuntary isolation should only be pursued as a last resort after all less-restrictive measures have failed.

Patient Education

Educating patients about TB disease helps ensure their successful completion of therapy. Health-care providers must take the time to explain clearly to patients what medication should be taken, how much, how often, and when. Patients should be clearly informed about possible adverse reactions to the medications they are taking and when to seek necessary medical attention. Providing patients with the knowledge they need regarding the consequences of **not** taking their medicine correctly is very important. In addition, patients should be educated about infection control measures and potential need for isolation (Table 6.1). HIV testing and counseling is recommended for all patients with TB disease in all health-care settings. The patient must first be notified that testing will be performed. The patient has the right to decline HIV testing and counseling (opt-out screening).

Table 6.1
Patient Education

Topics to Include When Educating Patients
• What medication should be taken, how much, how often, and when
• Possible adverse reactions to the medications
• When to seek necessary medical attention
• Consequences of not taking their medicine correctly
• TB infection control measures and potential need for isolation

HIV testing and counseling is recommended for all patients with TB disease in all health-care settings.

Case Management

Case management is a strategy used to ensure that patients complete treatment for TB disease. There are three elements of case management:

1. Assigning responsibility;
2. Conducting a regular systematic review; and
3. Developing a plan to address barriers to adherence.

Case managers are health department employees, usually nurses or public health professionals, who are assigned primary responsibility for the management of specific patients. Case managers are held accountable for ensuring that each patient is educated about TB and treatment, ensuring that therapy is continuous and complete, and confirming that all contacts are evaluated according to CDC/National Tuberculosis Controllers Association guidelines. Some specific responsibilities may be assigned to other persons such as clinic supervisors, outreach workers, health educators, social workers, and human service workers. Case management is a patient-centered strategy. Whenever possible, a worker who has the same cultural and linguistic background as the patient should be assigned as case manager, to be able to help develop an individualized treatment adherence plan with the patient.

Case managers are held accountable for ensuring that each patient is educated about TB and treatment, ensuring that therapy is continuous and complete, and confirming that all contacts are evaluated according to CDC/ National Tuberculosis Controllers Association guidelines.

Directly Observed Therapy (DOT)

DOT is a component of case management that helps ensure patients adhere to therapy. It is the method whereby a trained health-care worker or another trained designated person watches a patient swallow each dose of anti-TB drugs and documents it. DOT is the preferred core management strategy recommended by CDC for treatment of TB disease and, if resources allow, for latent tuberculosis infection (LTBI) treatment. DOT can reduce the development of drug resistance, treatment failure, or relapse after the end of treatment. Good case management, which includes establishing a relationship with the patient and addressing barriers to adherence, facilitates successful DOT.

DOT is the preferred core management strategy recommended by CDC for treatment of TB disease and, if resources allow, for latent tuberculosis infection (LTBI) treatment.

Nearly all the treatment regimens for drug-susceptible TB disease can be given intermittently if they are directly observed. Using intermittent regimens reduces the total number of doses a patient must take, as well as the total number of encounters with the health-care provider or outreach worker, making these regimens more cost-effective. Drug-resistant TB disease should always be treated with

a daily regimen and under direct observation. There are **no** intermittent regimens for treatment of multidrug-resistant (MDR) TB. If anti-TB drugs for the treatment of MDR TB need to be given twice daily, then DOT should be provided twice daily as well.

Nearly all the treatment regimens for drug-susceptible TB disease can be given intermittently if they are directly observed.

Drug-resistant TB disease should always be treated with a daily regimen and under direct observation. There are no intermittent regimens for treatment of multidrug-resistant (MDR) TB.

It is important that DOT be carried out at times and in locations that are as convenient as possible for the individual patient (Figures 6.1 and 6.2). Therapy may be directly observed in a medical office or clinic setting, but can also be observed by an outreach worker in the field (e.g., patient's home, place of employment, school, or other mutually agreed-upon place). In some situations, staff of correctional facilities or drug treatment programs, home health-care workers, maternal and child health staff, or designated community members may provide DOT. In general, family members should **not** be the providers of DOT.

Figure 6.1
Conducting DOT in a Clinic Setting

Figure 6.2
Conducting DOT in a Location Convenient for the Patient

DOT should be used for all children and adolescents with TB disease. Even when drugs are given by DOT, adherence to and tolerability of the regimen must be monitored closely. Parents should **not** be relied on to supervise DOT.

Incentives and Enablers

Incentives and enablers should be used to ensure adherence to therapy (Figure 6.3). Incentives are small rewards given to patients to encourage them to take their medicines and to keep DOT or clinic appointments. Enablers are things that help the patient receive treatment, such as bus fare to get to the clinic. Incentives and enablers should be chosen according to the patient's needs, and they are frequently offered along with DOT.

Figure 6.3
Incentives and Enablers

Fixed-Dose Combination Drugs

Although there is no evidence indicating that fixed-dose combination medications are superior to individual drugs, expert opinion suggests that these formulations should be used when DOT is given daily or when DOT is **not** possible. The use of fixed-dose combination capsules or tablets facilitates DOT administration by minimizing the chance for error through the use of fewer tablets and may reduce the risk of acquired drug resistance since one medication cannot be selectively taken. In the United States, the Food and Drug Administration (FDA) has approved fixed-dose combinations of isoniazid and rifampin (Rifamate®) and of isoniazid, rifampin, and pyrazinamide (Rifater®). Clinicians should become familiar with the management of TB disease using these fixed-dose combination drugs.

The use of fixed-dose combination capsules or tablets facilitates DOT administration by minimizing the chance for error through the use of fewer tablets and may reduce the risk of acquired drug resistance since one medication cannot be selectively taken.

Self-Administered Therapy

Patients on self-administered therapy should be asked routinely about adherence at follow-up visits. Pill counts should be performed consistently, and urine or blood tests can be used periodically to check for the presence of urine drug metabolites or appropriate blood serum level of the drugs. In addition, the response to treatment should be monitored closely for all patients. If culture results have not become negative after 2 months of treatment, the patient should be reevaluated and DOT should be considered for the remainder of treatment.

Study Questions

6.9 Inadequate treatment can lead to which of the following?
(choose the one best answer)

A. Treatment failure

B. Relapse

C. Ongoing transmission

D. Development of drug resistance

E. A, B, C, and D are all correct.

6.10 The responsibility for successful treatment is assigned to which of the following?
(choose the one best answer)

A. The patient

B. The health-care provider

C. The family of the patient

D. A, B, and C are all correct.

E. Only A and B are correct.

6.11 What should be included when educating a patient about TB treatment?
(choose the one best answer)

A. How to take the medication

B. Adverse reactions to the medications

C. Consequences of not taking the medication correctly

D. TB infection control measures

E. A, B, C, and D are all correct.

6.12 What is case management?
(choose the one best answer)

A. Includes assigning responsibilities, conducting a regular systematic review of the case, and developing a plan to address barriers to adherence.

B. Can be used to ensure that patients complete treatment for TB disease.

C. Can be used to identify all cases of TB from a source case.

D. A, B, and C are all correct.

E. Only A and B are correct.

6.13 What is DOT?
(choose the one best answer)

A. A supervisor watches a health-care worker give a patient a bottle of prescribed pills.

B. A physician sees the patient once a month and counts the remaining pills in the medication bottles.

C. A health-care worker or another designated person watches the patient swallow each dose of the prescribed drugs.

D. The nurse uses special urine tests to detect the presence of medicine in the patient's urine.

6.14 Which of the following statements about DOT is true?
(choose the one best answer)

A. Is the preferred core management strategy for treatment of TB disease.

B. Can reduce the development of drug resistance, treatment failure, or relapse after the end of treatment.

C. Parents can always be relied upon to give DOT to their children.

D. A, B, and C are all correct.

E. Only A and B are correct.

6.15 Which of the following statements about intermittent treatment regimens and DOT is true? (choose the one best answer)

A. Reduces the total number of doses the patient must take.

B. Reduces the total number of encounters with the health-care provider.

C. Are always used for drug-resistant TB disease.

D. A, B, and C are all correct.

E. Only A and B are correct.

6.16 DOT should always be used for all children and adolescents with TB disease. (circle the one best answer)

A. True

B. False

TB Disease Treatment Regimens

Current Anti-TB Drugs

Currently, there are 10 drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of TB disease (Table 6.2). In addition, the fluoroquinolones (levofloxacin, moxifloxacin, and gatifloxacin), although **not** approved by the FDA for TB disease, are commonly used to treat TB disease caused by drug-resistant organisms or for patients who are intolerant of some first-line drugs. Rifabutin, approved for use in preventing *Mycobacterium avium* complex disease in patients with HIV infection but **not** approved for TB disease, is useful for treating TB disease in patients concurrently taking drugs that interact with rifampin (e.g., certain antiretroviral drugs). Amikacin and kanamycin, nearly identical aminoglycoside drugs used in treating patients with TB disease caused by drug-resistant organisms, are **not** approved by the FDA for treatment of TB.

Of the approved drugs, isoniazid (INH), rifampin (RIF), ethambutol (EMB), and pyrazinamide (PZA) are considered first-line anti-TB drugs and form the core of standard treatment regimens (Figure 6.4) (Table 6.2). Rifabutin (RBT) and rifapentine (RPT) may also be considered first-line drugs under certain circumstances. RBT is used as a substitute for RIF in the treatment of all forms of TB caused by organisms that are known or presumed to be susceptible to this agent. RBT is generally reserved for patients for whom drug-drug interactions preclude the use of rifampin. Streptomycin (SM) was formerly considered to be a first-line drug and, in some instances, is still used in the initial treatment regimen. However, an increasing prevalence of resistance to SM in many parts of the world has decreased its overall usefulness. The remaining drugs are reserved for special situations such as drug intolerance or resistance.

INH, RIF, PZA, and EMB are considered first-line anti-TB drugs and form the core of standard treatment regimens.

Figure 6.4
First-line Anti-TB Agents
From left to right: INH, RIF, PZA, and EMB form the core of initial treatment regimens.

Table 6.2
Anti-TB Drugs Currently Used in the United States

Drug Classes	Anti-TB Drugs	Comments
First-line drugs	Isoniazid (INH)	INH, RIF, PZA, and EMB form the core of initial treatment regimen.
	Rifampin (RIF)	
	Pyrazinamide (PZA)	
	Ethambutol (EMB)	
	Rifabutin* (RBT)	May be used as a substitute for RIF in the treatment of all forms of TB caused by organisms that are known or presumed to be susceptible to this agent.
	Rifapentine (RPT)	May be used once weekly with INH in the continuation phase of treatment for HIV-negative patients with noncavitary, drug-susceptible pulmonary TB who have negative sputum smears at completion of the initial phase of treatment.
Second-line drugs	Streptomycin (SM)	• SM was formerly considered to be a first-line drug and in some instances, is still used in initial treatment. • Increasing prevalence of resistance to SM in many parts of the world has decreased its overall usefulness.
	Cycloserine	These drugs are reserved for special situations such as drug intolerance or resistance.
	Capreomycin	
	ρ-Aminosalicylic acid	
	Levofloxacin*	
	Moxifloxacin*	
	Gatifloxacin*	
	Amikacin/Kanamycin*	
	Ethionamide	

* **Not** approved by the U.S. Food and Drug Administration for use in the treatment of tuberculosis.

Rating System for TB Disease Treatment Recommendations

The recommended treatment regimens are based, in large part, on evidence from clinical trials and are rated on the basis of a system developed by the U.S. Public Health Service (USPHS) and the Infectious Diseases Society of America (IDSA) (Table 6.3).

TB Disease Treatment Regimens

There are four basic treatment regimens recommended for treating adults with TB disease caused by organisms that are known or presumed to be susceptible to INH, RIF, PZA, and EMB. Each treatment regimen consists of an initial 2-month treatment phase followed by a continuation phase of either 4 or 7 months (Table 6.5). The 4-month continuation phase is used for the majority of patients. Although these regimens are broadly applicable, there are modifications that should be made under specified circumstances (Tables 6.3 and 6.4).

There are four basic treatment regimens recommended for treating adults with TB disease caused by organisms that are known or presumed to be susceptible to INH, RIF, PZA, and EMB. Each treatment regimen consists of an initial 2-month treatment phase followed by a continuation phase of either 4 or 7 months.

Initial Phase

The initial phase of treatment is crucial for preventing the emergence of drug resistance and determining the ultimate outcome of the regimen. Four drugs—INH, RIF, PZA, and EMB—should be included in the initial treatment regimen until the results of drug-susceptibility tests are available. Each of the drugs in the initial regimen plays an important role. INH and RIF allow for short-course regimens with high cure rates. PZA has potent sterilizing activity, which allows further shortening of the regimen from 9 to 6 months. EMB helps to prevent the emergence of RIF resistance when primary INH resistance is present. If drug-susceptibility test results are known and the organisms are fully susceptible, EMB need **not** be included. For children whose clarity or sharpness of vision cannot be monitored, EMB is usually not recommended except when the risk of drug resistance is high or for children who have "adult-type" (upper lobe infiltration, cavity formation) TB disease.

Continuation Phase

The continuation phase of treatment is given for either 4 or 7 months. The 4-month continuation phase should be used in patients with uncomplicated, noncavitary, drug-susceptible TB, if there is documented sputum conversion within the first 2 months. The 7-month continuation phase is recommended only for

- Patients with cavitary or extensive pulmonary TB disease caused by drug-susceptible organisms and whose sputum culture obtained at the time of completion of 2 months of treatment is positive;
- Patients whose initial phase of treatment did **not** include PZA; or
- Patients being treated with once-weekly INH and RPT and whose sputum culture at the time of completion of the initial phase (i.e., after 2 months) is positive.

Table 6.3
Drug Regimens for Pulmonary TB in Adults Caused by Drug-Susceptible Organisms*

Initial Phase			Continuation Phase			
Regimen	**Drugs**	**Interval and Doses± §**	**Regimen**	**Drugs**	**Interval and Doses± §**	**Range of Total Doses**
1	**INH RIF PZA EMB**	7 days/week for 56 doses (8 weeks) **or** 5 days /week for 40 doses (8 weeks)¶	**1a**	**INH RIF**	7 days/week for 126 doses (18 weeks) **or** 5 days/week for 90 doses (18 weeks)	182–130 (26 weeks)
			1b#	**INH RIF**	2 days/week for 36 doses (18 weeks)	92–76 (26 weeks)
			1c**	**INH RPT**	1 day/week for 18 doses (18 weeks)¶	74–58 (26 weeks)
2	**INH RIF PZA EMB**	7 days/week for 14 doses (2 weeks), then 2 days/ week for 12 doses (6 weeks) **or** 5 days/week for 10 doses (2 weeks),¶ then 2 days/week for 12 doses (6 weeks)	**2a#**	**INH RIF**	2 days/week for 36 doses (18 weeks)¶	62–58 (26 weeks)
			2b**	**INH RPT**	1 day/week for 18 doses (18 weeks)¶	44–40 (26 weeks)
3	**INH RIF PZA EMB**	3 times weekly for 24 doses (8 weeks)	**3a**	**INH RIF**	3 times weekly for 54 doses (18 weeks)¶	78 (26 weeks)
4	**INH RIF EMB**	7 days/week for 56 doses (8 weeks) **or** 5 days/week for 40 doses (8 weeks)¶	4a	**INH RIF**	7 days/week for 217 doses (31 weeks) **or** 5 days/week for 155 doses (31 weeks)¶	273–195 (39 weeks)
			4b#	**INH RIF**	Twice weekly for 62 doses (31 weeks)¶	118–102 (39 weeks)

INH = isoniazid RIF = rifampin PZA = pyrazinamide EMB = ethambutol RPT = rifapentine

* For more information on strength of recommendation and quality of supporting evidence, refer to treatment of tuberculosis guidelines. *MMWR* 2003; 52 (No.RR-11).

± When DOT is used, drugs may be given 5 days/week and the necessary doses adjusted accordingly.

§ Patients with cavitation on initial chest x-ray and positive cultures at completion of 2 months of therapy should receive a 7-month continuation phase.

¶ Patients on regimens given less than 7 days a week should receive DOT.

\# Regimens given less than 3 times a week are **not** recommended for HIV-infected patients with CD4+ counts less than 100

** Used only for HIV-negative patients with negative sputum smears at completion of 2 months of therapy and who do **not** have cavitation on initial chest x-ray. For patients started on this regimen and found to have positive culture from the 2-month specimen, treatment should be extended an extra 3 months.

Table 6.4
Dosage Recommendations for the Treatment of TB in Adults and Children[1]

Dose in mg/kg (maximum dosage in parentheses)							
Drug	**Adults/Children[2]**			**Daily**	**1 time/week[3]**	**2 times/week[3]**	**3 times/week[3]**
INH	**Adults**			5 mg/kg (300 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)	15 mg/kg (900 mg)
	Children			10–15 mg/kg (300 mg)		20–30 mg/kg (900 mg)	
RIF	**Adults**			10 mg/kg (600 mg)		10 mg/kg (600 mg)	10 mg/kg (600 mg)
	Children			10–20 mg/kg (600 mg)		10–20 mg/kg (600 mg)	
RBT	**Adults**			5 mg/kg (300 mg)		5 mg/kg (300 mg)	5 mg/kg (300 mg)
	Children			Appropriate dosing for children unknown			
RPT	**Adults**				10 mg/kg (600 mg) (continuation phase)		
	Children			This drug is **not** approved for use in children			
PZA	**Adults**	**weight**	40–55 kg	18.2–25 mg/kg (1000 mg)		36.4–50 mg/kg (2000 mg)	27.3–37.5 mg/kg (1500 mg)
			56–75 kg	20–26.8 mg/kg (1500 mg)		40–53.6 mg/kg (3000 mg)	33.3–44.6 (2500 mg)
			76–90 kg	22.2–26.3 mg/kg (2000 mg)		44.4–52.6 mg/kg (4000 mg)	33.3–39.5 mg/kg (3000 mg)
	Children			15–30 mg/kg (2000 mg)		50 mg/kg (2000 kg)	
EMB[4]	**Adults**	**weight**	40–55 kg	14.5–20 mg/kg (800 mg)		36.4–50 mg/kg (2000 mg)	21.8–30 mg/kg (1200 mg)
			56–75 kg	16–21.4 mg/kg (1200 mg)		37.3–50 mg/kg (2800 mg)	26.7–35.7 mg/kg (2000 mg)
			76–90 kg	17.8–21.1 mg/kg (1600 mg)		44.4–52.6 mg/kg (4000 mg)	26.7–31.6 mg/kg (2400 mg)
	Children			15–20 mg/kg (1000 mg)		50 mg/kg (2500 mg)	

INH= isoniazid RIF= rifampin RBT= rifabutin RPT= rifapentine PZA= pyrazinamide EMB= ethambutol

[1] Although these regimens are broadly applicable, modifications may be needed for certain circumstances (patients on antiretroviral therapy [ART]). For more information, refer to treatment of tuberculosis guidelines. *MMWR* 2003; 52 (No.RR-11).

[2] For purposes of this document, adult dosing begins at age 15 years. Children weighing more than 40 kg should be dosed as adults. Adjust doses as the patient's weight changes.

[3] All patients prescribed an intermittent regimen should be given DOT.

[4] Ethambutol should be used with caution in young children since it is difficult to monitor their vision. However, if they have TB that is resistant to INH or RIF, a dose of 15 mg/kg per day can be used.

Treatment Completion

Treatment completion is defined primarily as the ingestion of the total number of doses prescribed within the specified time frame. The duration of therapy depends on the drugs used, the drug-susceptibility test results of the isolate, and the patient's response to therapy (see Chapter 4, Drug-Susceptibility Testing). Most patients with previously untreated pulmonary TB disease can be treated with either a 6-month or a 9-month regimen, although the 6-month regimen is used for the majority of patients. All 6-month regimens must contain INH, RIF, and initially, PZA. The goal is to complete all doses within 1 year (Table 6.5).

The duration of therapy depends on the drugs used, the drug susceptibility test results of the isolate, and the patient's response to therapy.

Most patients with previously untreated pulmonary TB disease can be treated with either a 6-month or a 9-month regimen, although the 6-month regimen is used for the majority of patients.

Table 6.5
TB Treatment Phases

Phase	Purpose	Treatment
Initial phase	• Kills most of the tubercle bacilli during the first 8 weeks of treatment, but some bacilli can survive longer • Prevents the emergence of drug resistance • Determines the ultimate outcome of the regimen	Initial 2-month treatment regimen • Includes four drugs in the treatment (usually INH, RIF, PZA, and EMB) • Each of the drugs plays an important role for short-course regimens with high cure rates • Multiple drugs are needed to prevent the development of drug-resistant TB disease
Continuation phase	• Kills remaining tubercle bacilli (after initial phase) • If treatment is **not** continued long enough, the surviving bacilli may cause TB disease in the patient at a later time	An addition of either 4 or 7 months of treatment • 4 months is used for majority of patients • 7 months is recommended only for persons » Who have drug-susceptible cavitary or extensive pulmonary TB disease and whose sputum culture obtained at the time of completion of 2 months of treatment is positive » Whose initial phase of treatment did **not** include PZA » Who are treated with once-weekly INH and RPT and whose sputum culture at the time of completion of the initial phase is positive
Treatment completion	Defines the number of doses ingested within a specified time frame Duration depends on • Drugs used • Drug susceptibility test results of the isolate • Patient's response to therapy	Most patients with previously untreated pulmonary TB disease can be treated with either • 6-month regimen (preferred) containing INH, RIF, and initially PZA or • 9-month regimen containing INH and RIF

Follow-Up After Treatment

Routine follow-up after treatment is **not** necessary for patients who have had a satisfactory response to a 6- or 9-month regimen with both INH and RIF (Table 6.6). Patients whose organisms were fully susceptible to the drugs being used should be instructed to promptly report the development of any symptoms, particularly prolonged cough, fever, or weight loss. Patients with resistance to both INH and RIF should be monitored for 2 years post-treatment. For patients with organisms resistant to INH or RIF, follow-up evaluation must be individualized.

Table 6.6
Follow-Up After Treatment

Patients	Type of Follow-Up
Have a satisfactory response to 6- or 9- month regimen with both INH and RIF	Routine follow-up after treatment is **not** necessary
Have organisms that were fully susceptible to drugs being used	Patients should promptly report any of the following symptoms: • Prolonged cough • Fever • Weight loss
Have organisms resistant to INH and RIF	Patients should be monitored for 2 years post-treatment
Have organisms resistant to INH or RIF	Follow-up must be individualized

Treatment Interruptions

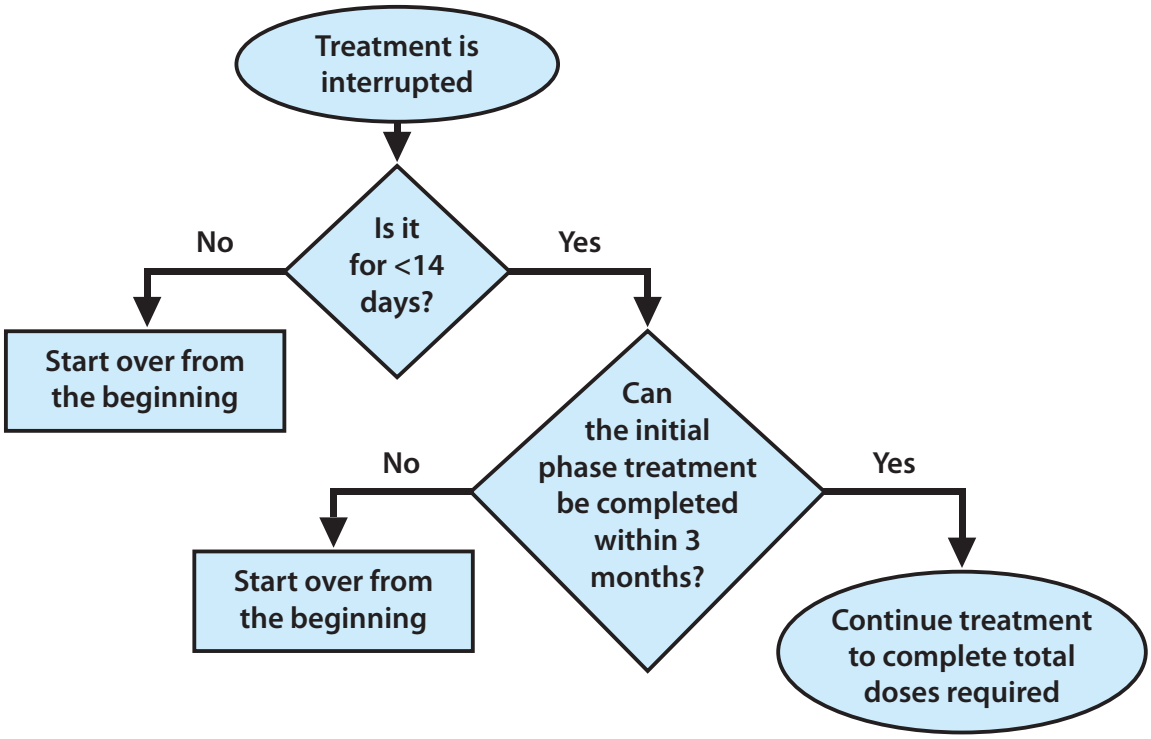
Interruptions in the treatment of TB disease are common. Health-care providers are responsible for deciding whether to restart a complete course of treatment or to continue as intended. These decisions should be based on when the interruption occurred and the duration of the interruption.

Treatment Interruption During Initial Phase

If the interruption occurred during the initial phase, the following guidelines apply (Figure 6.5) (Table 6.7):

- Lapse is ≥14 days–restart treatment from the beginning
- Lapse is <14 days–continue treatment to complete planned total number of doses (as long as all doses are completed within 3 months)

Figure 6.5
Algorithm for Management of Initial Phase Treatment Interruptions



Treatment Interruption During Continuation Phase

If the interruption occurred during the continuation phase, the following guidelines apply (Figure 6.6) (Table 6.7). If the patient received:

- ≥80% of doses, and sputum was acid-fast bacilli (AFB) smear negative on initial testing–further therapy may **not** be necessary;
- ≥80% of doses, and sputum was AFB smear positive on initial testing–continue therapy;
- <80% of doses, and lapse is less than 3 months in duration–continue therapy until all doses are completed (full course); or
- <80% of doses, and lapse is greater than 3 months in duration–restart therapy from the beginning of initial phase.

Figure 6.6
Algorithm for Management of Continuation Phase Treatment Interruptions

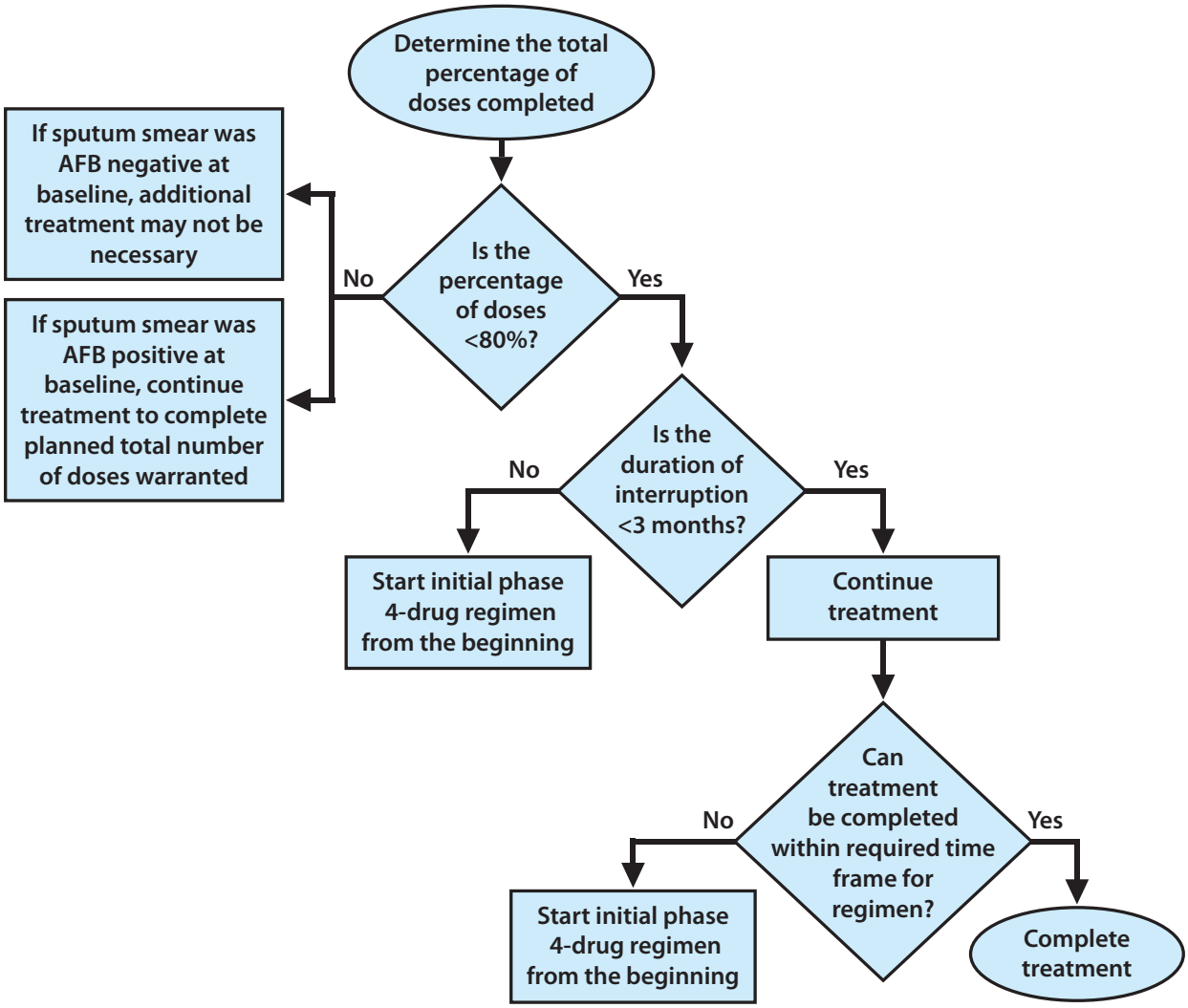


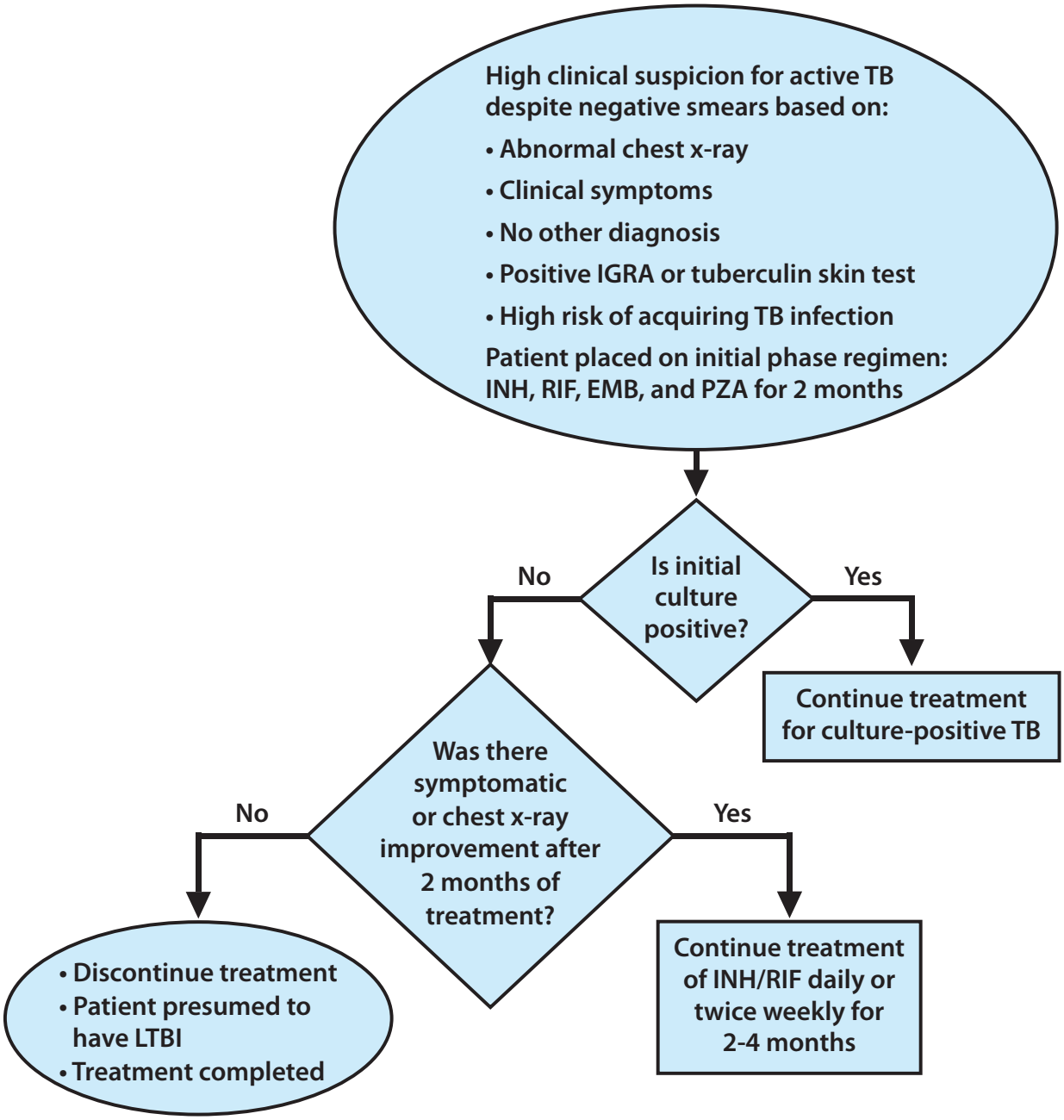
Table 6.7
Treatment Interruptions

When Interruption Occurs	Situation	Guidelines
During initial phase	Lapse is <14 days in duration	Continue treatment to complete planned total number of doses (as long as all doses are completed within 3 months)
	Lapse is ≥14 days in duration	Restart treatment from the beginning
During continuation phase	Received ≥80% of doses and sputum was AFB smear **negative** on initial testing	Further therapy may **not** be necessary
	Received ≥80% of doses and sputum was AFB smear **positive** on initial testing	Continue therapy until all doses are completed
	Received <80% of doses and lapse is <3 months in duration	Continue therapy until all doses are completed (full course) If treatment cannot be completed within recommended timeframe for regimen, restart therapy from the beginning
	Received <80% of doses and lapse is ≥3 months in duration	Restart therapy from the beginning, new initial and continuation phase

Decision to Treat Culture-Negative TB Disease

Alternative diagnoses must be considered carefully with appropriate diagnostic studies undertaken in patients who have what appears to be culture-negative pulmonary TB disease. Patients who, based on careful clinical and radiographic evaluation, are thought to have pulmonary TB disease should have treatment initiated with INH, RIF, PZA, and EMB even when the initial sputum smears are negative. Figure 6.7 provides an algorithm for treatment of culture-negative TB.

Figure 6.7
Algorithm to Guide Treatment of Culture-Negative TB



Study Questions

Indicate whether the following statements about the initial phase of treatment are true or false. (Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Statements about Initial Phase of Treatment	True or False
____ **6.17** Consists of 2 months of treatment.	**A.** True
____ **6.18** Is crucial for preventing the emergence of drug resistance.	**B.** False
____ **6.19** Treatment regimen usually consists of 6 drugs.	

Indicate whether the following statements about the continuation phase of treatment are true or false. (Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Statements about Continuation Phase of Treatment	True or False
____ **6.20** Consists of either 4 or 7 months of treatment.	**A.** True
____ **6.21** The 4-month continuation phase is used in the majority of patients.	**B.** False
____ **6.22** The 7-month continuation phase is usually only used for patients with extrapulmonary TB.	

6.23 Treatment completion is defined primarily as the ingestion of the total number of doses prescribed within the specified time frame.
(choose the one best answer)

A. True

B. False

6.24 The duration of therapy depends on which of the following?
(choose the one best answer)

A. Drugs used

B. Drug-susceptibility test results of the isolate

C. Patient's response to therapy

D. A, B, and C are all correct.

E. Only A and B are correct.

6.25 Which of the following statements about follow-up after treatment is true?
(choose the one best answer)

A. Follow-up evaluation must be individualized for patients with organisms resistant to INH or RIF or both.

B. Routine follow-up after treatment is **not** necessary for patients who have had a satisfactory response to a 6- or 9-month regimen with both INH and RIF.

C. Follow-up evaluation is **not** needed for patients with continued positive cultures.

D. A, B, and C are all correct.

E. Only A and B are correct.

The following patients have had an interruption in treatment. Match the patient with the treatment decision.
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Patient	Treatment Decision
____ **6.26** During the initial phase of treatment, Perry has had a lapse in therapy that was less than 14 days.	**A.** Restart treatment from the beginning
____ **6.27** During the initial phase of treatment, Walter has had a lapse in therapy that was greater than 14 days.	**B.** Continue treatment to complete planned total number of doses (as long as all doses are completed within 3 months)
____ **6.28** During the continuation phase of treatment, Desiree has had a lapse in therapy after receiving more than 80% of doses. She had a negative smear on initial testing.	**C.** Further treatment may not be necessary
____ **6.29** During the continuation phase of treatment, Maurine has had a lapse in therapy for cavitary TB after receiving less than 80% of doses. Her lapse is more than 3 months in duration.	**D.** Continue therapy until all doses are completed
____ **6.30** During the continuation phase of treatment, Ratcliff had a lapse in therapy after receiving more than 80% of doses. His sputum was AFB smear positive on initial testing.	
____ **6.31** During the continuation phase of treatment, Alex has had a lapse in therapy after receiving less than 80% of doses. His lapse is less than 3 months in duration.	

TB Disease Treatment Regimens for Specific Situations

TB disease treatment regimens for specific situations require special management and should be administered in consultation with a TB expert. Specific situations include the following people:

- Pregnant women
- Breast-feeding women
- Infants and children
- HIV-infected persons

TB disease treatment regimens for specific situations require special management and should be administered in consultation with a TB expert.

Pregnant Women

Untreated TB disease represents a greater hazard to a pregnant woman and her fetus than does its treatment. Because of the risk of TB to the fetus, treatment of TB in pregnant women should be initiated whenever the probability of maternal disease is moderate to high. The initial treatment regimen should consist of INH, RIF, and EMB. Although all of these drugs cross the placenta, they do **not** appear to have teratogenic effects. Streptomycin is the only anti-TB drug documented to have harmful effects on the human fetus (congenital deafness) and should **not** be used. Although detailed teratogenicity data are **not** available, PZA can probably be used safely during pregnancy and is recommended by the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD). If PZA is **not** included in the initial treatment regimen, the minimum duration of therapy is 9 months.

Untreated TB disease represents a greater hazard to a pregnant woman and her fetus than does its treatment.

Streptomycin is the only anti-TB drug documented to have harmful effects on the human fetus (congenital deafness) and should not be used.

For pregnant women with MDR TB, treatment should only be done in consultation with an MDR TB expert. Many of the medications currently used for treatment of MDR TB may be harmful to the fetus.

Breast-feeding

Breast-feeding should **not** be discouraged for women being treated with first-line anti-TB drugs, because the small concentrations of these drugs in breast milk do **not** produce toxicity in the nursing newborn. Conversely, drugs in breast milk should **not** be considered to serve as effective treatment for TB disease or for LTBI in a nursing infant. Pyridoxine (vitamin B_6) supplementation (25 mg/day) is recommended for all women taking INH who are either pregnant or breast-feeding. The amount of pyridoxine in multivitamins is variable, but generally less than the needed amount.

Infants and Children

Infants and children with TB disease should be treated with the regimens recommended for adults, with the exception that EMB is **not** used routinely in children. For children whose clarity or sharpness of vision cannot be monitored, EMB is usually not recommended except when the risk of drug resistance is high or for children who have "adult-type" (upper lobe infiltration, cavity formation) TB disease. In infants, TB is much more likely to disseminate; therefore, treatment should be started as soon as the diagnosis is suspected. Children commonly develop primary TB disease which generally affects the middle and lower lung. Children should be treated with three (rather than four) drugs in the initial phase (INH, RIF, and PZA). In general, extrapulmonary TB in children can be treated with the same regimens as pulmonary disease. Exceptions are disseminated TB and tuberculous meningitis, for which there are inadequate data to support 6-month therapy; thus 9 to 12 months of treatment is recommended.

In infants, TB is much more likely to disseminate; therefore, treatment should be started as soon as the diagnosis is suspected.

HIV-Infected Persons

Management of HIV and TB coinfection is complex, and the clinical and public health consequences associated with the failure of treatment and other negative outcomes are serious. HIV-infected patients are on numerous medications, some of which interact with anti-TB drugs. **It is therefore strongly recommended that experts in the treatment of HIV-related TB be consulted.** The treatment regimens listed in Table 6.3 are effective for people living with HIV, with two exceptions due to increased risk of developing acquired drug resistance:

- Once-weekly administration of INH and RPT in the continuation phase should **not** be used in any HIV-infected patient; and
- Patients with advanced HIV (CD4 counts less than 100) should be treated with daily or three times weekly therapy in both the initial and continuation phase.

Every effort should be made to use a rifamycin-based regimen for the entire course of therapy in coinfected patients. The key role of the rifamycins in the success of TB disease treatment mandates that the drug-drug interactions between the rifamycins and antiretroviral drugs be managed appropriately, rather than using TB treatment regimens that do **not** include a rifamycin or by withholding antiretroviral therapy until completion of anti-TB therapy.

Of particular concern is the interaction of rifamycins with antiretroviral agents and other anti-infective drugs. Rifampin can be used for the treatment of TB with certain combinations of antiretroviral agents. Rifabutin, which has fewer drug-drug interactions due to its decreased induction of the cytochrome P450 system, may also be used in place of rifampin and appears to be equally effective, although the doses of the rifabutin and antiretroviral agents may require adjustments and should be administered with expert consultation.

Therefore, patients with HIV-related TB disease should be treated with a regimen including a rifamycin for the full course of TB disease treatment, unless the isolate is resistant to the rifamycins or the patient has a severe side effect that is clearly due to the rifamycins.

HIV-infected patients are on numerous medications, some of which interact with anti-TB drugs. It is therefore strongly recommended that experts in the treatment of HIV-related TB be consulted.

Treatment Duration

Six months should be considered the minimum duration of treatment for HIV-infected adults, even for patients with culture-negative TB disease. If there is evidence of a slow or suboptimal response (e.g., cultures are still positive after 2 months of therapy), the continuation phase should be prolonged to 7 months (a total of 9 months of treatment). DOT and other adherence- promoting strategies should be used in all patients with HIV-related TB disease.

Predicting Drug Interactions Involving Rifampin

Much is known about the interactions of antiretroviral agents and RIF. In addition, knowledge of the mechanisms of drug interactions can help predict the likelihood of an interaction, even if that specific combination of drugs has **not** been formally evaluated. A major concern in treating TB disease in HIV-infected persons is the interaction of RIF with certain antiretroviral agents (some protease inhibitors [PIs] and nonnucleoside reverse transcriptase inhibitors [NRTIs]). Rifabutin, another rifamycin that has fewer drug-drug interactions, may be used as an alternative to RIF.

As new antiretroviral agents and more pharmacokinetic data become available, these recommendations are likely to be modified. For more information, see Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis at: www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/default.htm

Pregnancy in HIV-Infected Women

A number of issues complicate the treatment of the HIV-infected pregnant woman who has TB disease. Pregnancy alters the distribution and metabolism of a number of drugs, including antiretroviral drugs (there is very little information on whether the metabolism of anti-TB drugs is altered during pregnancy). Notably, the serum concentrations of protease inhibitors are decreased during the latter stages of pregnancy. There are no published data on drug-drug interactions between anti-TB and antiretroviral drugs among pregnant women. However, it is likely that the effects of RIF on protease inhibitors are exacerbated during pregnancy.

HIV-Infected Children

HIV-infected children with TB disease are at greater risk for severe, life-threatening manifestations (e.g., disseminated disease, meningitis). There are very limited data on the absorption, metabolism, and elimination of anti-TB drugs among children, particularly among very young children (< 2 years of age). For more information, please see Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis at: www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/specialpop.htm

HIV-infected children with TB disease are at greater risk for severe, life-threatening manifestations (e.g., disseminated disease, meningitis).

Persons with Additional Treatment Considerations

A number of medical conditions or disease characteristics require additional treatment considerations and TB treatment decisions should be made in consultation with a TB expert. These include:

- Renal insufficiency/end-stage renal disease
- Hepatic disease
- Extrapulmonary TB disease
- Drug-resistant TB disease
- Culture-negative TB disease

Renal Insufficiency and End-stage Renal Disease

Renal insufficiency complicates the management of TB disease because some anti-TB drugs are cleared by the kidneys. Alteration in dosing of anti-TB drugs is commonly necessary in patients with renal insufficiency and end-stage renal disease (ESRD) requiring hemodialysis. The dosage of anti-TB drugs should **not** be decreased because the peak serum concentrations may be low and smaller doses may decrease drug efficacy. Instead, the dosing interval of anti-TB drugs should be increased. Based on creatinine clearance, most anti-TB drugs can be given three times a week immediately after hemodialysis. Consultation with the patient's nephrologist is advised.

Renal insufficiency complicates the management of TB disease because some anti-TB drugs are cleared by the kidneys.

Alteration in dosing of anti-TB drugs is commonly necessary in patients with renal insufficiency and end-stage renal disease (ESRD) requiring hemodialysis.

Hepatic Disease

The treatment of TB disease in patients with unstable or advanced liver disease is problematic for several reasons:

- The likelihood of drug-induced hepatitis is greater;
- The implications of drug-induced hepatitis for patients with marginal hepatic reserve are potentially serious, even life-threatening; and
- Fluctuations in the indicators of liver function related to the pre-existing liver disease can confound monitoring for drug-induced hepatitis.

Thus, clinicians may consider regimens with fewer potentially hepatotoxic agents in patients with advanced or unstable liver disease. Expert consultation is advisable in treating such patients. It should be noted that TB disease itself may involve the liver, causing abnormal liver function; thus, **not** all abnormalities in liver function tests noted at baseline should be attributed to causes other than TB disease. The hepatic abnormalities caused by TB disease will improve with effective treatment.

Clinicians may consider regimens with fewer potentially hepatotoxic agents in patients with advanced or unstable liver disease. Expert consultation is advisable in treating such patients.

Extrapulmonary TB Disease

As a general rule, the principles used for the treatment of pulmonary TB disease also apply to extrapulmonary forms of the disease. A 6-month treatment regimen is recommended for patients with extrapulmonary TB disease, unless the organisms are known or strongly suspected to be resistant to the first-line drugs. If PZA cannot be used in the initial phase, the continuation phase must be increased to 7 months. The exception to these recommendations is central nervous system TB, for which the optimal length of therapy has **not** been established but some experts recommend 9 to 12 months. Most experts do recommend corticosteroids to be used as additional therapy for patients with TB meningitis and pericarditis. Consultation with a TB expert is recommended.

As a general rule, the principles used for the treatment of pulmonary TB disease also apply to extrapulmonary forms of the disease. A 6-month treatment regimen is recommended for patients with extrapulmonary TB disease, unless the organisms are known or strongly suspected to be resistant to the first-line drugs.

Drug-Resistant TB Disease

Drug-resistant TB disease can develop in two different ways, called primary and secondary resistance. Primary resistance occurs in persons who are initially exposed to and infected with resistant organisms. Secondary resistance, or acquired resistance, develops during TB therapy, either because the patient was treated with an inadequate regimen or because the patient did **not** take the prescribed regimen appropriately or because of other conditions such as drug malabsorption or drug-drug interactions leading to low serum levels (see Chapter 2, Transmission and Pathogenesis of Tuberculosis).

Drug-resistant TB disease can develop in two different ways:
- **Primary resistance**
  - » **Occurs in persons who are initially exposed to and infected with resistant organisms**
- **Secondary resistance, or acquired resistance**
  - » **Develops during TB therapy because of**
    - – **patient being treated with an inadequate regimen,**
    - – **patient not taking prescribed regimen appropriately,**
    - – **drug malabsorption, or**
    - – **drug-drug interactions leading to low serum levels**

Drug resistance in a patient with newly diagnosed TB disease may be suspected on the basis of previous treatment, contact with a known drug-resistant case, or time spent in a region in which drug resistance is common. Drug resistance can be proven only by drug-susceptibility testing (see Chapter 4, Diagnosis of Tuberculosis Disease).

Patients with strains of *M. tuberculosis* resistant to both INH and RIF (multidrug-resistant) are at high risk for

- Treatment failure;
- Relapse;
- Further acquired resistance; or
- Death.

These patients must be referred immediately to an expert in the management of drug-resistant TB disease; or consultation should be obtained from specialized treatment centers.

Patients with strains of *M. tuberculosis* resistant to both INH and RIF (multidrug-resistant) are at high risk for treatment failure, relapse, further acquired resistance, or death. These patients must be referred immediately to an expert in the management of drug-resistant TB disease; or consultation should be obtained from specialized treatment centers.

Management of patients with drug-resistant TB disease is based on the following guidelines:

- A single new drug should never be added to a failing regimen;
- In patients with MDR organisms resistant to first-line drugs in addition to INH and RIF, regimens employing four to six drugs that are new to the patient and to which the isolate shows in vitro susceptibility appear to be associated with better results;
- Patients with multidrug-resistant organisms should receive the highest priority for DOT, which should be administered either in the hospital, home, or other facility;
- The use of drugs to which there is demonstrated in vitro resistance is **not** encouraged because there is little or no efficacy of these drugs and alternative medications may be available;
- Resistance to RIF is associated in nearly all instances with cross-resistance to rifabutin and rifapentine (RPT);
- There is no cross-resistance between SM and the other injectable agents, amikacin, kanamycin, and capreomycin (although resistance to all may occur as independent events); cross-resistance between amikacin and kanamycin is not universal but frequently seen;
- Resistance to PZA is uncommon in the absence of resistance to other first-line drugs; if monoresistance to PZA is observed, consideration must be given to the possibility that the disease is caused by *M. bovis*, **not** *M. tuberculosis*; and
- Intermittent therapy should **not** be used in treating TB disease caused by drug-resistant organisms, except perhaps for injectable agents after the initiation phase (usually 2 to 3 months) of daily therapy.

Table 6.8 provides information on drug classes for TB, types of drug-resistant TB, and appropriate anti-TB drugs for treatment.

Table 6.8
Drug Classes for TB

Drug Classes	Anti-TB Drugs	Drug-Susceptible TB	Multidrug-Resistant TB (MDR TB)	Extensively Drug Resistant TB (XDR TB)
First-line oral drugs • Standard treatment for drug-susceptible TB • Four drugs for 6–9 months • Safe, effective, inexpensive • 95% cure • Based on solid scientific evidence from ~30 years of drug discovery and controlled clinical trials, 1943–72	INH	Susceptible	Resistance by definition	Resistance by definition
	RIF	Susceptible	Resistance by definition	Resistance by definition
	PZA	Susceptible	Resistance possible or likely	Resistance possible or likely
	EMB	Susceptible	Resistance possible or likely	Resistance possible or likely
Second-line drugs • Treatment based on laboratory drug-resistance testing and epidemiological information • Four to six drugs for 2 years	Aminoglycosides and Capreomycin	N/A	Resistance possible	Resistance by definition
	Quinolones	N/A	Resistance possible	Resistance by definition
	Thioamides	N/A	Resistance possible	Resistance possible or likely
	Cycloserine	N/A	Resistance possible	Resistance possible or likely
	ρ-Aminosalicylic Acid	N/A	Resistance possible	Resistance possible or likely

Culture-Negative TB Disease

Failure to isolate *M. tuberculosis* from appropriately collected specimens in persons who, because of clinical or radiographic findings, are suspected of having pulmonary TB disease does **not** exclude a diagnosis of TB disease. Low bacillary populations, temporal variations in the number of bacilli being expelled, and errors in specimen processing all may result in failure to isolate organisms from patients who have TB disease. It should be emphasized that alternative diagnoses must be considered carefully and appropriate diagnostic studies undertaken in patients who have what appears to be

culture-negative TB disease. At a minimum, patients suspected of having pulmonary TB disease should have three sputum specimens (using sputum induction with hypertonic saline if necessary) for AFB smear and culture as part of the diagnostic evaluation prior to or coincident with treatment initiation. Depending on the clinical features and differential diagnosis, other diagnostic testing, such as bronchoscopy with bronchoalveolar lavage and biopsy, should be considered before making a presumptive diagnosis of culture-negative TB disease.

Failure to isolate *M. tuberculosis* from appropriately collected specimens in persons who, because of clinical or radiographic findings, are suspected of having pulmonary TB disease does not exclude a diagnosis of TB disease.

Patients who, on the basis of careful clinical and radiographic evaluation, are thought to have a high likelihood of having pulmonary TB disease should have treatment initiated with INH, RIF, PZA, and EMB even when the initial sputum smears are negative. If *M. tuberculosis* is isolated in culture, treatment for TB disease should be continued. Patients who have negative cultures but who still are presumed to have pulmonary TB disease should have a thorough follow-up clinical and radiographic evaluation at the time 2 months of therapy has been completed to determine whether there has been a response that can be attributed to anti-TB treatment. If there is either clinical or radiographic improvement and **no** other etiology is identified, treatment should be continued for TB disease. A 4-month INH and RIF regimen for culture-negative TB disease has been demonstrated to be successful. However, because the results of cultures may **not** be known for 3 to 8 weeks and because of the possibility of drug resistance, use of two-drug therapy with INH and RIF alone is **not** recommended in the initial phase of treatment (i.e., first 2 months) while culture results are pending. The continuation phase can be shortened to 2 months using INH and RIF for HIV-negative patients once it is known that cultures are negative. However, HIV-infected patients with culture-negative pulmonary TB should be treated for a minimum of 6 months (total). Figure 6.7 provides an algorithm for treatment of culture-negative TB.

Patients who, on the basis of careful clinical and radiographic evaluation, are thought to have a high likelihood of having pulmonary TB disease should have treatment initiated with INH, RIF, PZA, and EMB even when the initial sputum smears are negative.

On occasion, patients who are being evaluated for pulmonary TB disease will be found to have positive AFB smears, but negative cultures. There are several potential explanations for this occurrence, including the possibilities that the acid-fast organisms are nontuberculous and difficult to culture, that they are nonviable tubercle bacilli, or that there was laboratory error. The approach taken in such cases should be individualized on the basis of clinical and radiographic findings. If suspicion of TB disease is high and the patient has positive AFB smears, even with negative cultures, the patient should be treated as if culture positive, using one of the recommended regimens.

Study Questions

6.32 Which drug is harmful to the fetus and should NOT be used with pregnant women during the initial treatment phase?
(choose the one best answer)

A. Isoniazid

B. Rifampin

C. Ethambutol

D. Streptomycin

6.33 Which of the following statements about infants and children is true?
(choose the one best answer)

A. Anti-TB drugs in breast milk can be considered effective treatment for TB disease or for LTBI in a nursing infant.

B. EMB is routinely used to treat children for TB disease.

C. Young children should be treated with three (rather than four) drugs in the initial phase.

D. TB disease is less likely to disseminate in children than in adults.

6.34 For HIV-infected patients, which of the following statements is true?
(choose the one best answer)

A. The minimum duration of treatment of TB disease for HIV-infected adults is 6 months.

B. If there is evidence of a slow or suboptimal response, the continuation phase should be prolonged to 7 months (a total of 9 months of treatment).

C. DOT and other adherence promoting strategies should be used in all patients with HIV-related TB disease.

D. A, B, and C are all correct.

E. Only A and B are correct.

TB patients can have additional medical problems or presentations. Match the problem or presentation with the appropriate type of TB disease treatment.
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Additional Medical Problems or Presentations	Type of Treatment
____ **6.35** End-stage renal disease ____ **6.36** Hepatic disease ____ **6.37** Extrapulmonary TB disease	**A.** Consider a regimen with fewer potentially hepatotoxic agents. **B.** Alteration in dosing anti-TB drugs is commonly necessary. Do not decrease dose of anti-TB drugs. Dosing interval should be increased to 3 times a week. **C.** Use the same principles as for pulmonary TB disease. A 6-month treatment regimen is recommended, unless the organisms are known or strongly suspected to be resistant to the first-line drugs.

6.38 Drug resistance in a patient with newly diagnosed TB disease may be suspected on the basis of which of the following?
(choose the one best answer)

A. Time spent in a region in which drug resistance is common

B. Contact with a known drug-resistant case

C. Previous TB treatment

D. A, B, and C are all correct.

E. Only A and B are correct.

6.39 Joanne has an *M. tuberculosis* strain that is resistant to both isoniazid and rifampin. What is Joanne at high risk for?
(choose the one best answer)

A. Treatment failure

B. Relapse

C. Further acquired resistance

D. A, B, and C are all correct.

E. Only A and B are correct.

Patient Monitoring

Adverse reactions to anti-TB drugs are relatively rare, but in some patients they may be severe. Clinicians who treat TB disease should be familiar with the methods of monitoring for adverse reactions and patients' response to treatment. In some situations (drug-resistant TB disease, pregnancy, HIV-infected patients), expert consultation should be sought.

Baseline Monitoring

Before starting treatment, adult patients should have certain baseline blood and vision tests to help detect any underlying problems that may complicate treatment. For children, only vision tests are necessary unless there are other medical conditions that may complicate treatment. Recommended examinations for baseline monitoring are included in Table 6.9.

Before starting treatment, adult patients should have certain baseline blood and vision tests to help detect any underlying problems that may complicate treatment.

For children, only vision tests are necessary unless there are other medical conditions that may complicate treatment.

Table 6.9
Recommended Examinations for Baseline Monitoring

Patient	Recommended Test
All patients	Measure aminotransferases (i.e., AST, ALT), bilirubin, alkaline phosphatase, and serum creatinine and a platelet count
Patients at risk for hepatitis B or C (e.g., injection drug user, born in Asia or Africa, or HIV infected)	Conduct serologic tests
Patients who are taking EMB	Test visual acuity (Snellen chart) and color vision (Ishihara)
HIV-infected patients	Obtain CD4+ lymphocyte count

Monitoring During Treatment

Patients with TB disease should have clinical evaluations at least monthly to identify possible adverse reactions to medications and to assess adherence (Table 6.10).

As a routine practice, it is **not** necessary to monitor liver or renal function or platelet count for patients being treated with first-line anti-TB drugs unless there were abnormalities at baseline or there are clinical reasons to obtain measurements. Patients who have stable abnormalities of hepatic or renal function at baseline should have repeat measurements early in the course of treatment, then less frequently to ensure that conditions have **not** worsened.

Monthly repeat testing of visual acuity (Snellen) and color vision (Ishihara) is recommended for patients receiving an EMB dose exceeding 15–20 mg/kg (the recommended range) and for patients receiving EMB for more than 2 months. Patients receiving EMB should be questioned regarding visual disturbances at monthly intervals. Patients should be educated regarding the possible visual side effects of EMB and should be instructed to immediately report vision changes to their health-care provider.

Table 6.10
Monitoring During Treatment

Patient	Recommended Test
All patients	Repeat at least monthly clinical evaluations to • Identify possible adverse reactions to medications • Assess adherence
Patients who are taking EMB	• Question monthly regarding visual disturbances • Repeat monthly testing for visual acuity (Snellen chart) and color vision (Ishihara) for patients whose dose exceeds 15–20 mg/kg and those who have been receiving EMB for >2 months
Patients who have extrapulmonary TB disease	Evaluation depends on • Sites involved • Ease with which specimens can be obtained

Study Questions

6.40 For baseline monitoring, children only need vision tests unless there are other medical conditions that may complicate treatment.
(circle the one best answer)

A. True

B. False

Match the patient with the type of monitoring that should occur during treatment.
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Patients	Monitoring During Treatment
____ **6.41** Pauline is being treated with first-line anti-TB drugs. She had no abnormalities at baseline and no clinical problems.	**A.** Repeat measurements early in the course of treatment, then less frequently to ensure that condition does not worsen.
____ **6.42** Don had stable abnormalities of hepatic function at baseline.	**B.** Repeat visual acuity and color vision.
____ **6.43** Percy has been on first-line anti-TB drugs that include ethambutol for greater than 2 months.	**C.** Not necessary to monitor liver or renal function or platelet count.

Evaluating Response to Treatment

It is important for clinicians to evaluate a patient's response to treatment to determine the efficacy of the treatment and to identify any adverse reactions. Clinicians use three methods to determine whether a patient is responding to treatment:

1. Clinical evaluation
2. Bacteriological examination
3. Chest radiograph

It is important for clinicians to evaluate a patient's response to treatment to determine the efficacy of the treatment and to identify any adverse reactions.

Clinical Evaluation

Patients should have clinical evaluations at least monthly to

- Identify possible adverse reactions to medications;
- Assess adherence; and
- Determine treatment efficacy.

Although each patient responds to treatment at a different pace, all TB symptoms should gradually improve and eventually go away. Patients whose symptoms do **not** improve during the first 2 months of treatment, or whose symptoms worsen after improving initially, should be reevaluated for adherence issues and development of drug resistance.

Adverse Reactions to Anti-TB Drugs

In addition to the microbiological evaluations, it is essential that patients have clinical evaluations to identify possible adverse effects of the anti-TB drugs (Table 6.11). Monitoring for adverse reactions must be individualized. The type and frequency of monitoring should depend on the drugs used and the patient's risk for adverse reactions (e.g., age or alcohol use). At minimum, patients should be seen monthly during therapy and questioned by health-care providers concerning adverse reactions, even if no problems are apparent.

Adverse reactions to anti-TB drugs are relatively rare, but in some patients they may be severe. Mild adverse effects can generally be managed with symptomatic therapy. The drug or drugs must be discontinued for more severe effects. It is important that first-line drugs **not** be stopped without adequate justification. Proper management of serious adverse reactions often requires expert consultation.

Patients should be specifically instructed to look for symptoms associated with the most common reactions to the medications they are taking. They should also be instructed to seek medical attention immediately should these symptoms occur. All patients receiving INH, RIF, or PZA should immediately report any symptoms suggestive of hepatitis (nausea, loss of appetite, vomiting, persistently dark urine, yellowish skin or eyes, malaise, unexplained elevated temperature for more than 3 days, or abdominal tenderness). If the symptoms suggest adverse reactions, the patient should be instructed to stop the medication, and appropriate laboratory testing should be performed.

Patients should be specifically instructed to look for symptoms associated with the most common reactions to the medications they are taking. They should also be instructed to seek medical attention immediately should these symptoms occur.

Table 6.11
Common Adverse Reactions to TB Drugs

Caused by	Adverse Reaction	Signs and Symptoms	Significance of Reaction*
Any drug	Allergic	• Skin rash	May be serious or minor
EMB	Eye damage	• Blurred or changed vision • Changed color vision	Serious
INH PZA RIF	Hepatic toxicity	• Abdominal pain • Abnormal liver function test results • Dark urine • Fatigue • Fever for 3 or more days • Flu-like symptoms • Lack of appetite • Nausea • Vomiting • Yellowish skin or eyes	Serious
INH	Nervous system damage	• Dizziness; tingling or numbness around the mouth	Serious
	Peripheral neuropathy	• Tingling sensation in hands and feet	Serious
PZA	Stomach upset	• Stomach upset • Vomiting • Lack of appetite	May be serious or minor
	Gout	• Abnormal uric acid level** • Joint aches	Serious
RIF	Bleeding problems	• Easy bruising • Slow blood clotting	Serious
	Discoloration of body fluids	• Orange urine, sweat, or tears • Permanently stained soft contact lenses	Minor
	Drug interactions	• Interferes with certain medications such as birth control pills, birth control implants, and methadone treatment	May be serious or minor
	Sensitivity to the sun	• Frequent sunburn	Minor

* Patients should stop medication for serious adverse reactions and consult a clinician immediately. Patients can continue taking medication if they have minor adverse reactions.

** Asymptomatic elevated uric acid levels are expected with PZA treatment. Acute gouty arthritis, which is rare without preexisting gout, is a contraindication to PZA use.

Common Adverse Reactions to TB Disease Treatment

The items listed below are common adverse reactions to TB treatment:

- Gastrointestinal problems
- Hepatitis
- Rash
- Drug fever

Gastrointestinal Problems

Gastrointestinal reactions to the anti-TB drugs are common, particularly in the first few weeks of therapy. These reactions include:

- Upset stomach
- Nausea
- Poor appetite
- Abdominal pain

In the presence of gastrointestinal symptoms, measure

- Serum aminotransferases (i.e., AST, ALT) and
- Bilirubin

Hepatic Toxicity

Liver injury can be caused by three of the first-line TB disease drugs, INH, RIF and PZA. Significant liver toxicity is indicated by AST ≥3 times the upper limit of normal in the presence of symptoms, or ≥5 times the upper limit of normal in the absence of symptoms (Table 6.12). If the AST and ALT are <5 times the upper limit of normal, toxicity can be considered mild; an AST or ALT of 5–10 times normal defines moderate toxicity; and >10 times normal is severe. In addition to elevation of the AST and ALT, occasionally there are disproportionate increases in bilirubin and alkaline phosphatase. This pattern is more consistent with RIF hepatotoxicity.

Table 6.12
Hepatic Toxicity

AST and ALT Level	Levels of Toxicity
AST and ALT <5 times the upper limit of normal	Mild
AST or ALT 5–10 times the normal limit	Moderate
AST or ALT >10 times the normal limit	Severe

Rash

All drugs used in treating TB disease can cause a rash. The response to a patient with a rash depends upon its severity. The rash may be minor, affecting a limited area or being predominantly manifested as itching. In this case, antihistamines should be given for symptomatic relief, but all TB disease medications can be continued.

All drugs used in treating TB disease can cause a rash.

Drug Fever

Recurrence of fever in a patient who has been receiving therapy for several weeks should suggest drug fever, especially if the patient is showing microbiologic and radiographic improvement. It should be noted, however, that fever from TB may persist for as long as 2 months after therapy has been initiated.

Bacteriologic Examination

Important treatment decisions concerning the continuation-phase regimen are based on the microbacteriological status at the end of the initial phase of treatment (i.e., at least 2 months). Patients whose cultures have **not** become negative after 3 months of therapy should be reevaluated for potential drug-resistant disease, as well as for potential failure to adhere to the regimen. Patients who have positive cultures after 4 months of treatment should be considered as having failed treatment and managed accordingly.

Patients whose cultures have not become negative after 3 months of therapy should be reevaluated for potential drug-resistant disease, as well as for potential failure to adhere to the regimen.

Positive Sputum Cultures Prior to Treatment

For patients whose sputum culture is positive prior to treatment, the best way to measure the efficacy of therapy is to obtain specimens for culture at least monthly until two consecutive specimens are negative on culture (Table 6.13). Patients with multidrug-resistant TB should have sputum AFB smears and cultures performed monthly for the entire course of treatment.

Negative Sputum Cultures Prior to Treatment

For patients with negative sputum cultures prior to treatment for pulmonary disease, the major indicators of response to therapy are the chest radiograph and the clinical evaluation (Table 6.13). The intervals at which chest radiography should be repeated depend on the clinical circumstances and the differential diagnosis that is being considered. If the radiograph does **not** improve after the patient has received 2 months of treatment, the abnormality may be the result of either previous (**not** current) TB disease or another reason.

Table 6.13
Response to Treatment for Pulmonary TB Disease

Bacteriologic Status	Recommendations for Response to Treatment
Positive sputum cultures prior to treatment	• Obtain specimens for culture at least monthly until two consecutive specimens are negative on culture • Perform monthly sputum AFB smears and cultures on MDR TB patients for entire course of treatment • A repeat chest radiograph after 2 months of treatment may be useful but is **not** essential
Negative sputum cultures prior to treatment	• Repeat chest radiograph at intervals based on clinical circumstances and differential diagnosis • If radiograph does not improve after patient has received 2 months of treatment, abnormality may be due to » Previous (not current) TB disease » Another reason
Cultures have **not** become negative after 3 months of therapy	Reevaluate for • Potential drug-resistant disease • Potential failure to adhere
Cultures are still positive after 4 months of treatment	Consider as having failed treatment and manage accordingly

Chest Radiograph

For patients with positive cultures at diagnosis, a repeat chest radiograph at completion of 2 months of treatment may be useful, but is **not** essential. For patients with culture-positive TB, a chest radiograph at completion of treatment provides a baseline for comparison with any future films. For patients with cultures that are initially negative, a chest radiograph is necessary after 2 months of treatment, and a radiograph at completion of treatment is desirable. Generally, follow-up after completion of therapy is **not** necessary.

For patients with cultures that are initially negative, a chest radiograph is necessary after 2 months of treatment, and a radiograph at completion of treatment is desirable.

Study Questions

6.44 How often should patients have clinical evaluations to identify possible adverse reactions to medications and to assess adherence and to determine treatment efficacy?
(circle the one best answer)

A. Weekly

B. Twice a month

C. Once a month

D. Every 6 weeks

6.45 LaRue has been receiving TB treatment for 2 months. She is experiencing nausea, vomiting, abdominal pain, malaise, and persistently dark urine. What could be the cause?
(circle the one best answer)

A. TB disease has spread to her abdomen.

B. She has hepatic toxicity due to adverse reaction to TB medications.

C. She has an adverse reaction to EMB.

Match the characteristic of an adverse reaction to TB therapy with the type of adverse reaction.
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Characteristic	Adverse Reaction
____ **6.46** Can be caused by three of the first-line TB drugs.	**A.** Gastrointestinal problems
____ **6.47** Can cause a recurrence of fever in a patient who has been receiving therapy for several weeks.	**B.** Hepatic toxicity
____ **6.48** Is common particularly in the first few weeks of therapy.	**C.** Rash
____ **6.49** Can be caused by all drugs used in treating TB disease.	**D.** Drug fever

Match the patient with the type of measures that should be taken to determine how the patient is responding to treatment.
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Patients	Measures for Determining the Patient's Response to Treatment
____ **6.50** Carol had a positive sputum cultures prior to treatment and has multidrug-resistant TB disease. ____ **6.51** Tom's culture has not become negative after 3 months of treatment. ____ **6.52** Roxanne had negative sputum cultures prior to treatment. ____ **6.53** Burl had positive sputum cultures prior to treatment. ____ **6.54** Mike had positive sputum cultures after 4 months of treatment.	**A.** Obtain specimens for culture at least monthly until 2 consecutive specimens are negative on culture. **B.** Repeat chest radiographs at intervals based on clinical circumstances and the differential diagnosis. **C.** Perform sputum AFB smears and cultures monthly for the entire course of treatment. **D.** Reevaluate for potential drug-resistant TB disease, as well as for potential failure to adhere to the regimen. **E.** Consider as having failed treatment and manage accordingly.

Chapter Summary

The major goals for treatment of TB disease include

- Cure the individual patient;
- Minimize risk of death and disability; and
- Reduce transmission of *M. tuberculosis* to other persons.

To ensure that these goals are met, TB disease must be treated for at least 6 months or longer. Most of the bacteria are killed during the first 8 weeks of treatment; however, there are persistent organisms that require longer treatment. If treatment is **not** continued for a long enough duration, the surviving bacteria may cause the patient to become ill and infectious again.

There are several options for daily and intermittent therapy, but the goal of treatment for TB disease should be to provide the safest and most effective therapy in the shortest period of time. Given adequate treatment, almost all patients will recover and be cured.

Regimens for the treatment of TB disease must contain multiple drugs to which the bacteria are susceptible. The standard of care for initiating treatment of TB disease is a four-drug regimen. Treatment with a single drug can lead to the development of a bacterial population resistant to that drug. Likewise, the addition of a single drug to a failing anti-TB regimen can lead to additional resistance. When two or more drugs to which in vitro susceptibility has been demonstrated are given together, each helps prevent the emergence of tubercle bacilli resistant to the others.

Responsibility for successful treatment is assigned to the health-care provider, **not** the patient. Health-care professionals should consult their health department's TB control program to ensure their TB patients are able to adhere to a prescribed treatment regimen. The TB control program should assist the health-care professional in evaluating patient barriers to adherence and recommend directly observed therapy (DOT) and the use of incentives and enablers that may assist the patient in completing the recommended therapy.

Currently, there are 10 drugs approved by the U.S. FDA for the treatment of TB disease. In addition, the fluoroquinolones (levofloxacin, moxifloxacin, and gatifloxacin), although **not** approved by the FDA for TB disease, are commonly used to treat TB disease caused by drug-resistant organisms or for patients who are intolerant of some first-line drugs. Rifabutin, approved for use in preventing *Mycobacterium avium* complex disease in patients with HIV infection but **not** approved for TB disease, is useful for treating TB disease in patients concurrently taking drugs that interact with rifampin (e.g., certain antiretroviral drugs). Amikacin and kanamycin, nearly identical aminoglycoside drugs used in treating patients with TB disease caused by drug-resistant organisms, are not approved by the FDA for treatment of TB.

Of the approved drugs, INH, RIF, EMB, and PZA are considered the first-line anti-TB drugs and form the core of standard treatment regimens. RBT and RPT may also be considered first-line drugs under certain circumstances. RBT is used as a substitute for RIF in the treatment of all forms of TB caused by organisms that are known or presumed to be susceptible to this agent. The drug is generally reserved for patients who have intolerance to RIF or for whom drug-drug interactions preclude the use of rifampin. SM was formerly considered to be a first-line drug and, in some instances, is still used in the initial treatment regimen. However, an increasing prevalence of

resistance to SM in many parts of the world has decreased its overall usefulness. The remaining drugs are reserved for special situations such as drug intolerance or resistance.

There are four basic treatment regimens recommended for treating adults with TB disease caused by organisms that are known or presumed to be susceptible to INH, RIF, PZA, and EMB. Each treatment regimen consists of an initial 2-month treatment phase followed by a continuation phase of either 4 or 7 months. The 4-month continuation phase is used for the majority of patients. Although these regimens are broadly applicable, there are modifications that should be made under specified circumstances.

Adverse reactions to anti-TB drugs are relatively rare, but in some patients they may be severe. Clinicians who treat TB disease should be familiar with the methods of monitoring for adverse reactions and patients' response to treatment. In some situations (drug-resistant TB disease, pregnancy, HIV-infected patients), expert consultation should be sought.

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Chapter 7
Tuberculosis Infection Control

Table of Contents

Chapter Objectives

After working through this chapter, you should be able to

- Describe the factors that determine the infectiousness of a tuberculosis (TB) patient;
- Explain the main goals of a TB infection control program;
- Discuss the three levels of an effective TB infection control program;
- Explain the purpose and the characteristics of a TB airborne infection isolation room; and
- Describe the circumstances when respirators and surgical masks should be used.

Introduction

M. tuberculosis can be transmitted in virtually any setting. Clinicians should be aware that transmission has been documented in health-care settings where health-care workers (HCWs) and patients come in contact with persons with infectious TB who

- Have unsuspected TB disease,
- Have **not** received adequate or appropriate treatment, or
- Have **not** been separated from others.

Health-care settings in this context include clinics and hospitals, as well as nontraditional facility-based settings such as emergency medical services, correctional facilities, home-based health-care and outreach settings, long-term care facilities, and homeless shelters. People who work or receive care in health-care settings (as referenced above) are at higher risk for becoming infected with *M. tuberculosis*; therefore, it is necessary to have a TB infection control plan as part of a general infection control program designed to ensure the following:

- Prompt detection of TB;
- Airborne precautions; and
- Treatment of persons who have been suspected or confirmed to have TB disease (see Chapter 2, Transmission and Pathogenesis of Tuberculosis).

People who work or receive care in health-care settings are at higher risk for becoming infected with *M. tuberculosis*; therefore, it is necessary to have a TB infection control plan.

Study Question

7.1 In which of the following health-care settings can TB be transmitted?
(circle the one best answer)

F. Where TB patients have **not** received adequate and appropriate treatment.

G. Where TB patients have **not** been separated from others.

H. Where persons who have unsuspected TB disease come into contact with others.

I. A, B, and C are all correct.

J. Only A and B are correct.

Infectiousness

The infectiousness of a TB patient is directly related to the number of droplet nuclei carrying *M. tuberculosis* (tubercle bacilli) that are expelled into the air. Depending on the environment, these tiny particles can remain suspended in the air for several hours. *M. tuberculosis* is transmitted through the air, **not** by surface contact. Infection occurs when a person inhales droplet nuclei containing *M. tuberculosis*, and the droplet nuclei traverse the mouth or nasal passages, upper respiratory tract, and bronchi to reach the alveoli of the lungs. Persons with extrapulmonary TB disease may have concurrent unsuspected pulmonary or laryngeal TB disease. Except for laryngeal TB disease, extrapulmonary TB disease is rarely infectious; however, transmission from extrapulmonary sites has been reported to occur during aerosol-producing procedures such as autopsies and tissue irrigation. The characteristics of a patient with TB disease that are associated with infectiousness include, but are not limited to, those listed in Table 7.1.

The infectiousness of a TB patient is directly related to the number of droplet nuclei carrying *M. tuberculosis* (tubercle bacilli) that are expelled into the air.

Infection occurs when a person inhales droplet nuclei containing *M. tuberculosis*, and the droplet nuclei traverse the mouth or nasal passages, upper respiratory tract, and bronchi to reach the alveoli of the lungs.

Table 7.1
Infectiousness of People Known to Have or Suspected of Having TB Disease*

Factors Associated with Noninfectiousness	Factors Associated with Infectiousness
No cough	Presence of a cough
No cavity in the lung	Cavity in the lung
No acid-fast bacilli on sputum smear	Acid-fast bacilli on sputum smear
Extrapulmonary (non-pulmonary) TB disease	TB disease of the lungs, airway, or larynx
Receiving adequate treatment for 2 weeks or longer	**Not** receiving adequate treatment
Not undergoing cough-inducing procedures	Undergoing cough-inducing procedures (e.g., bronchoscopy, sputum induction, and administration of aerosolized medications)
Negative sputum cultures	Positive sputum cultures

* Infectiousness depends on a variety of factors. Clinicians should consider all of these factors when determining whether a TB patient should be considered infectious.

In general, young children with pulmonary TB disease are **less** likely than adults to be infectious, because children are sometimes unable to produce sputum when they cough, or may have paucibacillary TB. However, it is still possible for children to transmit *M. tuberculosis* to others if they have infectious characteristics, such as a positive AFB smear or cavity on a chest radiograph.

In general, young children with pulmonary TB disease are less likely than adults to be infectious, because children are sometimes unable to produce sputum when they cough, or may have paucibacillary TB.

For most patients, infectiousness appears to decline rapidly after adequate and appropriate treatment is started; however, the rate of decline varies from patient to patient. Some patients with unrecognized or inadequately treated drug-resistant TB disease may remain infectious for weeks or even months. Patients with drug-resistant TB disease may **not** respond to the initial drug regimen, acquire further drug resistance, and remain infectious until they receive adequate treatment.

Infectiousness appears to decline rapidly after adequate and appropriate treatment is started; however, the rate of decline varies from patient to patient.

Persons with extrapulmonary TB disease are usually noninfectious unless they also have pulmonary disease, TB disease located in the oral cavity or the larynx, or extrapulmonary disease that includes an open abscess or lesion in which the concentration of organisms is high. Pulmonary TB should be ruled out when there is a diagnosis of extrapulmonary TB disease. Table 7.2 indicates the criteria for patients to be considered noninfectious.

Table 7.2
Criteria for Patients to Be Considered Noninfectious

Criteria
Patients can be considered noninfectious when they meet all of the following three criteria: 1. They have three consecutive negative AFB sputum smears collected in 8- to 24-hour intervals (at least one being an early morning specimen); 2. Their symptoms have improved clinically (for example, they are coughing less and they **no longer** have a fever); **and** 3. They are compliant with an adequate treatment regimen for 2 weeks or longer.

It is important to consider the environmental factors that enhance the probability that *M. tuberculosis* will be transmitted (Table 7.3).

Table 7.3
Environmental Factors that Enhance the Probability that *M. tuberculosis* Will Be Transmitted

Factor	Description
Concentration of infectious bacilli	The more bacilli in the air, the more probable that *M. tuberculosis* will be transmitted
Space	Exposure in small, enclosed spaces
Ventilation	Inadequate local or general ventilation that results in insufficient dilution or removal of infectious droplet nuclei
Air circulation	Recirculation of air containing infectious droplet nuclei
Specimen handling	Improper specimen handling procedures that generate infectious droplet nuclei
Air pressure	Positive air pressure in infectious patient's room that causes *M. tuberculosis* organisms to flow to other areas

Study Questions

Indicate if the following statements about infectiousness are true or false.
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Patients		True or False
____ **7.2**	Children are more likely than adults to be infectious.	**A.** True
____ **7.3**	For most patients, infectiousness appears to decline rapidly after adequate treatment is started.	**B.** False
____ **7.4**	Some patients with unrecognized or inadequately treated drug-resistant TB disease may remain infectious for weeks or even months.	
____ **7.5**	Patients with drug-resistant TB disease may **not** respond to the initial drug regimen, acquire further drug resistance, and may remain infectious until they receive adequate treatment.	

7.6 Patients can be considered noninfectious when they meet which of the following criteria?
(choose the one best answer)

A. They are compliant with an adequate regimen for 2 weeks or longer.

B. Their symptoms have improved clinically.

C. They have three consecutive negative sputum smears collected in 8- to 24-hour intervals (at least one being an early morning specimen).

D. A, B, and C are all correct.

E. Only A and B are correct.

7.7 Which of the following environmental factors can enhance the probability that *M. tuberculosis* will be transmitted?
(choose the one best answer)

A. Concentration of infectious bacilli in the air

B. Exposure in small, enclosed spaces

C. Inadequate local or general ventilation that results in insufficient dilution or removal of infectious droplet nuclei

D. A, B, and C are all correct.

E. Only A and B are correct.

TB Infection Control Measures

TB infection control measures should be based on a careful assessment of risk for transmission of TB in the facility or setting. The goals of effective TB infection control programs are to

- Detect TB disease early and promptly;
- Isolate those who have or are suspected of having TB disease (airborne precautions); and
- Treat people who have or who are suspected of having TB disease.

TB infection control measures should be based on a careful assessment of risk for transmission of TB in the facility or setting.

Detection of TB Disease

The primary risk to health-care workers (HCWs) and the general population is the undiagnosed or unsuspected patient with TB disease. Within health-care settings, protocols should be implemented and enforced to promptly identify, isolate, separate, and either transfer or manage persons who have suspected or confirmed TB disease. Personnel who admit patients to facilities should be trained to detect signs and symptoms of TB disease. People suspected of having TB disease should be given a diagnostic evaluation as soon as possible (see Chapter 4, Diagnosis of Tuberculosis Disease). Clinicians and other HCWs should suspect TB disease in people who have any of the symptoms listed in Table 7.4 and isolate them until TB is excluded.

Table 7.4
Symptoms of TB Disease

Symptoms
People who have any of the following symptoms should be evaluated for TB disease: • Persistent cough (3 weeks or longer); • Chest pain; • Bloody sputum; • Weight loss or loss of appetite; • Fever; • Chills; • Night sweats; • Malaise; or • Fatigue

The primary risk to health-care workers (HCWs) and the general population is the undiagnosed or unsuspected patient with TB disease.

Airborne Precautions

TB airborne precautions should be initiated for any patient who has signs or symptoms of TB disease (suspected TB), or who has documented infectious TB disease and remains infectious in spite of treatment.

TB airborne precautions should be initiated for any patient who has signs or symptoms of TB disease (suspected TB), or who has documented infectious TB disease and remains infectious in spite of treatment.

Persons who have or are suspected of having infectious TB disease should be placed in an area away from other patients, preferably in an airborne infection isolation (AII) room. An AII room is a single-occupancy patient-care room in which environmental factors are controlled to minimize transmission of infectious agents. If a facility does **not** have an AII room, patients should be placed in a room that has been designated for isolation of persons with suspected or known infectious TB disease and, if possible, referred to a facility with an AII room.

A patient who has drug-susceptible TB of the lung, airway, or larynx, who is on standard multidrug antituberculosis treatment, and who has had a substantial clinical and bacteriologic response to therapy (e.g., reduction in cough, resolution of fever, and progressively decreasing quantity of AFB on smear result) is probably no longer infectious. However, because culture and drug-susceptibility results are not usually known when the decision to discontinue airborne precautions is made, all patients with suspected TB disease should remain under airborne precautions until they have had three consecutive negative AFB sputum smear results, each collected in 8- to 24-hour intervals, with at least one being an early morning specimen; have received standard multidrug antituberculosis treatment (minimum of 2 weeks); and have demonstrated clinical improvement.

Airborne precautions in a health-care or congregate setting may be discontinued when a patient has been on adequate therapy for 2 weeks or longer, symptoms improve, and there have been three consecutive, negative AFB sputum smear results.

Treatment

Patients who have confirmed TB disease, or who are considered highly probable to have TB disease, should promptly start appropriate treatment (see Chapter 6, Treatment of Tuberculosis Disease).

Study Questions

7.8 Which of the following is NOT a goal of an effective TB infection control program?
(choose the one best answer)

A. Detect TB disease early and promptly.

B. Isolate from others those people who have or are suspected of having TB disease.

C. Ensure everyone wears a personal respirator.

D. Treat people who have or are suspected of having TB disease.

7.9 The primary risk to health-care workers and the general population is the undiagnosed or unsuspected patient with TB disease.
(choose the one best answer)

A. True

B. False

7.10 TB airborne precautions should be initiated for which of the following patients?
(choose the one best answer)

A. Any patient who has signs or symptoms of TB disease

B. Any patient who has documented infectious TB disease and remains infectious in spite of treatment

C. Any patient who has TB meningitis

D. A, B, and C are all correct.

E. Only A and B are correct.

TB Infection Control Program

A TB infection control program should be based on the following three levels of hierarchy (Table 7.8):

1. **Administrative controls,** which reduce risk of exposure;
2. **Environmental controls,** which prevent spread and reduce concentration of droplet nuclei; and
3. **Respiratory-protection controls,** which further reduce risk of exposure in special areas and circumstances.

1. Administrative Controls

The first and most important level of a TB infection control program is the use of administrative measures to reduce the risk of exposure to persons who might have TB disease. Administrative controls consist of implementing the following activities:

- Assigning someone the responsibility and authority for TB infection control in the health-care setting;
- Conducting a TB infection control risk assessment of the setting;
- Developing and instituting a written TB infection control plan to ensure prompt detection, separation from others (into an AII room if possible), and treatment of persons who have suspected or confirmed TB disease;
- Ensuring the availability of recommended laboratory processing, testing, and reporting of results;
- Implementing effective work practices for managing patients who may have TB disease;
- Ensuring proper cleaning, sterilization, or disinfection of equipment that might be contaminated (e.g., endoscopes);
- Educating, training, and counseling HCWs, patients, and visitors about TB infection and disease;
- Testing and evaluating workers who are at risk for exposure to TB disease;
- Applying epidemiology-based prevention principles, including the use of setting-related TB infection control data;
- Using posters and signs to remind patients and staff of proper cough etiquette (covering mouth when coughing) and respiratory hygiene; and
- Coordinating efforts between local health department and high-risk health-care and congregate settings.

The first and most important level of a TB infection control program is the use of administrative measures to reduce the risk for exposure to persons who might have TB disease.

Health-Care Worker Education and Training

Health-care worker (HCW) education and training on TB infection and disease is an essential part of a TB infection control program and can increase adherence to TB infection control measures. Education and training should emphasize the increased risks posed by an undiagnosed person with TB disease in a health-care setting and the specific measures to reduce this risk. Health-care settings should document that all HCWs, including physicians, have received training relevant to their work setting. Resources for TB education and training can be found on the following websites:

- CDC DTBE website (www.cdc.gov/tb);
- Find TB Resources website (www.findtbresources.org); and
- Regional Training and Medical Consultation Centers' TB Training and Education Products website (https://sntc.medicine.ufl.edu/rtmccproducts.aspx.)

All health-care settings should conduct an annual evaluation for follow-up education and training based on the

- Number of untrained or new HCWs;
- Changes in the organization and services of the health-care setting; and
- Availability of new TB infection control information.

Facility Risk Assessment

Health-care and congregate settings should conduct an annual evaluation of the risk for transmission of *M. tuberculosis*. The risk assessment determines the type of administrative, environmental, and respiratory-protection controls needed by examining the

- Number of patients with TB disease in the setting;
- Promptness of detection, isolation, and evaluation of patients with suspected or confirmed TB disease;
- Evidence of transmission of *M. tuberculosis* in the setting; and
- Community rate of TB disease.

Health-care and congregate settings should conduct an annual evaluation of the risk for transmission of *M. tuberculosis*.

Risk Classification

The purpose of the risk classification is to determine the need for a TB testing program for HCWs and the frequency of testing. The risk classification, or risk level, will vary; however, all settings should perform risk classification as part of risk assessment to determine the need for and frequency of a HCW testing program, regardless of the likelihood of encountering persons with TB disease. Baseline TB testing should be conducted for HCWs upon hiring (see Chapter 3, Testing for Tuberculosis Infection and Disease). The three TB risk classifications are indicated in Table 7.5.

Table 7.5
TB Risk Classifications

Risk Classification	Need for Testing	Frequency of Testing
Low risk	Should be used for settings in which persons with TB disease are **not** expected to be encountered.	Exposure to *M. tuberculosis* in these settings is unlikely, and further testing is **not** needed unless exposure has occurred.
Medium risk	Should be used for facilities in which the risk assessment has determined that HCWs will possibly be exposed to persons with TB disease.	Repeat testing should be done annually.
Potential ongoing transmission	Should be temporarily assigned to any setting where there is evidence of person-to-person transmission of *M. tuberculosis* in the past year.	Testing should be repeated every 8 to 10 weeks until there is **no** evidence of ongoing transmission.

2. Environmental Controls

The second level of hierarchy is the use of environmental controls to prevent the spread and reduce the concentration of droplet nuclei and includes:

- Primary environmental controls; and
- Secondary environmental controls (Table 7.6).

The second level of hierarchy is the use of environmental controls to prevent the spread and reduce the concentration of droplet nuclei.

Table 7.6
Environmental Controls

Primary Environmental Control	Secondary Environmental Control
Controls the source of infection by diluting and removing contaminated air and by using general ventilation • Uses natural ventilation (e.g., open doors, windows) • Uses mechanical ventilation equipment to circulate and move air in a building • Uses local exhaust ventilation (e.g., hoods, tents, or booths)	Controls airflow in areas adjacent to the source and cleans air • Controls the airflow to prevent contamination of air in areas adjacent to the source (AII rooms) • Cleans the air by using high efficiency particulate air (HEPA) filtration or ultraviolet germicidal irradiation (UVGI)

Primary Environmental Controls

Primary environmental controls consist of controlling the source of infection by using local exhaust ventilation (e.g., hoods, tents, or booths) and diluting and removing contaminated air by using general ventilation.

Ventilation is the movement and the replacement of air in a building with air from the outside or with clean, recirculated air. When fresh air enters a room, it dilutes the concentration of particles in room air, such as droplet nuclei. There are two types of ventilation:

- Natural ventilation
- Mechanical ventilation

Natural Ventilation

Natural ventilation relies on cross ventilation in a building designed for good air exchange; for example, the use of open doors and windows to bring in air from outside. Natural ventilation can be useful for nontraditional facility-based and congregate settings that do not have a central ventilation system. In these settings, waiting rooms, shelter dormitories, or other rooms in which people congregate should have an operable window, door, or skylight that is kept open as often as possible. Fans can be used to help distribute the air (Figure 7.1). If the direction of airflow is unknown, staff should sit near the fresh air source and clients should sit near the exhaust location (Figure 7.2). This can help protect staff from droplet nuclei expelled by patients with unidentified TB disease. In addition to these environmental measures, cough etiquette and respiratory hygiene should be encouraged to further reduce risk (Figure 7.3).

Figure 7.1
Exhaust Fan Used for Distributing Air

Figure 7.2
Natural Ventilation in TB Exam or Counseling Room

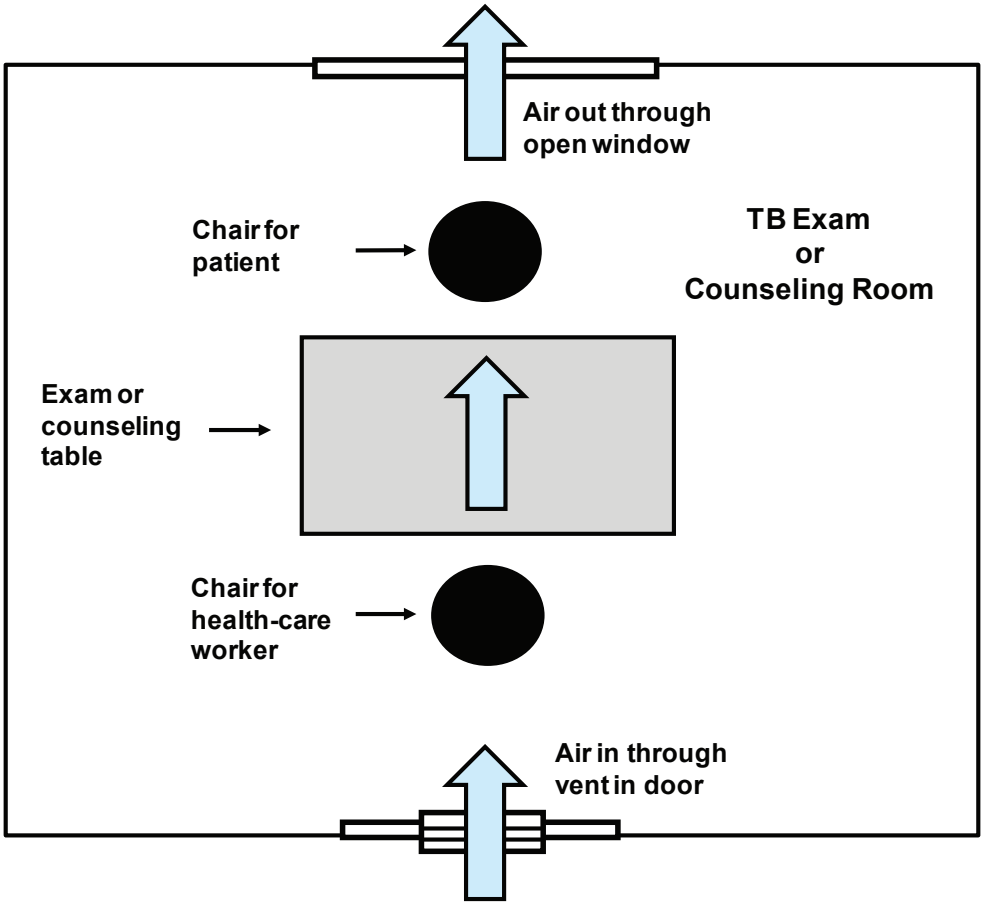


Figure 7.3
Person with Infectious TB in Waiting Room

Mechanical Ventilation

Mechanical ventilation refers to the use of equipment to circulate and move air in a building. Mechanical ventilation should be used by hospitals, TB clinics, and other health-care and congregate settings expecting to see a confirmed or suspected TB patient. Mechanical ventilation consists of

- Local exhaust ventilation; and
- General ventilation.

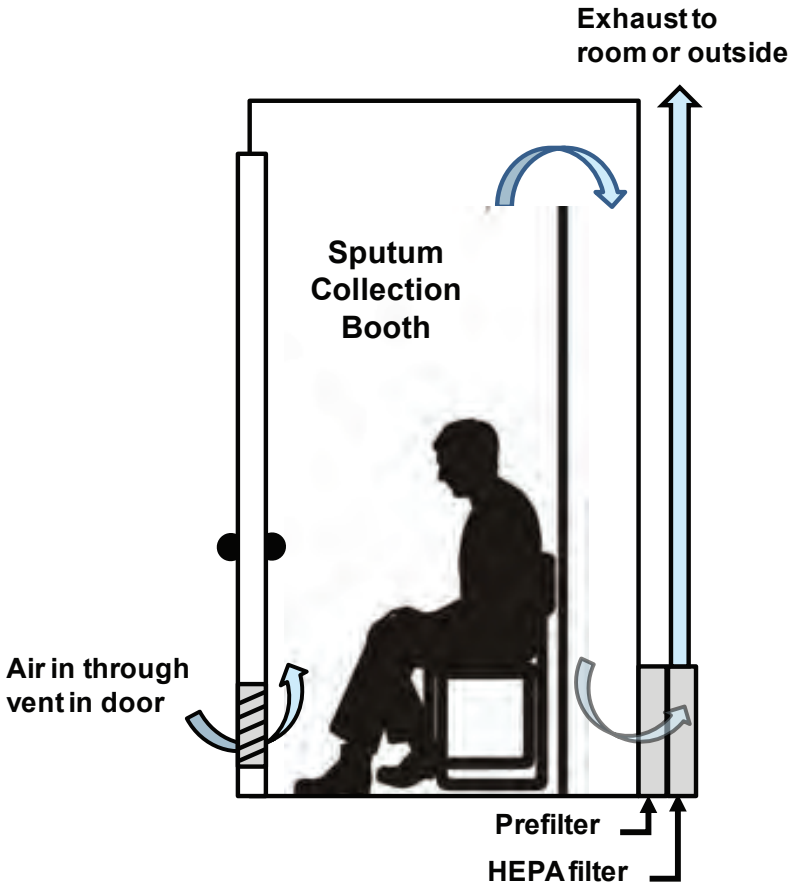
Local exhaust ventilation stops airborne contaminants before they spread into the general environment. Local exhaust ventilation includes the use of

- External hoods;
- Booths; and
- Tents.

Local exhaust ventilation should be used for cough-inducing and aerosol-generating procedures (Figure 7.4). If local exhaust ventilation **cannot** be used, cough-inducing and aerosol-generating procedures should be performed in an AII room. If an AII room is **not** available, the procedures should be performed outdoors and away from

- People;
- Windows; and
- Air intakes.

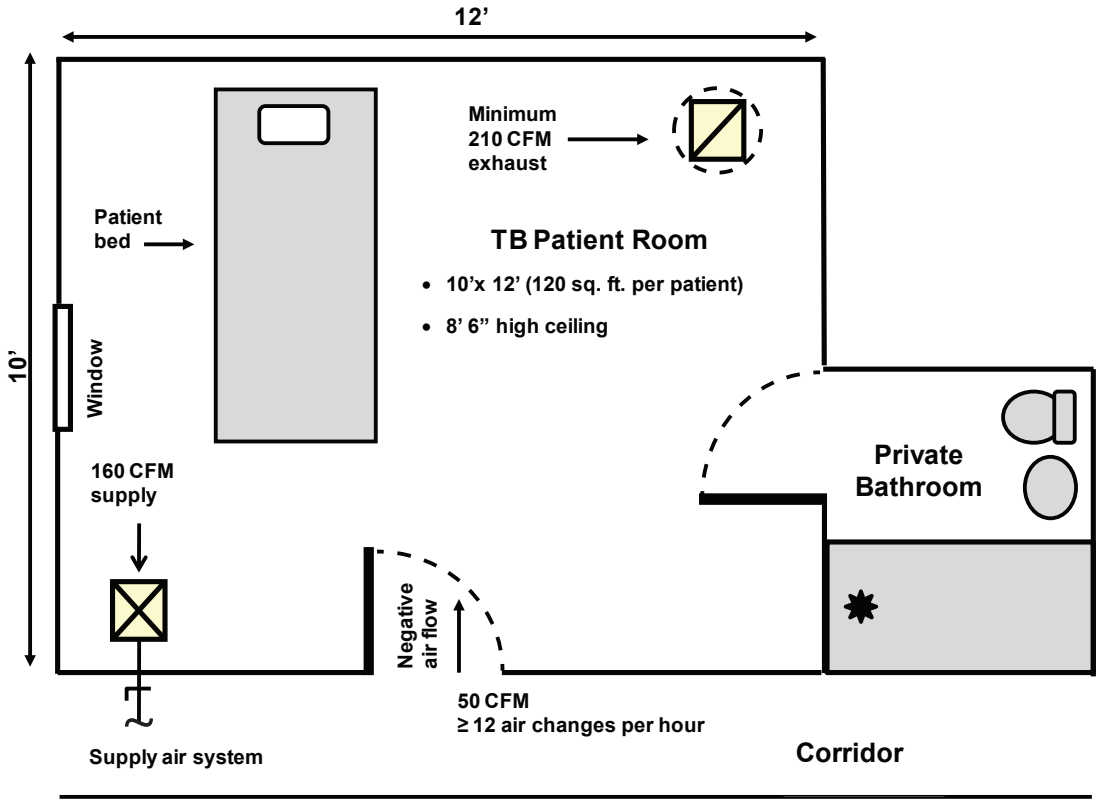
Figure 7.4
Local Exhaust in Sputum Collection Booth



General ventilation systems maintain air quality in health-care settings by the

- Dilution of contaminated air;
- Removal of contaminated air; and
- Control of airflow patterns in the patient's procedure room or setting (e.g., negative pressure in AII rooms) (Figure 7.5).

Figure 7.5
Airborne Infection Isolation (AII) Room



TB AII rooms are designed to prevent the spread of droplet nuclei expelled by a patient with TB disease. In TB clinics, hospitals, and other inpatient settings, patients known to have TB disease or suspected of having TB disease should be placed in a TB AII room immediately. Health-care facilities that provide care for patients with suspected or confirmed TB disease should have at least one AII room. Medical facilities in correctional settings should also have at least one AII room. The need for additional AII rooms should be based on the TB risk assessment for the setting.

In TB clinics, hospitals, and other inpatient settings, patients known to have TB disease or suspected of having TB disease should be placed in a TB AII room immediately.

Health-care facilities that provide care for patients with suspected or confirmed TB disease and medical facilities in correctional settings should have at least one AII room.

One characteristic of AII rooms is their negative pressure relative to other parts of the facility. Negative pressure causes air to flow from the corridors into the AII room. The air from the AII room **cannot** escape to the other parts of the health-care setting when the door is closed and the ventilation system is operating properly. The doors and windows of AII rooms must be kept closed as much as possible in order to maintain negative pressure, and the pressure must be checked periodically to make sure that it remains negative. Air from the AII room can be exhausted directly to the outdoors, where the droplet nuclei will be diluted in the outdoor air, or passed through a special high efficiency particulate air (HEPA) filter that removes most (99.97%) of the droplet nuclei before it is returned to the general circulation. If a HEPA filter is **not** used, the air should be exhausted directly to the outside away from air-intake vents, persons, and animals, in accordance with applicable federal, state, and local regulations on environmental discharges.

One characteristic of AII rooms is the negative pressure relative to other parts of the facility. Negative pressure allows air to flow from the corridors into the AII room.

Air from the AII room can be exhausted directly to the outdoors, where the droplet nuclei will be diluted in the outdoor air, or passed through a special high efficiency particulate air filter that removes most (99.97%) of the droplet nuclei before it is returned to the general circulation.

In existing health-care settings, AII rooms should have airflow of six or more air changes per hour (ACH). In new or renovated health-care settings, AII rooms should have airflow of at least 12 ACH. When feasible, the airflow in existing health-care setting AII rooms should be increased to 12 ACH by

- Adjusting or modifying the ventilation system; or
- Using air-cleaning methods: room-air recirculation units containing HEPA filters or ultraviolet germicidal irradiation (UVGI) systems that increase the equivalent ACH.

It is important that AII rooms be single-patient rooms with a private bathroom. Entry of visitors and HCWs should be restricted and monitored to minimize the transmission of *M. tuberculosis*. All HCWs who enter an AII room should wear N95 disposable filtering facepiece respirators (see Respiratory-Protection Controls). An N95 respirator should be fitted correctly before using. Visitors should be offered and encouraged to use respiratory protection (i.e., N95 respirator) and instructed by HCWs on how to use it.

Health-care settings with AII rooms should observe the policies and practices indicated in Table 7.7.

Table 7.7
Policies and Practices for Airborne Infectious Isolation (AII) Rooms in Health-Care Settings

Policies and Practices
• Keep doors and windows closed as much as possible;
• Maintain an adequate number of AII rooms;
• Check negative pressure by monitoring and recording the direction of airflow on a daily basis;
• Perform diagnostic and treatment procedures in the AII room;
• Ensure patients adhere to AII precautions;
• Group AII rooms in one part of the health-care setting;
• Schedule patients with suspected and confirmed infectious TB disease for procedures when few HCWs and no other patients are present;
• Provide a surgical mask for patients with suspected or confirmed infectious TB disease during transport, in waiting areas, and when others are present; and
• Review environmental control maintenance procedures and logs to determine if maintenance is being conducted properly and regularly.

Secondary Environmental Controls

Secondary environmental controls consist of controlling the airflow to prevent contamination of air in areas adjacent to the source (AII rooms) and cleaning the air by using HEPA filtration (Figure 7.6) or ultraviolet germicidal irradiation (UVGI) (Figure 7.7). HEPA filters can be used to filter droplet nuclei from the air and must be used when discharging air from:

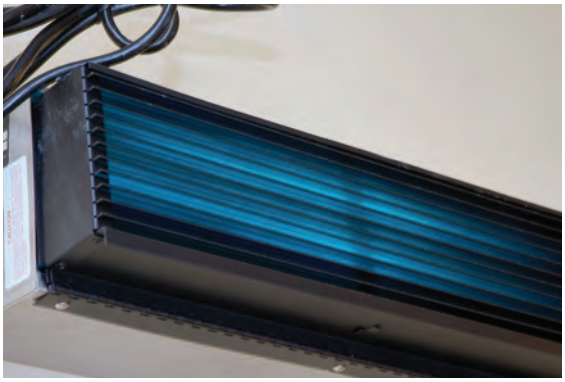
- Local exhaust ventilation booths or enclosures directly into the surrounding room or area; and
- An AII room (or other negative-pressure room) into the general ventilation system (e.g., in settings in which the ventilation system or building configuration makes venting the exhaust to the outside impossible).

Secondary environmental controls consist of controlling the airflow to prevent contamination of air in areas adjacent to the source (AII rooms) and cleaning the air by using HEPA filtration or UVGI.

UVGI is an air-cleaning technology that consists of the use of special lamps that give off germicidal ultraviolet irradiation (wave length=254 nm). The lamps are used to inactivate the tubercle bacilli contained in the droplet nuclei. Overexposure to UV light can be harmful to the skin and eyes; lamps must be installed in the upper part of rooms or corridors or placed in exhaust ducts. Regular, appropriate maintenance is essential to ensure UVGI lamps are operating correctly.

Figure 7.6
HEPA Filter

Figure 7.7
Ultraviolet Germicidal Irradiation (UVGI)



3. Respiratory-Protection Controls

Respiratory-protection control is the third level of a TB infection control program and consists of the use of personal protective equipment in situations that pose a high risk for exposure to TB disease (Figure 7.8). Use of respiratory protection can further reduce risk for exposure of HCWs to droplet nuclei expelled into the air. The following measures can be taken to reduce risk for exposure:

- Implementing a respiratory-protection program;
- Training HCWs on respiratory protection; and
- Educating patients on respiratory hygiene and the importance of cough etiquette.

Respiratory-protection control is the third level of a TB infection control program and consists of the use of protective equipment in situations that pose a high risk for exposure to TB disease.

Figure 7.8
Health-Care Worker and Infectious TB Patient Using Respiratory Protection

All health-care settings that use respiratory-protection controls are required by the Occupational Safety and Health Administration (OSHA) to develop, implement, and maintain a respiratory-protection program.

Administrative and environmental controls minimize the number of areas in which exposure to *M. tuberculosis* might occur and therefore minimize the number of persons exposed. These control measures also reduce, but do **not** eliminate, the risk for exposure in limited areas. In these settings, respiratory protection should be used by all persons, including HCWs and visitors. These settings include:

- TB AII rooms;
- Rooms where cough-inducing or aerosol generating procedures are done;
- Ambulances and other vehicles transporting infectious TB disease patients; and
- Homes of infectious TB disease patients (for HCWs; other persons should not visit the homes of infectious persons).

The effectiveness of a respiratory-protection program requires the development of written standard procedures. Standard procedures should include information and guidance for the proper selection, use, and care of respirators. Settings where HCWs use respiratory protection to prevent transmission of *M. tuberculosis* should develop, implement, and maintain a respiratory-protection program. The program should provide HCWs with annual training on TB control, TB infection control, and respiratory protection, including fit-testing.

Settings where HCWs use respiratory protection to prevent transmission of *M. tuberculosis* should develop, implement, and maintain a respiratory-protection program.

The minimum respiratory protection is a filtering face-piece respirator and must be selected from those approved by CDC/National Institute for Occupational Safety and Health (NIOSH) under Title 42 CFR, Part 84. It must meet one of the following specifications:

- Nonpowered air-purifying respirators (N95, N99, N100, R95, R99, R100, P95, P99, and P100), including disposables;
- Powered air-purifying respirators (PAPRs) with high-efficiency filters; or
- Supplied-air respirators.

It is important that respirators fit different face sizes and features properly. It is also important to understand the difference between respirators and surgical masks.

Respirators are designed to protect HCWs and other individuals from inhaling droplet nuclei (Figure 7.9). Surgical masks are designed to reduce the number of droplets being exhaled into the air by persons with infectious TB disease when they breathe, talk, cough, or sneeze (Figure 7.10). Persons suspected or confirmed to have infectious TB disease should be given, and encouraged to use, a surgical mask to minimize the risk of expelling droplet nuclei into the air.

Respirators are designed to protect HCWs and other individuals from inhaling droplet nuclei.

Surgical masks are designed to reduce the number of droplets being exhaled into the air by persons with infectious TB disease when they breathe, talk, cough, or sneeze.

Figure 7.9
Respirator for Health-Care Workers

Health-care worker wearing a respirator

Respirators

- Designed to filter out droplet nuclei from being inhaled by the health-care worker and other individuals.
- Should properly fit different face sizes and features.
- Should **NOT** be worn by the patient.

Figure 7.10
Surgical Mask for Persons with Infectious TB Disease

Infectious TB patient wearing a surgical mask

Surgical masks

- Designed to stop droplet nuclei from being spread (exhaled) by the patient.
- Should **NOT** be worn by the health-care worker

Table 7.8
TB Infection-Control Program: Level of Controls

Administrative Controls
• Assign responsibility for TB infection control • Conduct TB risk assessment • Develop and institute a written TB infection-control plan • Ensure the timely availability of recommended laboratory processing, testing, and reporting of results • Implement effective work practices for the management of patients with suspected or confirmed TB disease • Ensure proper cleaning and sterilization or disinfection of potentially contaminated equipment • Train and educate health-care workers • Test and evaluate health-care workers for TB infection and disease • Apply epidemiology-based prevention principles • Use posters and signs demonstrating and advising respiratory hygiene and cough etiquette • Coordinate efforts with the local or state health department.
Environmental Controls
• Reduce concentration of infectious droplet nuclei through the following technologies: » Ventilation technologies, including – Natural ventilation – Mechanical ventilation » High efficiency particulate air filtration (HEPA) » Ultraviolet germicidal irradiation (UVGI)
Respiratory Protection Controls
• Implement a respiratory-protection program • Train health-care workers on respiratory protection • Educate patients on respiratory hygiene and the importance of covering their cough • Test HCWs for mask fit and functionality

Study Questions

Case study– Jose

Jose, the Harris County TB Control Manager, is conducting a risk assessment to determine the type of administrative, environmental, and respiratory-protection controls that are needed in his area.

7.11 What things should Jose examine?
(choose the one best answer)

A. Number of patients with TB disease in the setting and the community rate of TB disease

B. Evidence of transmission of *M. tuberculosis* in the setting

C. Promptness of detection, isolation, and evaluation of patients with suspected or confirmed TB disease.

D. A, B, and C are all correct.

E. Only A and B are correct.

Match the setting and testing characteristics for each type of TB risk classification.
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Setting and Testing Characteristics	TB Risk Classification
____ **7.12** Temporarily assigned to any setting with evidence of person-to-person transmission of *M. tuberculosis* in the past year.	**A.** Low-risk classification
____ **7.13** Setting where persons with TB disease are **not** expected to be encountered.	**B.** Medium-risk classification
____ **7.14** Facilities in which the risk assessment has determined that health-care workers will possibly be exposed to persons with TB disease.	**C.** Potential ongoing transmission classification
____ **7.15** Repeat testing is not needed unless exposure has occurred.	
____ **7.16** Repeat testing should be done every 8 to 10 weeks until there is no evidence of ongoing transmission.	
____ **7.17** Repeat testing should be done annually.	

Indicate whether the types of environmental controls below are primary or secondary controls. (Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Environmental Controls	Primary/Secondary Controls
____ **7.18** HEPA filtration	**A.** Primary control
____ **7.19** Natural, mechanical, and local exhaust ventilation	**B.** Secondary control
____ **7.20** Ultraviolet germicidal irradiation	
____ **7.21** Controls airflow in areas adjacent to the source and cleans air	
____ **7.22** Controls the source of infection by diluting and removing contaminated air and by using general ventilation	

Indicate if the following statements about TB airborne infection isolation (AII) rooms are true or false. (Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Statements about TB AII Rooms	True or False
____ **7.23** Designed to prevent the spread of the droplet nuclei to other rooms in the facility.	**A.** True
____ **7.24** Have positive pressure relative to other parts of the facility.	**B.** False
____ **7.25** Air from the AII room is exhausted directly to the outdoors, or passes through a special filter that removes all of the droplet nuclei.	
____ **7.26** Entry of visitors and health-care workers should be restricted and monitored to minimize the transmission of *M. tuberculosis*.	
____ **7.27** Patients staying in AII rooms should wear N95 disposable filtering face-piece respirators.	
____ **7.28** AII rooms can be used for multiple patients.	

7.29 Which of the following respiratory protection measures reduces risk for exposure to TB disease? (choose the one best answer)

A. Implementing a respiratory-protection program

B. Training health-care workers on respiratory protection

C. Educating patients on respiratory hygiene and the importance of cough etiquette

D. A, B, and C are all correct.

E. Only A and B are correct.

7.30 Which of the following statements about respiratory protection is true? (choose the one best answer)

A. Respirators are designed to protect health-care workers and other individuals from inhaling droplet nuclei.

B. Surgical masks are designed to reduce the number of droplets being exhaled into the air by persons with infectious TB disease.

C. Health-care workers can wear surgical masks for protection against droplet nuclei, and persons with infectious TB disease can wear respirators to prevent the spread of TB.

D. A, B, and C are all correct.

E. Only A and B are correct.

Match the activities with the type of TB infection control.
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Activities	TB Infection Controls
____ **7.31** Use natural exhaust ventilation and mechanical ventilation to remove contaminated air.	**A.** Administrative controls
____ **7.32** Use personal protective equipment in situations that pose a high risk for exposure to TB disease.	**B.** Environmental controls
____ **7.33** Assign someone the responsibility and authority for TB infection control in the health-care setting.	**C.** Respiratory protection controls
____ **7.34** Ensure the availability of recommended laboratory processing, testing, and reporting of results.	
____ **7.35** Control the airflow to prevent contamination of air in areas adjacent to the source and clean the air by using HEPA filtration or UVGI.	
____ **7.36** Conduct a TB infection control risk assessment of the setting.	

TB Infection Control in Nontraditional Facility-Based Settings

All nontraditional facility-based settings where patients with TB disease receive care should establish and follow a TB infection control program. These settings include but are **not** limited to

- Correctional facilities;
- Homeless shelters;
- Long-term care facilities;
- Home-based health-care and outreach settings; and
- Emergency medical services (EMS) (Table 7.9).

All nontraditional facility-based settings where patients with TB disease receive care should establish and follow a TB infection control program.

Correctional Facilities

TB disease can be a substantial health concern in correctional facilities. TB outbreaks in correctional facilities can lead to transmission in surrounding communities. Health-care settings in correctional facilities should be classified as at least **medium risk** based on the possibility of exposure to persons with TB disease. Correctional facilities overall are classified as minimal risk or non-minimal risk based on the TB risks of the population housed in the facility. A respiratory-protection program should be implemented with at least one AII room available where inmates with suspected or confirmed TB disease can be isolated immediately. Those inmates who must be transported should wear a surgical mask during transport. Correctional facilities should maintain a tracking system for inmate TB testing and treatment, and establish a mechanism for sharing this information with state and local health departments and other correctional facilities.

Homeless Shelters

TB disease is more common in the homeless population than in the general population. Several factors in the shelter environment can influence the likelihood of *M. tuberculosis* transmission, including crowding and the state of the ventilation system. The absolute number and population density of persons sharing the same breathing space is important. If all other factors are constant, the size of the shelter population is directly proportional to the likelihood that someone with infectious TB will be present and that someone else will become infected. Conversely, the smaller the population and less crowded the shelter, the lower the risk. Homeless shelters should implement a tracking system for clients and establish a mechanism for sharing this information with state and local health departments when appropriate.

Long-Term Care Facilities

TB disease poses a health risk in long-term care facilities (LTCFs) such as hospice and skilled-nursing facilities. Transmission of *M. tuberculosis* has occurred in LTCFs and pulmonary TB disease has been documented in HIV-infected patients and other immunocompromised patients residing in hospices. LTCFs must have adequate administrative and environmental controls if they accept patients with suspected or confirmed infectious TB disease. These include airborne precaution capabilities and a respiratory-protection program. People most at risk in LTCFs include

- Patients;
- HCWs;
- Visitors; and
- Volunteers

Home-Based Health-Care and Outreach Settings

Transmission of *M. tuberculosis* has been documented in home-based health-care and outreach settings. HCWs in these settings should be able to

- Evaluate signs and symptoms of TB disease for early detection and treatment;
- Educate patients on the importance of reporting symptoms and signs of TB disease; and
- Wear an N95 personal respirator when entering homes of persons with suspected or confirmed infectious TB disease or when transporting such persons in an enclosed vehicle.

Emergency Medical Services (EMS)

Although the overall risk is low, there has been documented transmission of *M. tuberculosis* in EMS occupational settings. EMS personnel should be included in

- Comprehensive training, education, and testing programs for TB infection; and
- Follow-up testing as indicated by the risk classification of the setting.

Drivers, HCWs, and other staff transporting patients with suspected or confirmed TB should wear an N95 respirator, and the patients should wear a surgical mask. In addition, ambulances should allow for the maximum amount of outdoor air to be circulated in the vehicle.

Table 7.9
TB Infection Control for Nontraditional Settings

Setting	Transmission of *M. tuberculosis*	Screening/testing	Recommendations
Correctional facilities	• Substantial health concern • TB outbreaks in these settings can lead to transmission in surrounding communities • Heath-care settings in these facilities are at least medium risk	• All correctional staff should be screened and tested for TB annually	• Implement a respiratory-protection program with at least one AII room or have a transfer policy • Inmates with suspected or confirmed TB disease should be isolated immediately and wear a surgical mask when being transported outside of an AII room • Facilities should maintain a tracking system for sharing information with state and local health departments and other correctional facilities
Homeless shelters	• Occurs in these settings • More common in homeless shelters than in general population • Frequent visitors are at risk of exposure	• Symptom screening	• Evaluate the resident for signs and symptoms of TB disease for early detection and treatment • Educate staff on importance of reporting signs and symptoms of TB disease

Setting	Transmission of *M. tuberculosis*	Screening/testing	Recommendations
Long-term care facilities	• Occurs in these settings • Poses a health risk to patients, health-care workers, visitors, and volunteers	• New employees and residents should receive symptom screening and possibly testing upon entry	• Must have adequate administrative and environmental controls that include » Airborn precaution capabilities » Respiratory-protection program • Patients with suspected or confirmed infectious TB disease should **not** stay in LTCFs unless adequate administrative and environmental controls are in place
Home-based health-care and outreach settings	• Occurs in these settings	• Symptom screening • Employees should receive annual screening and/or testing	• Evaluate the resident for signs and symptoms of TB disease for early detection and treatment • Educate patients and staff on importance of reporting signs and symptoms of TB disease • Wear an N95 respirator when entering homes of persons suspected of having infectious TB disease
Emergency medical services	• Low health concern	• Include a comprehensive employee screening program to test for TB infection • Conduct follow-up testing as indicated by the risk classification of the setting	• Drivers, health-care workers, and other staff should wear an N95 respirator in a high-risk situation • Persons with suspected TB who are transported in an ambulance should wear a surgical mask • Ambulances should allow for maximum amount of outdoor air to circulate in the vehicle

Study Question

7.37 Which of the following statements about TB infection control in nontraditional settings is true?
(choose the one best answer)

A. All nontraditional settings where patients with TB disease receive care should establish and follow a TB infection control program.

B. Nontraditional settings include correctional facilities, homeless shelters, long-term care facilities, home-based health-care, and emergency medical services.

C. Emergency medical services has a documented overall high level of transmission of *M. tuberculosis*.

D. A, B, and C are all correct.

E. Only A and B are correct.

TB Infection Control in the Home

Patients who are suspected to have, or have, confirmed TB disease are frequently sent home after starting treatment, even though they may still be infectious. Patients with TB disease can be sent home even if they do **not** have three negative sputum smears, if the following criteria are met:

- A follow-up plan has been made with the local TB program;
- The patient is on standard TB treatment, and directly observed therapy (DOT) has been arranged;
- No infants or children less than 5 years of age or persons with immunocompromising conditions are present in the household; and
- The patient is willing to remain isolated in the home except for health-care associated visits until the patient has negative sputum smear results.

Patients who have suspected or confirmed TB disease are more likely to have already transmitted TB infection to members of their household before their TB disease was diagnosed and treatment was started. However, TB patients and members of their household should take steps to prevent the further spread of TB infection after they return home (Table 7.10). Patients with TB disease should

- Be instructed to cover their mouth and nose when coughing or sneezing;
- Sleep alone and **not** in a room with other household members; and
- **Refrain** from having visitors in the home until they are noninfectious.

HCWs who visit TB patients in their homes should take the following precautions to protect themselves from exposure to *M. tuberculosis* (Table 7.10):

- Instruct patients to cover their mouth and nose with a tissue when coughing or sneezing;
- Wear a respirator when visiting the home of a patient with infectious TB disease or when transporting a patient with infectious TB disease in a vehicle; and
- Collect specimens in a well ventilated area, away from other household members

In addition, HCWs whose responsibilities include visiting infectious patients should participate in an annual TB testing program.

Table 7.10
TB Infection Control in the Home

Steps that Patients Can Take to Prevent the Further Transmission of TB in the Home	Precautions for Health-Care Workers to Take to Protect Themselves from Exposure to *M. tuberculosis*
• Cover their mouth and nose when coughing or sneezing • Sleep alone and **not** in a room with other household members • **Refrain** from having visitors in the home until they are noninfectious.	• Instruct patients to cover their mouth and nose with a tissue when coughing or sneezing • Wear a respirator when visiting the home of a patient with infectious TB disease or when transporting a patient with infectious TB disease in a vehicle • Collect specimens in a well-ventilated area, away from other household members

Study Questions

7.38 Elton was just diagnosed with TB and is considered infectious. Lilian, his nurse, is instructing him about steps he can take to prevent the spread of TB infection to others when he returns home today. Which of the following steps should Lilian mention? (choose the one best answer)

A. Cover his mouth and nose when coughing or sneezing.

B. Do **not** have visitors until he is noninfectious.

C. It is ok to sleep in the same room with his wife.

D. A, B, and C are all correct.

E. Only A and B are correct.

Lilian will be conducting DOT at Elton's home starting tomorrow. Which of the following precautions should Lilian take to protect herself from exposure to TB?
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Precautions for Health-Care Workers Visiting the Home of a TB Patient Who May Be Infectious	Yes or No
____ **7.39** Spray the room where they will meet with a disinfectant before Elton enters it.	**A.** Yes (take this precaution)
____ **7.40** Wear a respirator when visiting Elton's home.	**B.** No (this is not an effective precaution)
____ **7.41** Wear a surgical mask when visiting Elton's home.	
____ **7.42** Collect specimens in a well-ventilated area, away from other household members.	
____ **7.43** Refrain from touching any surfaces in the home.	

Chapter Summary

M. tuberculosis can be transmitted in virtually any setting. Clinicians should be aware that transmission has been documented in health-care settings where HCWs and patients come in contact with persons with infectious TB who

- Have unsuspected TB disease,
- Have **not** received adequate treatment, or
- Have **not** been isolated from others.

The infectiousness of a TB patient is directly related to the number of droplet nuclei carrying *M. tuberculosis* (tubercle bacilli) that are expelled into the air. Depending on the environment, these tiny particles can remain suspended in the air for several hours. *M. tuberculosis* is transmitted only through the air, **not** by surface contact. Infection occurs when a person inhales droplet nuclei containing *M. tuberculosis*, and the droplet nuclei traverse the mouth or nasal passages, upper respiratory tract, and bronchi to reach the alveoli of the lungs. Persons with extrapulmonary TB disease may have concurrent unsuspected pulmonary or laryngeal TB disease. Except for laryngeal TB disease, extrapulmonary TB disease is rarely infectious; however, transmission from extrapulmonary sites has been reported to occur during aerosol-producing procedures such as autopsies and tissue irrigation.

For most patients, infectiousness appears to decline rapidly after adequate and appropriate treatment is started; however, the rate of decline varies from patient to patient. Some patients with unrecognized or inadequately treated drug-resistant TB disease may remain infectious for weeks or even months. Patients with drug-resistant TB disease may **not** respond to the initial drug regimen and may remain infectious until they receive adequate treatment.

TB infection control measures should be based on a careful assessment of risk for transmission of TB in the facility or setting. The goals of effective TB infection control programs are to

- Detect TB disease early and promptly;
- Isolate those who have or are suspected of having TB disease (airborne precautions); and
- Treat people who have or are suspected of having TB disease.

The primary risk to HCWs and the general population is the undiagnosed or unsuspected patient with TB disease. Within health-care settings, protocols should be implemented and enforced to promptly identify, isolate, and either transfer or manage persons who have suspected or confirmed TB disease. Personnel who admit patients to facilities should be trained to detect signs and symptoms of TB disease.

A TB infection control program should be based on the following three levels of hierarchy:

1. **Administrative controls,** which reduce risk of exposure;
2. **Environmental controls,** which prevent spread and reduce concentration of droplet nuclei; and
3. **Respiratory-protection controls,** which further reduce risk of exposure in special areas and circumstances.

The first and most important level of a TB infection control program is the use of administrative measures to reduce the risk for exposure to persons who might have TB disease.

The second level of hierarchy is the use of environmental controls to prevent the spread and reduce the concentration of infectious droplet nuclei and includes primary and secondary controls.

Respiratory-protection control is the third level of a TB infection control program and consists of the use of protective equipment in situations that pose a high risk for exposure to TB disease. Use of respiratory protection can further reduce HCW risk of exposure to droplet nuclei expelled into the air.

All nontraditional facility-based settings where patients with TB disease receive care should establish and follow a TB infection control program. These settings include but are **not** limited to

- Correctional facilities;
- Homeless shelters;
- Long-term care facilities;
- Home-based health-care and outreach settings; and
- Emergency medical services;

Patients who are suspected to have, or have, confirmed TB disease are frequently sent home after starting treatment, even though they may still be infectious. Patients with TB disease can be sent home even if they do **not** have three negative sputum smears, if the following criteria are met:

- A follow-up plan has been made with the local TB program;
- The patient is on standard TB treatment, and DOT has been arranged;
- No infants or children less than 5 years of age or persons with immunocompromising conditions are present in the household unless they have been evaluated and started on treatment; and
- The patient is willing to remain isolated in the home except for health-care associated visits until the patient has negative sputum smear results.

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Chapter 8
Community Tuberculosis Control

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Chapter Objectives

After working through this chapter, you should be able to

- Describe the roles and responsibilities for tuberculosis (TB) control and prevention in the public health sector; and
- Describe the roles and responsibilities for TB control and prevention in the private health sector.

Introduction

State and local health departments have the primary responsibility for preventing and controlling TB. However, TB control is a complex undertaking and requires the collaborative efforts of a broad range of persons, organizations, and institutions both inside and outside the public health sector. These various persons and organizations have a role in improving the detection of TB cases, one of the most important responsibilities of TB control, and include

- Clinicians;
- Community health centers;
- Hospitals;
- Academic institutions;
- Medical professional organizations;
- Community-based organizations;
- Correctional facilities;
- Civil surgeons; and
- Pharmaceutical and biotechnology industries.

State and local health departments have the primary responsibility for preventing and controlling tuberculosis (TB).

Roles and Responsibilities of the Public Health Sector Providers

The essential role of the public health sector in TB control is to plan, coordinate, and evaluate TB control and prevention efforts. This role requires that state and local health departments focus and provide oversight on the following critical elements:

- Planning and policy development;
- Contact investigation;
- Clinical and diagnostic services for patients with TB and their contacts;
- Training and education;
- Surveillance data and information management; and
- Monitoring and evaluation.

The essential role of the public health sector in TB control is to plan, coordinate, and evaluate TB control and prevention efforts.

Planning and Policy Development

State and local TB control programs have the responsibility for developing TB control policies and procedures. A TB control plan should be developed in collaboration with community stakeholders and experts in medical and nonmedical TB management. Laboratory directors and professional organizations also make excellent partners to collaborate with when developing TB control policies.

A TB control plan should be developed in collaboration with community stakeholders and experts in medical and nonmedical TB management.

The plan should be based on an understanding of local epidemiologic data and on the capabilities and capacities of clinical and support services for clients. Fiscal resources available for TB control also determine the plan's scope and direction, as well as ongoing indicators of program performance (program evaluation). Policies and procedures should reflect national, state, and local standards of care and should offer guidance in the management of LTBI and TB disease.

A written TB control plan should be updated regularly and distributed widely to partners. The TB control plan should

- Assign specific roles and responsibilities;
- Define essential pathways of communication between providers, laboratories, and the public health system;
- Assign sufficient resources, both human and financial, to ensure its implementation, including a responsible case manager for each suspected and verified case of TB disease;
- Provide provisions for expert consultation and oversight for TB-related matters to clinicians, institutions, and communities;
- Provide special guidance to local laboratories that process TB-related samples;
- Assist local authorities in conducting contact or outbreak investigations and directly observed therapy (DOT); and
- Provide culturally appropriate information to patients, persons at risk, and the community.

A written TB control plan should be updated regularly and distributed widely to partners.

Systems to minimize or eliminate financial and cultural barriers to TB control should be integral to the plan. Persons with TB disease and persons at high risk for TB should receive culturally appropriate education about TB and clinical services, including treatment, without consideration for their ability to pay.

The plan should be consistent with current legal statutes related to TB control. Relevant laws and regulations should be reviewed periodically and updated as necessary to ensure consistency with currently recommended clinical and public health practice (e.g., mandatory reporting laws, institutional infection control procedures, hospital and correctional system discharge planning, and involuntary confinement laws). The health department is legally responsible for ensuring that

a complete and timely contact investigation is done for the TB cases reported in its jurisdiction. Health departments should work closely with providers in the nonpublic health sector to ensure prompt reporting of suspected TB cases. They should understand the public health aspects of TB, including the need for prompt reporting and the facilitating role of the jurisdictional health agency in case management. Federal agencies should take the lead in resolving interstate TB-control issues, including movement of TB patients across state lines and multistate TB outbreaks.

The health department is legally responsible for ensuring that a complete and timely contact investigation is done for the TB cases reported in its area. Health departments should work closely with providers in the nonpublic health sector to ensure prompt reporting of suspected TB cases.

Clinical and Diagnostic Services for Patients with TB Disease and Their Contacts

TB control programs should ensure that patients with suspected or confirmed TB disease have ready access to diagnostic and treatment services that meet national standards. These services are often provided by state and/or locally supported TB specialty clinics and staffed by health department personnel or by contracted service providers. However, persons may seek medical care for TB infection or disease in the private medical sector. Regardless of where a person receives medical care, the primary responsibility for ensuring the quality and completeness of all TB-related services rests with state and local public health agencies. To ensure that standards of care are met, health departments should develop and maintain close working relationships with

- Local laboratories;
- Pharmacies; and
- Health-care providers.

Regardless of where a person receives medical care, the primary responsibility for ensuring the quality and completeness of all TB-related services rests with state and local public health agencies.

Clinical facilities should provide screening, diagnostics, and monitoring tests, including radiology services.

Radiology services include access to radiograph equipment, trained radiograph technicians, and radiograph interpretation by a qualified person. Radiograph findings and reports should be available within 24 hours.

Radiograph findings and reports should be available within 24 hours.

Coordinating care with other health-care providers and facilities is crucial to the prevention and control of TB. TB patients often receive care in a variety of settings, including

- Private practices;
- Hospitals;
- HIV clinics;
- Community clinics;
- Correctional facilities; and
- Nursing homes.

Treatment plans must be specific to individual patient needs. As patients move among these settings, continuity of care may be compromised unless a system is in place to provide coordination of care.

Expert medical consultation in TB should be available to the health-care community, especially for pediatric TB cases and for patients who have drug-resistant disease. Consultants may be health department employees or clinicians with TB expertise who are under contract with the health department.

Laboratory services should also be readily accessible to perform and provide results of AFB smear examinations within 24 hours of specimen collection. TB prevention and control programs should work closely with laboratories to ensure the rapid delivery of specimens to the laboratory and prompt reporting of AFB smear results, culture results, and results of drug-susceptibility tests to the clinician and health department. Laboratory services should also be available to provide monitoring of bacteriologic response to therapy.

Laboratory services should be readily accessible to perform and provide results of acid-fast bacilli (AFB) smear examinations within 24 hours of specimen collection.

Training and Education

TB control programs should provide education and training in the clinical and public health aspects of TB to all program staff. Staff members should receive education at regular intervals on their particular responsibilities in the program and should demonstrate proficiency in those areas. Based on the local epidemiology and needs, TB programs should also educate health-care providers (both public and private), community members, public health officials, and policy makers on TB prevention and control.

Based on the local epidemiology and needs, TB programs should educate health-care providers (both public and private), community members, public health officials, and policy makers on TB prevention and control.

To ensure the availability of a competent TB workforce that understands and meets the needs of its community, state TB programs should use resources from CDC, the CDC-funded Regional Training and Medical Consultation Centers (RTMCCs), National Institutes of Health (NIH)-supported TB curriculum centers, the National TB Controllers Association (NTCA), and other national and local agencies to create and implement education activities. State and local TB programs should develop education and training programs with groups such as those listed in Table 8.1.

Table 8.1
Groups Needing TB Education and Training Programs

Agencies and Other Organizations	Schools
• Local health-care providers • Community-based organizations • Health-care institutions	• Medicine • Nursing • Pharmacy • Dentistry • Public health

Surveillance and Information Management

Surveillance and information management systems should be a priority of all TB control programs. Information technology can improve care of patients with TB disease through standardized collection of data and tracking of test results. Other benefits include ready access to details of treatment regimens, administration of DOT, and drug-drug interactions. Advancements in information technology allow for the analysis and rapid distribution of epidemiologic data, as well as management of individualized treatment plans.

Monitoring and Evaluation

The systematic monitoring and evaluation of TB program activities is a critical factor in enhancing program performance. Evaluation techniques provide TB programs with an evidence-based means of assessing and improving their TB-control strategies by helping them understand what causes good or bad program performance. Evaluation can also be used for the following:

- Program advocacy;
- Assessing staffing needs;
- Focusing training and capacity building;
- Directing limited resources to the most productive activities;
- Accounting for available resources;
- Generating additional resources; and
- Recognizing achievement.

TB control programs should develop priorities for program evaluation based on the TB issues or challenges in their jurisdiction and the way services are organized. In general, the first priority for evaluation efforts should be to focus on those activities and outcomes that relate most directly to the key strategies of TB control, which include:

- Identifying patients with infectious TB disease and administering a complete course of treatment;
- Finding TB patient contacts and other persons at high risk with LTBI and treating them; and
- Interrupting transmission of *M. tuberculosis* in high-risk settings.

TB control programs should develop priorities for program evaluation based on the TB issues or challenges in their jurisdiction and the way services are organized.

Targets for program performance have been established by CDC to assist TB control programs in treating TB patients, identifying and examining their contacts, and improving the quality of case reporting for national surveillance. In addition, national objectives have been set for completing treatment for LTBI among contacts of infectious cases of TB disease. These national objectives for program performance provide a starting point for state and local TB control programs to use for program evaluation, but each TB control program should establish methods to evaluate its performance; for additional information, go to www.cdc.gov/tb/ .

Targets for program performance have been established by CDC to assist TB control programs in treating TB patients, identifying and examining their contacts, and improving the quality of case reporting for national surveillance.

National objectives have been set for completing treatment for LTBI among contacts of infectious cases of TB disease.

Other program areas that should be monitored through formal evaluation methods are

- Timeliness and completeness of reporting of TB cases and suspected cases;
- How often a recommended treatment regimen for patients with TB disease and LTBI is used; and
- The quality of the program's databases for surveillance and case management.

Study Questions

8.1 What should a written TB control plan be based on?
(choose the one best answer)

A. Local epidemiologic data and ongoing indicators of program performance.

B. Fiscal resources available for TB control.

C. Capabilities and capacities of clinical and support services for clients.

D. A, B, and C are all correct.

E. Only A and B are correct.

8.2 Which of the following is legally responsible for ensuring that a complete and timely contact investigation is done for the TB cases reported in its area/agency?
(choose the one best answer)

A. Health department

B. Hospitals

C. Private physicians

D. A, B, and C are all correct.

E. Only A and B are correct.

8.3 What should clinical facilities provide for TB patients and their contacts?
(choose the one best answer)

A. Screening, diagnosis, and monitoring tests.

B. Radiology services including access to radiograph equipment, trained radiograph technicians, and radiograph interpretation by a qualified person.

C. Radiograph findings and reports within 24 hours.

D. A, B, and C are all correct.

E. Only A and B are correct.

8.4 Laboratory services should provide results of AFB smear examinations within what time period? (choose the one best answer)

A. 24 hours

B. 72 hours

C. 1 week

D. 2 weeks

8.5 TB programs are responsible for educating health-care providers (both public and private), community members, public health officials, and policy makers on TB prevention and control. (choose the one best answer)

A. True

B. False

8.6 Surveillance data and information management systems should be a priority for all TB programs. (choose the one best answer)

A. True

B. False

Roles and Responsibilities of Specific Private Health Sector Providers

The private health sector plays an important role in TB prevention and control and includes the following stakeholders:

- Clinicians;
- Community health centers;
- Hospitals;
- Academic institutions;
- Medical professional organizations;
- Community-based organizations;
- Correctional facilities;
- Civil surgeons; and
- Pharmaceutical and biotechnology industries.

To the extent possible, this varied group of providers should look for new ways to educate medical practitioners, and promote clinical and public health expertise necessary for TB elimination.

To the extent possible, this varied group of providers should look for new ways to educate medical practitioners, and promote clinical and public health expertise necessary for TB elimination.

Clinicians

Clinicians in medical practice in the non-public health sector play a vital role in TB control throughout communities in the United States. Hospital or clinic-based medical practitioners, including those working in emergency departments, are usually the first source of medical care for persons with TB disease. These providers may also provide ongoing management of TB patients.

The role of medical practitioners in TB control will increase as TB morbidity in the United States decreases and jurisdictions reduce or even eliminate public health clinical services for TB. Private medical providers should strive for the following goals:

- Understand prevalent medical conditions, including those with public health implications, of populations within their practice;
- Be aware of applicable state laws and regulations for reporting diseases and the need to report TB cases;
- Recognize the range of responsibilities that arise when TB disease is suspected in a patient under medical evaluation, including the following:
  - The need for prompt establishment of diagnosis;
  - Use of consultants and hospitalization if indicated;
  - Reporting the suspected TB case to the state and local public health agency and cooperating with subsequent public health activities; and
  - Developing, in partnership with the public health agency, a treatment plan that optimizes the likelihood that the patient will complete the recommended course of therapy;
- Incorporate current recommendations for diagnosis, standard treatment of TB disease, and targeted testing and treatment of LTBI;
- Be able to place and read tuberculin skin tests or administer blood tests for TB infection, rule out suspected TB disease, and administer and monitor treatment for LTBI;
- Screen all new patients for symptoms of TB disease and risk factors for LTBI and give those with risk factors a TB skin or blood test; and
- For patients receiving treatment, review risk factors that can suppress the immune system

Expert medical consultation in TB should be available to the health-care community, especially for patients who have drug-resistant disease or medical diagnoses that might affect the course or the outcome of treatment. Consultants may be employees of the health department or clinicians with expertise who are under contract with the health department.

The role of medical practitioners in TB control will increase as TB morbidity in the United States decreases and jurisdictions reduce or even eliminate public health clinical services for TB.

Community Health Centers

Community health centers typically provide primary health-care services to populations that encounter barriers to those services at other sites in the health-care system, and include persons who are

- Low-income and their families;
- Immigrants and refugees;
- Uninsured;
- Homeless; and
- Poor women and children.

Patients at high risk for TB disease often receive primary and emergency health care in emergency rooms or in community health centers. For example, community health centers in certain inner-city areas might serve primarily homeless persons, whereas centers in neighborhoods in which certain racial and ethnic populations are concentrated might become predominant health-care providers for immigrants and refugees. Newly arriving refugee families are frequently directed to community health centers to receive federally supported health-screening services, which might include targeted testing and treatment for LTBI. Persons with symptoms of TB disease might go first for evaluation and care to a community health center. For these reasons, community health centers are a critical part of efforts to control and prevent TB disease, and, therefore, need to perform the following tasks:

- Provide their medical staff with the skills and knowledge needed to conduct a TB risk assessment of their clients, diagnose and initiate treatment for TB disease, and diagnose and treat LTBI;
- Develop close working relationships with consultant physicians, hospitals, and clinical laboratories;
- Develop close working relationships with the public health agency that serves their jurisdiction;
- Arrange for reporting patients with suspected TB disease, ensuring availability of diagnostic services (e.g., sputum smears for acid-fast bacilli, cultures for *M. tuberculosis*, and chest radiographs), and providing consultation and referral of patients for diagnosis, treatment, and hospitalization, as indicated;
- Understand federal and state programs that support screening, diagnostic, and treatment services for patients at high risk and make prevention, diagnosis, and treatment of TB disease a high priority;
- Educate patients about the personal and public health implications of TB disease and LTBI, and motivate them to accept prevention and curative services; and
- Establish recommended TB infection control practices to protect patients and staff.

Community health centers typically provide primary health-care services to populations that encounter barriers to receiving those services at other sites in the health-care system.

Community health centers are a critical part of efforts to control and prevent TB disease.

Hospitals

Hospitals play a critical role in TB control and prevention and provide multiple services that are instrumental to the diagnosis, treatment, and control of TB infection and disease. Hospitals with active outpatient and emergency room services often serve as sites of acute and primary medical care for homeless persons, inner-city residents, immigrants and refugees, and other persons at high risk for TB disease. Also, hospital staff members often provide medical consultation services for the diagnosis and management of TB disease by public health and community clinicians. Laboratory services provided by hospitals for community-based medical care providers might include key diagnostic tests for TB disease. To prevent further spread of infection, hospitals should perform the following tasks:

- Develop TB infection control policies to ensure that patients suspected of having infectious TB disease are isolated in airborne infection isolation (AII) rooms and that effective TB infection control measures are implemented;
- Report any patient with a suspected or confirmed diagnosis of TB disease to their state and local public health agency promptly;
- Develop a written policy and plan for prevention of the nosocomial transmission of TB disease in their facility;
- Provide training and ongoing education of their medical and house staff in the prevailing diseases of the populations to which they provide care; and
- Ensure patients with TB are discharged on a standard anti-TB regimen with advance arrangements coordinated between the hospital and the jurisdictional public health agency to enhance patient follow-up.

Hospitals with active outpatient and emergency room services often serve as sites of acute and primary medical care for homeless persons, inner-city residents, immigrants and refugees, and other persons at high risk for TB disease.

Academic Institutions

Academic institutions (including schools of medicine, pharmacy, public health, and nursing) have the obligation and the opportunity to contribute to TB control in the United States and worldwide. Students from diverse disciplines, including the clinical and laboratory sciences, nursing, epidemiology, and health services, should be introduced to applicable concepts of public health in general and, because TB is a major cause of preventable illness and death in developing countries, to TB in particular.

Academic institutions can provide benefits to other participants in TB control. Conferences, grand rounds, and other presentations are a source of continuing education for private medical practitioners and other community-based health-care workers. Also, trained specialists and researchers at academic institutions can provide clinical, radiographic, and epidemiologic consultation to medical practitioners and public health agencies. A majority of academic institutions manage university-based hospitals, which often serve populations at high risk for TB infection and

disease. University hospitals can become models for TB risk assessment of patients, inpatient care, and infection-control practice, and they can serve as tertiary care sites for an entire community or region. To aid communities in the fight against TB, academic institutions have a responsibility to perform the following tasks:

- Incorporate TB education into their curricula;
- Serve as repositories of expertise in the treatment and management of TB infection and disease, and as a resource for public health and community-based clinicians and other health-care workers;
- Partner with public health agencies to improve TB control, which can include providing additional sites for education and training, opportunities for clinical research, and, for patients with TB disease, a systematic transition from hospital to outpatient care, including DOT; and
- Provide leadership in conducting research in diagnostics, drugs, and vaccines for TB infection and disease.

University hospitals can become models for TB risk assessment of patients, inpatient care, and infection-control practice, and they can serve as tertiary care sites for an entire community or region.

Medical Professional Organizations

Medical professional organizations are critical partners in TB control efforts owing to their involvement with medical practice, research, education, advocacy, and public health. Greater participation of the nonpublic health medical sector is needed to maintain clinical expertise in the diagnosis and management of TB in an era of declining incidence. Organizations whose memberships include primary-care medical practitioners can make significant contributions to the control, prevention, and elimination of TB by performing the following tasks:

- Training and educating their members and other health professionals regarding the clinical and public health aspects of the risk assessment, diagnosis, treatment, control, and prevention of TB disease;
- Providing professional leadership on clinical practice and control of TB by participating in the development or endorsement of guidelines, influencing professional school curricula, and establishing and supporting fellowship training programs, as applicable;
- Providing support for adequate funding for TB control and research through public education campaigns; and
- Endorsing the importance of greater U.S. involvement in global control of TB by linking U.S.-based health professionals with those from other parts of the world.

Greater participation of the nonpublic health medical sector is needed to maintain clinical expertise in the diagnosis and management of TB in an era of declining incidence.

Community-Based Organizations

Community-based organizations (CBOs) can be particularly effective in providing information and education on TB disease to their constituencies. As part of the communities they serve, CBOs are often highly regarded, and their messages might be accepted more positively than those delivered by the state and/or local health department. Organizations providing services to populations at risk for TB disease should perform the following tasks:

- Partner with the state and local public health TB program and medical care providers from the community to facilitate access to diagnostic, treatment, and prevention services for the target population;
- Become involved in support initiatives, such as state and local TB advisory committees and coalitions; and
- Coordinate with public health agencies and educational institutions to develop education programs that are tailored culturally and linguistically to their populations.

As part of the communities they serve, CBOs are often highly regarded, and their messages might be accepted more positively than those delivered by the state and/or local health department.

Correctional Facilities

Correctional facilities are common sites of TB transmission. Prevalence of TB disease and LTBI are substantially higher in prisons and jails than in the general population. TB disease is believed to be the leading cause of death for prisoners worldwide.

Targeted testing and treatment of LTBI in correctional facilities have been demonstrated to have a substantial public health impact. Testing and treatment activities for LTBI are carried out more easily in prisons because the length of stay is generally sufficient to permit completion of a course of treatment. Jails are convenient sites for targeted testing, but subsequent treatment of LTBI has proved challenging.

Correctional facilities have the responsibility of limiting the transmission of TB within the institution and protecting their inhabitants and staff from exposure because of their communal living arrangements. This is a particular challenge in jails because of the short lengths of stay for the majority of detainees. Abrupt and unexpected transfers of detainees among institutions might occur with little consideration for health issues; therefore, correctional facilities have a responsibility in the community to perform the following tasks:

- Coordinate with the jurisdictional public health agency to develop and maintain an accurate epidemiologic profile of the risk for TB infection and disease in the inmate population;
- Develop written polices based on the local epidemiology of TB, establish effective programs to screen for TB disease, respond promptly when cases occur within the facility, provide targeted testing and treatment programs for inhabitants and detainees with LTBI, and provide ongoing, competency-based education for all staff members;

- Establish ongoing working relations with public health agencies, hospitals, and other community partners for policy development, consultation and referral;
- Develop firm linkages for referral of persons under treatment for TB disease and LTBI upon discharge;
- Develop TB infection control programs to protect inhabitants, detainees, staff, and visitors from exposure to TB disease following requirements of the Occupational Safety and Health Administration (OSHA) and other regulatory agencies;
- Evaluate, in coordination with the local health department, the effectiveness of the institutional TB-control program to eliminate transmission within the facility on a continual basis; and
- Develop ongoing education programs for staff and inmates regarding TB.

Correctional facilities have the responsibility of limiting the transmission of TB within the institution and protecting their inhabitants and staff from exposure.

Civil Surgeons

Civil surgeons are licensed physicians who are certified by the U.S. Citizenship and Immigration Services (CIS) to conduct a required health screening examination, including testing for LTBI and TB disease, of foreign-born persons living in the United States who apply for permanent residency. CDC has responsibility for providing guidance on screening and treatment, but has no regulatory role in monitoring the quality or outcomes of these examinations.

Civil surgeons are a critical component of TB control because of their access to a high-risk population. U.S.-based immigration screening can identify foreign-born persons with LTBI for whom treatment is indicated and detect TB disease. Although civil surgeons receive immigration-focused training, little information is available on the knowledge, attitudes, and practices of civil surgeons. To further the cause of TB elimination, civil surgeons should perform the following tasks:

- Understand current guidelines for the diagnosis and treatment of TB disease and LTBI;
- Establish a working relationship with state and local public health agencies, and report suspected and confirmed cases of TB; and
- Develop a referral mechanism for evaluation for TB disease and LTBI of persons seeking adjustment of immigration status.

Because of their access to foreign-born persons at high risk, civil surgeons are a critical component of TB control.

Pharmaceutical and Biotechnology Industries

Pharmaceutical and biotechnology industries are partners in TB control because of their essential role in developing new diagnostics, drugs, and vaccines. Although development of new tools for diagnosis, treatment, and prevention of TB has been deemed essential to the effort to combat the disease globally and to move toward its elimination, progress in these fields has been slow. New non-profit organizations are working with public and private partners to facilitate the development of essential new tools. These organizations include

- The Global Alliance for Tuberculosis Drug Development (www.tballiance.org);
- The Aeras Global Tuberculosis Vaccine Foundation (www.aeras.org); and
- The Foundation for Innovative New Diagnostics (www.finddiagnostics.org).

Although development of new tools for diagnosis, treatment, and prevention of TB has been deemed essential to the effort to combat the disease globally and to move toward its elimination, progress in these fields has been slow.

These organizations have provided venues for identifying and addressing obstacles to the development of new tools against TB among private industry, public and academic researchers, and philanthropic organizations. To further contribute to TB control and prevention efforts, the pharmaceutical and biotechnology industries should perform the following tasks:

- Understand the dimensions of the global TB epidemic and realize their key role in developing the necessary tools for diagnosis, treatment, and prevention of TB disease;
- Respond to the current surge of interest in TB globally by reexamining the costs of new product development and by considering potential new public and private funding and the markets for such products in developing countries;
- Contribute their perspectives and become involved in coalitions such as the Global Partnership to Stop Tuberculosis, the Global Alliance for Tuberculosis Drug Development, and the Foundation for Innovative New Diagnostics; and
- Coordinate with other stakeholders to ensure access to essential products for those whose lives are at stake.

Study Questions

8.7 The role of medical practitioners in TB control will decrease as TB morbidity in the United States decreases and jurisdictions reduce or even eliminate public health clinical services for TB.
(choose the one best answer)

A. True

B. False

8.8 Why do community health centers play a critical role in efforts to control and prevent TB disease? (choose the one best answer)

A. They provide primary health-care services to populations that may encounter barriers to those services at other sites in the health-care system.

B. Persons with symptoms of TB disease might go there first for evaluation and care.

C. They have the primary responsibility for coordinating TB program integration in their area.

D. A, B, and C are all correct.

E. Only A and B are correct.

8.9 Which of the following tasks should hospitals perform to prevent the further spread of infection?
(choose the one best answer)

A. Develop a written policy and plan for prevention of the nosocomial transmission of TB disease in their facility.

B. Develop TB infection control policies to ensure that patients suspected of having infectious TB disease are isolated in AII rooms.

C. Report any patient with a suspected or confirmed diagnosis of TB disease to their state and local public health agency promptly.

D. A, B, and C are all correct.

E. Only A and B are correct.

8.10 Which of the following is NOT a responsibility of academic institutions?
(choose the one best answer)

A. Incorporate TB education into their curricula.

B. Serve as repositories of expertise in the treatment and management of TB infection and disease.

C. Develop questionnaires for screening all new patients in the community.

D. Partner with public health agencies to improve TB control.

E. Provide leadership in conducting research in diagnostics, drugs, and vaccines for TB infection and disease.

8.11 Why are medical professional organizations critical partners in TB control efforts?
(choose the one best answer)

A. They are involved with medical practice and research.

B. They provide TB education.

C. They provide support for adequate funding for TB control and research.

D. A, B, and C are all correct.

E. Only A and B are correct.

8.12 Why are community-based organizations particularly effective in providing information and education on TB disease to their constituencies?
(choose the one best answer)

A. They are often highly regarded by the populations they serve.

B. Their messages might be accepted more positively than those delivered by the state and/or local health department.

C. They have unlimited funds to purchase quality educational materials.

D. A, B, and C are all correct.

E. Only A and B are correct.

8.13 TB is believed to be the leading cause of death for prisoners worldwide.
(choose the one best answer)

A. True

B. False

8.14 Which of the following statements about civil surgeons is true?
(choose the one best answer)

A. Are a critical component of TB control because of their access to foreign-born persons at high risk for TB.

B. Conduct required health screening examinations, including testing for LTBI and TB disease in foreign-born persons living in the United States who apply for permanent residency.

C. Provide treatment for all TB patients that they identify.

D. A, B, and C are all correct.

E. Only A and B are correct.

8.15 Which of the following statements is true about pharmaceutical and biotechnology industries involved in TB?
(choose the one best answer)

A. Their essential role is to develop new diagnostics, drugs, and vaccines.

B. New public-private partnerships can help identify and address obstacles to developing new tools for TB.

C. New tools for diagnosis, treatment, prevention and elimination of TB are being developed quite rapidly to meet the need both domestically and internationally.

D. A, B, and C are all correct.

E. Only A and B are correct.

Match the primary responsibility with the appropriate health sector.
(Choose the one best answer and write the letter for the correct answer on the line next to the question number.)

Primary Responsibility	Health Sector
____ **8.16** Plan, coordinate, and evaluate TB control and prevention efforts.	**A.** Public health sector (TB programs, state and local public health agencies)
____ **8.17** Ensure the quality and completeness of all TB-related services.	**B.** Private health sector (clinicians, community health centers, hospitals, academic institutions, correctional facilities, homeless shelters, etc.)
____ **8.18** Are usually the first sources of medical care for persons with TB disease and need to be able to provide appropriate diagnostic and treatment services or referral.	

Chapter Summary

State and local health departments have the primary responsibility for preventing and controlling TB. However, TB control is a complex undertaking and requires the collaborative efforts of a broad range of persons, organizations, and institutions both inside and outside the public health sector. These various persons and organizations have a role in improving the detection of TB cases, one of the most important responsibilities of TB control, and include:

- Clinicians;
- Community health centers;
- Hospitals;
- Academic institutions;
- Medical professional organizations;
- Community-based organizations;
- Correctional facilities;
- Civil surgeons; and
- Pharmaceutical and biotechnology industries.

The essential role of the public health sector is to plan, coordinate, and evaluate TB control and prevention efforts. This role requires that state and local health departments focus on the following critical elements:

- Planning and policy development;
- Clinical and diagnostic services for patients with TB and their contacts;
- Training and education;
- Surveillance data and information management; and
- Monitoring and evaluation.

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Appendix A
Glossary

Acid-fast bacilli (AFB) smear
An examination of a specimen (e.g., sputum) that has been spread onto a glass slide, stained, washed in an acid solution, and then placed under the microscope for examination; used to detect acid-fast bacilli in a specimen. Acid-fast bacilli are not decolorized by acid-alcohol after having been stained with dyes such as basic fuchsin.

Active case finding
Identifying unreported cases of TB disease by actively searching for them (e.g., laboratory and pharmacy audits).

Adenopathy
Swelling or enlargement of the lymph nodes.

Adult-type TB
A clinical presentation of TB disease more typical of an adult. Characterized by upper lobe infiltration and cavitation associated with sputum production.

Airborne infection isolation (AII)
Isolation of patients infected with organisms that are spread via airborne droplet nuclei <5 microns in diameter.

Airborne infection isolation (AII) room
Single-occupancy patient-care room in which environmental factors are controlled to minimize the transmission of infectious agents that are usually spread from person to person by droplet nuclei associated with coughing or aerosolization of contaminated fluids. AII rooms typically have specific requirements for controlled ventilation, air pressure, and air filtration.

Alveoli
The small air sacs at the end of airways in the lung.

Amikacin
An injectable second-line drug in the aminoglycoside class that is used for patients with drug-resistant tuberculosis whose isolate has demonstrated or presumed susceptibility to the drug.

Aminoglycoside
A class of broad-spectrum antibiotics active against gram-negative bacteria; can cause renal toxicity and ototoxicity. Aminoglycosides used to treat TB include streptomycin, amikacin, and kanamycin.

Amprenavir
An inhibitor of HIV-1 protease. It is used in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Anergy
Inability to react to skin-test antigens because of a weakened immune system. (Anergic)

Anergy testing
Conducted by giving skin tests using two substances other than tuberculin; done to determine whether a person is anergic. People who do not react to any of the substances, including tuberculin, after 48 to 72 hours (that is, people who have less than 5 mm of induration to all of the skin tests) are considered to have cutaneous anergy to those antigens.

Antiretroviral agents
The categories of antiretroviral agents currently available for the treatment of HIV-1 infection are nucleoside reverse transcriptase inhibitors (NRTI), nucleotide reverse transcriptase inhibitors (NtRTI) and nonnucleoside reverse transcriptase inhibitors (NNRTI), and protease inhibitors (PI).

Apex
The narrow, somewhat conical upper part of a lung. (Plural: apices)

Bacille Calmette-Guérin (BCG) vaccine
Vaccine made from biologic substances derived from a strain of *Mycobacterium bovis* that was attenuated by Calmette and Guérin at the Pasteur Institute in Lille, France. An early version of BCG was first administered to humans in 1921. It is widely used in the World Health Organization's (WHO) immunization programs in highly TB-prevalent countries to reduce risk of life-threatening TB meningitis and disseminated disease in children and adolescents.

Boosted reaction
An increased response of the immune system to a second or subsequent occasion on which it encounters a specific antigen.

Bronchiectasis
Persistent and progressive dilation of bronchi or bronchioles as a consequence of inflammatory disease, obstruction, or congenital abnormality. Symptoms include fetid breath and paroxysmal coughing, with the expectoration of mucopurulent matter.

Bronchoscopy
An examination of the interior of the tracheo-bronchial tree with a flexible fiberoptic device; it is used for inspection, performance of endobronchial diagnostic tests, taking of specimens for biopsy and culture, or removal of foreign bodies.

Capreomycin
A second-line injectable drug that is used for patients with drug-resistant tuberculosis.

Cavity
A hollow space within the lung, visible on a chest radiograph, which may contain many tubercle bacilli; often occurs in people with severe pulmonary TB disease.

Close contacts
Persons who had prolonged, frequent, or intense contact with a person with TB while he or she was infectious. Close contacts are more likely to become infected with *M. tuberculosis* than contacts who see the person with TB less often.

Creatinine
A waste product of protein metabolism that is found in the urine. It can be measured to assess overall kidney function. An abnormally elevated blood creatinine level is seen in those individuals with kidney insufficiency and kidney failure.

Culture
Organisms grown on or in media (liquid or solid substances containing nutrients) so that they can be identified; a positive culture for *M. tuberculosis* contains tubercle bacilli, whereas a negative culture contains no detectable tubercle bacilli.

Cycloserine
A second-line drug that is used for treating patients with drug-resistant tuberculosis.

Delavirdine
A nonnucleoside reverse transcriptase inhibitor of the human immunodeficiency virus type 1 (HIV-1). It is used in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Delayed-type hypersensitivity
An increased reactivity to specific antigens mediated by lymphocytes and not by antibodies.

Demographic factors
Factors such as country of origin, age, gender, ethnic or racial group, and occupation.

Directly observed therapy (DOT)
A strategy used to help patients adhere to treatment; it means that a health-care worker or another designated person watches the TB patient swallow each dose of the prescribed drugs.

Droplet nuclei
Very small droplets, 1 to 5 microns in diameter, that may be expelled when a person who has infectious TB coughs or sneezes; they can remain suspended in the air for several hours, depending on the environment.

Drug-resistant TB
TB disease caused by *Mycobacterium tuberculosis* organisms that are resistant to at least one first-line antituberculosis drug.

Efavirenz
A nonnucleoside reverse transcriptase inhibitor of the human immunodeficiency virus type 1 (HIV-1). It is used in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Ethambutol (EMB)
A first-line drug for treating all forms of TB. It is included in initial treatment regimens primarily to prevent emergence of rifampin (RIF) resistance when primary resistance to isoniazid (INH) may be present.

Ethionamide
A second-line drug used for patients with drug-resistant tuberculosis disease.

Extensively drug-resistant TB (XDR TB)
Extensively drug-resistant TB is a rare type of MDR TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs.

Extrapulmonary TB
TB disease that occurs in places other than the lungs, such as the lymph nodes, the pleura, the brain, the kidneys, the larynx, or the bones.

False-negative reaction
A negative skin test reaction in a person infected with *M. tuberculosis*.

False-positive reaction
A positive skin test reaction in a person not infected with *M. tuberculosis*.

Fluorochrome staining
The use of any fluorescent dye (e.g., auramine, rhodamine) used to label or stain. Must be viewed using a fluorescence microscope.

Fluoroquinolones
A class of synthetic broad-spectrum antibacterial drugs. Examples of fluoroquinolones used to treat TB are levofloxacin, moxifloxacin, gatifloxacin, and ofloxacin.

Gatifloxacin
A fluoroquinolone used as a second-line drug in the treatment of TB.

Granuloma
Chronic inflammatory lesion characterized by large numbers of cells of various types (e.g., macrophages, lymphocytes, fibroblasts, and giant cells).

Hemoptysis
The expectoration of blood or of blood-stained sputum.

Hepatotoxicity
Injury to the liver; can be a side effect of medications.

High-risk congregate settings
Settings where there is a high risk of TB transmission; examples may include correctional facilities, nursing homes, homeless shelters, hospitals, residential facilities for persons living with AIDS, and other health care facilities.

High-risk racial or ethnic minority populations
Populations that have higher rates of TB infection or disease. This may include Asians and Pacific Islanders, Hispanics, African Americans, Native Americans.

Hilar
Relating to, affecting, or located near the depression in the medial surface of a lung that forms the opening through which the bronchus, blood vessels, and nerves pass. Seen in the center of a chest radiograph.

Indinavir
An inhibitor of HIV-1 protease. It is used in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Induration
A palpable, raised, hardened area.

Infectiousness
The infectiousness of a person with TB disease is directly related to the number of tubercle bacilli that he or she expels into the air. Persons who expel many tubercle bacilli are more infectious than patients who expel few or no bacilli.

Interferon gamma release assay (IGRA)
A test that detects the presence of *M. tuberculosis* infection by measuring the immune response to the TB bacteria in whole blood.

Isoniazid (INH)
A first-line drug for treatment of all forms of TB.

Kanamycin
An injectable second-line drug in the aminoglycoside class that is used for patients with drug-resistant tuberculosis.

Latent TB infection (LTBI)
Persons with latent TB infection have *M. tuberculosis* organisms in their bodies but do not have TB disease, have no symptoms, and are noninfectious. Such persons usually have a positive reaction to the TST or IGRA.

Levofloxacin
A fluoroquinolone used as a second-line drug in the treatment of TB.

Lymphadenopathy
Swelling of the lymph nodes.

Macrophage
A type of white blood cell that ingests foreign material; found in the alveoli of the lungs.

Mantoux tuberculin skin test (TST)
Skin test used to detect TB infection. In the United States, it is performed by using a 27-gauge needle and syringe to inject 0.1 ml containing 5 tuberculin units of purified protein derivative (PPD) between the layers of the skin (intradermally), usually on the forearm; the reaction to this test, the induration (palpable hardened area), is measured 48 to 72 hours after the injection and is classified as positive or negative depending on the size of the induration and the patient's risk factors for TB.

Mediastinal
Pertaining to the space in the thoracic cavity behind the sternum and between the two pleural sacs (containing the lungs).

Miliary TB
TB disease that occurs when tubercle bacilli enter the bloodstream and are carried to all parts of the body, where they grow and cause disease in multiple sites; so named because the chest radiograph of patients with miliary TB often looks as though millet seeds are scattered throughout the lung.

Moxifloxacin
A fluoroquinolone used as a second-line drug in the treatment of TB.

Multidrug-resistant TB (MDR TB)
TB disease caused by *Mycobacterium tuberculosis* organisms that are resistant to more than one anti-TB drug. MDR TB is defined as resistance to at least isoniazid and rifampin. It is more difficult to treat than drug-susceptible TB.

Mycobacterium avium
A nontuberculous mycobacteria (NTM) causing disease primarily in domestic fowl and other birds. This bacterium can also cause opportunistic infections in immunocompromised persons; often disseminated infections.

Mycobacterium bovis
A type of tuberculous mycobacteria; the bovine variety of the tubercle bacillus. Before the pasteurization of milk became common practice, these mycobacteria were often spread to humans through contaminated milk; in the United States today, *M. bovis* rarely affects humans.

Mycobacterium gordonae
A type of nontuberculous mycobacteria (NTM); *M. gordonae* is one of the least pathogenic of the mycobacteria.

Mycobacterium intracellulare
A nontuberculous mycobacteria (NTM) found in lung lesions and sputum of humans; may cause bone and tendon-sheath lesions in rabbits; some strains are pathogenic for mice.

Mycobacterium tuberculosis
A type of tuberculous mycobacteria; a gram-positive bacterium that causes tuberculosis. It is sometimes called the tubercle bacillus.

***Mycobacterium tuberculosis* complex**
The *M. tuberculosis* complex includes seven other TB-causing mycobacteria: *M. bovis, M. africanum, M. microti, M. canetti, M. caprae, M. pinnipedii,* and *M. mungi*.

Nelfinavir
An inhibitor of HIV-1 protease. It is used in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Nevirapine
A nonnucleoside reverse transcriptase inhibitor of the human immunodeficiency virus type 1 (HIV-1). It is used in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Nonnucleoside reverse transcriptase inhibitors (NNRTI)
Antiretroviral agents used for the treatment of HIV-1 infection.

Nontuberculous mycobacteria (NTM)
Mycobacteria other than those comprising the *M. tuberculosis* complex. NTM may cause pulmonary disease resembling TB; however, NTM are NOT usually spread from person to person. Just how and why people become infected with NTM is not clear. Although the germs are found easily in water and soil, they do not affect most people.

Nucleotide reverse transcriptase inhibitors (NtRTI)
Antiretroviral agents used for the treatment of HIV-1 infection.

Palpating
A light feathery touch with the fingertips to feel for any induration. A sweeping motion is used to search the forearm for the indurated reaction.

Para-amino salicylic acid (PAS)
An oral drug used in treatment of drug-resistant tuberculosis.

Paradoxical reaction
A temporary exacerbation of symptoms, signs, or radiographic manifestations after initiation of treatment for TB disease.

Pathogenesis
The origin and development of disease.

Paucibacillary
Having or made up of few bacilli.

Peripheral neuropathy
Injury to the nerves that supply sensation to the arms and legs, causing a tingling sensation or a weakened sense of touch in the hands and feet.

Pleural effusion
The collection of fluid (including blood) in the pleural space.

Polymerase chain reaction (PCR)
The first practical system for in vitro amplification of DNA and, as such, one of the most important recent developments in molecular medicine.

Primary TB
TB disease occurring soon after the initial infection with *M. tuberculosis*. Occurs commonly in children or in immunocompromised hosts. Primary TB is characterized by intrathoracic adenopathy, mid- and lower-lung zone infiltrates, and the absence of cavitation.

Protease inhibitors (PI)
Antiretroviral agents used for the treatment of HIV-1 infection.

Pyrazinamide (PZA)
A first-line drug for the treatment of all forms of TB.

QuantiFERON-TB Gold In-Tube test (QFT-GIT)
A whole-blood test for diagnosing TB infection. QFT-GIT measures the patient's immune reactivity to *Mycobacterium tuberculosis*, the bacterium that causes TB.

Reticuloendothelial diseases
Diseases of the phagocytic system of the body, including the fixed macrophages of tissues, liver, and spleen.

Rifabutin
Used as a substitute for rifampin (RIF) in the treatment of all forms of TB caused by organisms that are known or presumed to be susceptible to this drug. The drug is generally reserved for patients who are receiving any medication having unacceptable interactions with RIF or have experienced intolerance to RIF.

Rifampin (RIF)
A first-line drug for treatment of all forms of TB. Rifamycins are an essential component of all short-course regimens.

Rifamycin
A class of drugs that include rifampin, rifabutin, and rifapentine.

Rifapentine (RPT)
May be used once weekly with INH in the continuation phase of treatment for HIV-seronegative patients with noncavitary, drug-susceptible pulmonary TB who have negative sputum smears at completion of the initial phase of treatment.

Ritonavir
An inhibitor of HIV-1 protease. It is used in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Saquinavir
An inhibitor of HIV-1 protease. It is used in combination with other antiretroviral agents for the treatment of HIV-1 infection.

Silicosis
A form of lung disease resulting from occupational exposure to and inhalation of silica dust over a period of years, usually associated with concurrent tobacco use; characterized by a slowly progressive fibrosis of the lungs, it results in impairment of lung function.

Skin-test conversion
A negative tuberculin skin test reaction which increases in size by ≥10 mm within 2 years; indicative of recent infection with *M. tuberculosis*.

Streptomycin (SM)
An aminoglycoside used as a second-line drug in the treatment of TB. Among patients likely to have acquired *M. tuberculosis* in a high-incidence country, the relatively high rate of resistance to SM limits its usefulness.

Symptoms suggestive of hepatitis or hepatotoxicity
Symptoms include nausea, loss of appetite, vomiting, persistently dark urine, yellowish skin, malaise, unexplained elevated temperature for more than 3 days, or abdominal tenderness.

T-SPOT®.*TB* test
A cellular in vitro blood test for the diagnosis of active and latent TB infection that enumerates the response of effector T-cells that have been sensitized to *Mycobacterium tuberculosis*.

Targeted testing
Targeting testing is the tuberculin skin testing of groups for which rates of TB are substantially higher than for the general population.

Transmission
Transmission occurs when a person inhales droplet nuclei containing *M. tuberculosis*, and the droplet nuclei traverse the mouth or nasal passages, upper respiratory tract, and bronchi to reach the alveoli of the lungs.

Tubercle bacilli
Mycobacterium tuberculosis organisms.

Ultraviolet germicidal irradiation (UVGI)
A sterilization method that uses ultraviolet light to break down microorganisms.

Virulence
The ability of any agent of infection to produce disease. The virulence of a microorganism (such as a bacterium or virus) is associated with the severity of the disease it is capable of causing.

Volar surface
Palm-side-up surface of the forearm, about 2 to 4 inches below the elbow.

Ziehl-Neelsen or Kinyoun
Methods for staining acid-fast bacteria; acid-fast organisms appear red, other tissue elements light blue; basic fuchsin dye.

Appendix B
Answers to the Study Questions

Chapter 1
Overview of Tuberculosis Epidemiology in the United States

#	Answer
1.1	B
1.2	B
1.3	B
1.4	A
1.5	A
1.6	C
1.7	E
1.8	D
1.9	C
1.10	E
1.11	D
1.12	E
1.13	C

Chapter 2
Transmission and Pathogenesis

#	Answer	#	Answer
2.1	B	2.18	B
2.2	E	2.19	B
2.3	A	2.20	B
2.4	B	2.21	A
2.5	E	2.22	A
2.6	B	2.23	E
2.7	C	2.24	D
2.8	B	2.25	B
2.9	C	2.26	A
2.10	B	2.27	B
2.11	A	2.28	A
2.12	B	2.29	C
2.13	B	2.30	F
2.14	A	2.31	E
2.15	A	2.32	B
2.16	B	2.33	A
2.17	B	2.34	D

Chapter 3
Testing for Tuberculosis Infection and Disease

#	Answer	#	Answer
3.1	E	3.17	A
3.2	E	3.18	A
3.3	A	3.19	B
3.4	C	3.20	A
3.5	B	3.21	B
3.6	C	3.22	A
3.7	A	3.23	B
3.8	D	3.24	A
3.9	A	3.25	A
3.10	E	3.26	A
3.11	B	3.27	A
3.12	C	3.28	B
3.13	A	3.29	A
3.14	D	3.30	A
3.15	C	3.31	A
3.16	B	3.32	B

Chapter 4
Diagnosis of Tuberculosis

#	Answer	#	Answer
4.1	A	4.18	D
4.2	B	4.19	B
4.3	A	4.20	A
4.4	B	4.21	A
4.5	B	4.22	A
4.6	A	4.23	B
4.7	A	4.24	A
4.8	A	4.25	C
4.9	A	4.26	A
4.10	A	4.27	B
4.11	B	4.28	A
4.12	A	4.29	A
4.13	C	4.30	D
4.14	D	4.31	D
4.15	E	4.32	D
4.16	B	4.33	B
4.17	A		

Chapter 5
Treatment of Latent Tuberculosis Infection

#	Answer	#	Answer
5.1	B	5.15	E
5.2	B	5.16	D
5.3	A	5.17	B
5.4	B	5.18	A
5.5	B	5.19	B
5.6	A	5.20	C
5.7	A	5.21	E
5.8	C	5.22	D
5.9	B	5.23	E
5.10	B	5.24	D
5.11	A	5.25	A
5.12	B	5.26	E
5.13	E	5.27	D
5.14	D	5.28	E

Chapter 6
Treatment of Tuberculosis Disease

#	Answer	#	Answer
6.1	D	6.28	C
6.2	A	6.29	A
6.3	B	6.30	D
6.4	A	6.31	D
6.5	B	6.32	D
6.6	A	6.33	C
6.7	A	6.34	D
6.8	D	6.35	B
6.9	E	6.36	A
6.10	B	6.37	C
6.11	E	6.38	D
6.12	E	6.39	D
6.13	C	6.40	A
6.14	E	6.41	C
6.15	E	6.42	A
6.16	A	6.43	B
6.17	A	6.44	C
6.18	A	6.45	B
6.19	B	6.46	B
6.20	A	6.47	D
6.21	A	6.48	A
6.22	B	6.49	C
6.23	A	6.50	C
6.24	D	6.51	D
6.25	E	6.52	B
6.26	B	6.53	A
6.27	A	6.54	E

Chapter 7
Tuberculosis Infection Control

#	Answer	#	Answer
7.1	D	7.23	A
7.2	B	7.24	B
7.3	A	7.25	A
7.4	A	7.26	A
7.5	A	7.27	B
7.6	D	7.28	B
7.7	D	7.29	D
7.8	C	7.30	E
7.9	A	7.31	B
7.10	E	7.32	C
7.11	D	7.33	A
7.12	C	7.34	A
7.13	A	7.35	B
7.14	B	7.36	A
7.15	A	7.37	E
7.16	C	7.38	E
7.17	B	7.39	B
7.18	B	7.40	A
7.19	A	7.41	B
7.20	B	7.42	A
7.21	B	7.43	B
7.22	A		

Chapter 8
Community Tuberculosis Control

#	Answer
8.1	D
8.2	A
8.3	D
8.4	A
8.5	A
8.6	A
8.7	B
8.8	E
8.9	D
8.10	C
8.11	D
8.12	E
8.13	A
8.14	E
8.15	E
8.16	A
8.17	A
8.18	B

Appendix C
PowerPoint Slide Set

PowerPoint Slide Set

The Core Curriculum is accompanied by a PowerPoint slide set for use in presentations and training programs. Images of the slides are included in this appendix. The slide set may be downloaded from the CDC DTBE website at www.cdc.gov/tb.

Core Curriculum on Tuberculosis:
What the Clinician Should Know

Sixth Edition 2013

National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention
Division of Tuberculosis Elimination

CDC

1

Core Curriculum Contents

Chapters	Content
1	Overview of Tuberculosis (TB) Epidemiology in the United States
2	Transmission and Pathogenesis of TB
3	Testing for TB Infection and Disease
4	Diagnosis of TB Disease
5	Treatment for Latent TB Infection
6	Treatment for TB Disease
7	TB Infection Control
8	Community TB Control

2

Chapter 1. Overview of TB Epidemiology in the United States

3

Progress Toward TB Elimination in the U.S.

- 1989: Release of A Strategic Plan for the Elimination of Tuberculosis in the United States, *MMWR* 1989; 38 (Suppl. No. S-3), with goal of TB elimination in 2010
- 1985–1992: Resurgence of TB in the United States, fueled by several factors
- In response to resurgence, U.S. renewed commitment and support for TB control
- In 1993, upward trend was reversed; that decline has continued

4

Factors Contributing to the Increase in TB Morbidity: 1985-1992

- Emerging HIV/AIDS epidemic
- Immigration from countries where TB was common
- Transmission of TB in congregate settings
- Development of multidrug-resistant (MDR) TB

Decades of funding cuts had impaired effectiveness of TB control programs

5

Factors Contributing to the Decrease in TB Morbidity Since 1993

- Success attributed to increased efforts to
  - Promptly identify persons with TB
  - Initiate appropriate treatment
  - Ensure completion of therapy
- But TB elimination faces barriers

6

Areas of Concern Remain

- U.S. TB cases occur largely in high-risk populations
- In these populations, TB is difficult to detect, diagnose, and treat
- Global TB epidemic persists
- Current TB control measures are limited; new tests, vaccines, drugs needed

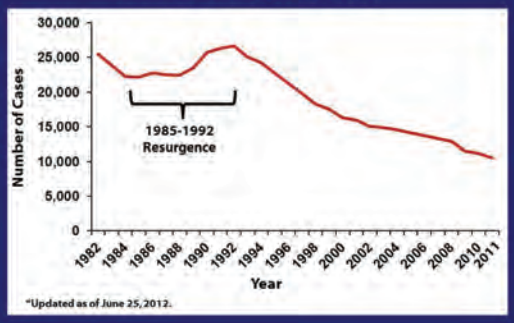
7

TB Disease Trends in the United States

- During resurgence, 1985–1992, reported TB cases increased every year
- 1993–2011: cases decreased
  - 1993–2002: cases decreased 5%-7% annually
  - 2003–2008: decreased at a more moderate 3%-5%
  - 2009: declined 10.6% from 2008
  - 2010–2011: cases resumed moderate decreases (average 4.5% from 2009)
- 10,528 cases reported in 2011

8

Reported TB Cases United States, 1982–2011*



*Updated as of June 25, 2012.

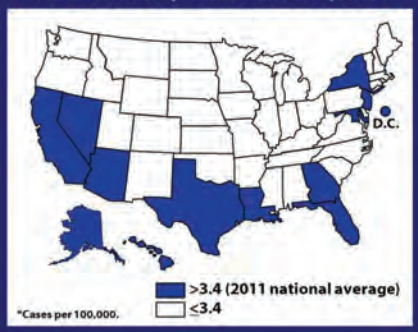
9

TB Trends, United States

- While TB is declining overall, high rates persist among some groups
- Local epidemiology affects trends in individual areas
- 2011: total of 37 states reported a rate <3.4/100,000 (national average for the year)
- 12 states + D.C. reported a rate >3.4/100,000
  - These areas = 67% of the 2011 national total
  - Also had substantial decreases in TB, 1992–2011

10

TB Case Rates,* United States, 2011



*Cases per 100,000.

11

Reported Cases of TB by Country of Origin, United States

- Cases among U.S.-born and foreign-born persons declining, but much less so in foreign born
- 2002: First year foreign-born persons accounted for majority of U.S. TB cases (51%)
  - 2011, accounted for 62%
- In foreign-born persons, TB cases roughly level:
  - 1993–2008: TB cases averaged 7,700/year
  - 2009-2011: TB cases averaged 6,700/year
- In U.S.-born persons: 1993–2011, TB cases decreased from 17,438 to 3,981

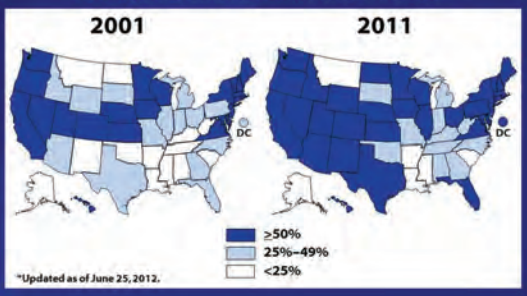
12

Percentage of TB Cases among Foreign-Born Persons in the U.S., 2001 and 2011

- Number of states with <25% of cases in foreign-born: down from 13 to 6
- Number of states with 25% -49% of cases in foreign-born: down from 14 to 11
- Number of states with ≥50% of cases in foreign-born: *up* from 23 to 34

13

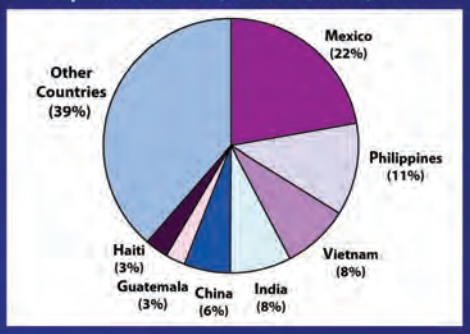
Percentage of TB Cases Among Foreign-Born Persons, United States*



*Updated as of June 25, 2012.

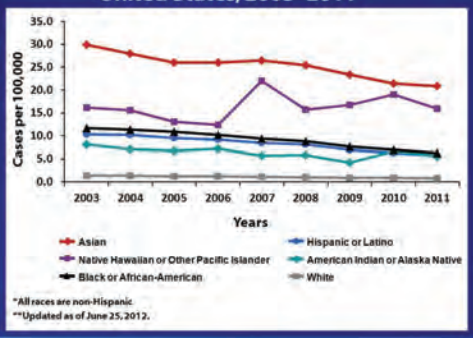
14

Countries of Birth of Foreign-Born Persons Reported with TB, United States, 2011



15

TB Case Rates by Race/Ethnicity* United States, 2003–2011**



*All races are non-Hispanic
**Updated as of June 25, 2012.

16

Factors Likely Contributing to Burden of TB in Minorities

- In foreign-born minorities, TB may result from infection in country of origin
- Some minority groups have unequal distribution of TB risk factors (e.g., HIV infection), contributing to increased exposure to TB or increased risk of developing disease once infected with *M. tuberculosis*
- Lower socioeconomic status and crowded housing are linked to increased TB risk

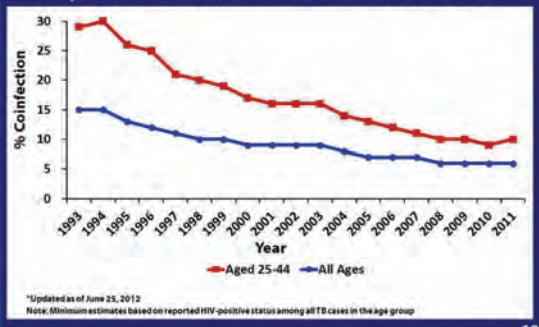
17

HIV-Infected Persons, United States, 1993–2011*

- Persons coinfected with HIV and *M. tuberculosis* are at high risk of developing TB disease
- In persons with TB, all ages, percentage of HIV coinfection decreased from 15% to 6%
  - In age group 25–44, decreased from 29% to 10%

18

Estimated HIV Coinfection in Persons Reported with TB, United States, 1993–2011*



*Updated as of June 25, 2012
Note: Minimum estimates based on reported HIV-positive status among all TB cases in the age group

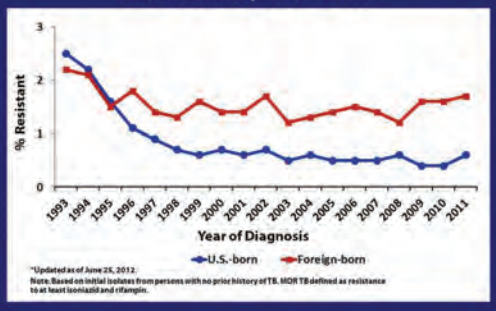
19

Multidrug-Resistant (MDR) TB Remains a Serious Public Health Concern in the United States

- MDR TB has decreased in foreign born and U.S. born, but decline greater in U.S. born
- 1993–2011, proportion of primary MDR TB in foreign born increased from 25% to 83%

20

Primary MDR TB in U.S.-Born vs. Foreign-Born Persons United States, 1993–2011*



*Updated as of June 25, 2012.
Note: Based on initial isolates from persons with no prior history of TB. MDR TB defined as resistance to at least isoniazid and rifampin.

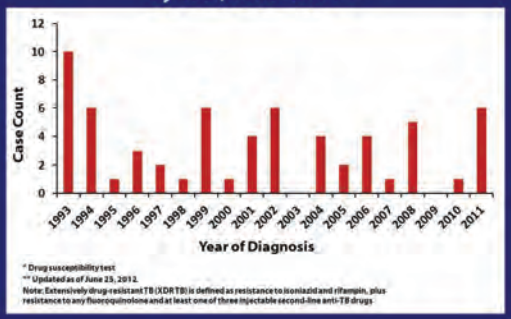
21

Extensively Drug-Resistant (XDR) TB in the United States

- XDR TB is a rare type of MDR TB
  - Resistant to INH, RIF, fluoroquinolones, and ≥1 of 3 injectable 2nd-line drugs
- No apparent trend for XDR TB in the U.S.

22

XDR TB Case Count Defined on Initial DST* by Year, 1993–2011**



* Drug susceptibility test
** Updated as of June 25, 2012.
Note: Extensively drug-resistant TB (XDR TB) is defined as resistance to isoniazid and rifampin, plus resistance to any fluoroquinolone and at least one of three injectable second-line anti-TB drugs

23

Persons at Higher Risk for Exposure to or Infection with TB

- Close contacts of person known or suspected to have active TB
- Foreign-born persons from areas where TB is common
- Persons who visit TB-prevalent countries
- Residents and employees of high-risk congregate settings

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Persons at Higher Risk for Exposure to or Infection with TB (cont.)

- Health care workers (HCWs) who serve high-risk clients
- Populations defined locally as having increased incidence of latent *M. tuberculosis* infection or TB disease, such as medically underserved, low-income persons who abuse drugs or alcohol
- Children and adolescents exposed to adults at increased risk for infection or disease

25

Chapter 2. Transmission and Pathogenesis of TB

26

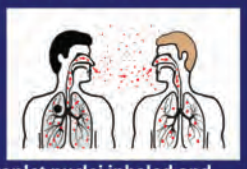
Introduction

- Airborne disease caused by the bacterium *Mycobacterium tuberculosis (M. tb)*
- *M. tb* complex (*M. tb, M. bovis, M. africanum, M. microti, M. canetti, M. caprae, M. pinnipedii, and M. mungi*) can cause TB disease
- Majority of TB cases caused by *M. tb*
- *M. tb* organisms also called tubercle bacilli

27

Transmission of *M. tuberculosis*

- *M. tb* spread via airborne particles called droplet nuclei
- Expelled when person with infectious TB coughs, sneezes, shouts, or sings



- Transmission occurs when droplet nuclei inhaled and reach the alveoli of the lungs, via nasal passages, respiratory tract, and bronchi

28

Probability TB Will Be Transmitted

- Susceptibility of the exposed person
- Infectiousness of person with TB (i.e., number of bacilli TB patient expels into the air)
- Environmental factors that affect the concentration of *M. tb* organisms
- Proximity, frequency, and duration of exposure (e.g., close contacts)
- Can be transmitted from children, though less likely

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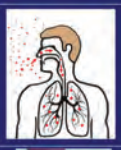
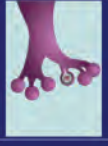
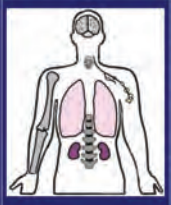
Pathogenesis

	Droplet nuclei containing tubercle bacilli are inhaled, enter the lungs, and travel to the alveoli.
	Tubercle bacilli multiply in the alveoli.

30

Pathogenesis



A small number of tubercle bacilli enter the bloodstream and spread throughout the body. The tubercle bacilli may reach any part of the body, including areas where TB disease is more likely to develop (such as the brain, larynx, lymph node, lung, spine, bone, or kidney).

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Pathogenesis

Within 2 to 8 weeks, special immune cells called macrophages ingest and surround the tubercle bacilli. The cells form a barrier shell, called a granuloma, that keeps the bacilli contained and under control (LTBI).

If the immune system cannot keep the tubercle bacilli under control, the bacilli begin to multiply rapidly (TB disease). This process can occur in different areas in the body, such as the lungs, kidneys, brain, or bone.

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Latent TB Infection (LTBI)

- Granulomas may persist (LTBI), or may break down to produce TB disease
- 2 to 8 weeks after infection, LTBI can be detected via TST or interferon-gamma release assay (IGRA)
- The immune system is usually able to stop the multiplication of bacilli
- Persons with LTBI are not infectious and do not spread organisms to others

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TB Disease

- In some, the granulomas break down, bacilli escape and multiply, resulting in TB disease
- Can occur soon after infection, or years later
- Persons with TB disease are usually infectious and can spread bacteria to others
- Positive *M. tb* culture confirms TB diagnosis

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Sites of Disease

- Lungs (pulmonary): most common site; usually infectious
- Miliary: occurs when bacilli spread to all parts of the body; rare, but fatal if untreated
- Central nervous system: usually occurs as meningitis, but can occur in brain or spine

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Sites of Disease (cont.)

Outside the lungs (extrapulmonary): usually not infectious, unless person has

- Concomitant pulmonary disease,
- Extrapulmonary disease in the oral cavity or larynx, or
- Extrapulmonary disease with open site, especially with aerosolized fluid.

36

Risk of Developing Disease
Normal Immune System

- **Untreated, 5% of infected persons with normal immunity develop TB in first 1–2 years post infection, another 5% later in life**
- **Thus, about 10% of infected persons with normal immunity will develop TB at some point in life if not treated**

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Risk of Developing Disease (cont.)
Weak Immune System

- **Persons with weak immunity at increased risk of progressing to TB disease**
  - Untreated HIV infection highest risk factor: risk of developing TB disease is 7%–10% *each year*;
  - Children <5 years of age also at increased risk

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LTBI vs. TB Disease

Person with LTBI (Infected)	Person with TB Disease (Infectious)
Has a small amount of TB bacteria in his/her body that are alive, but inactive	Has a large amount of active TB bacteria in his/her body
Cannot spread TB bacteria to others	May spread TB bacteria to others
Does **not** feel sick, but may become sick if the bacteria become active in his/her body	May feel sick and may have symptoms such as a cough, fever, and/or weight loss
Usually has a TB skin test or TB blood test reaction indicating TB infection	Usually has a TB skin test or TB blood test reaction indicating TB infection
Radiograph is typically normal	Radiograph may be abnormal
Sputum smears and cultures are negative	Sputum smears and cultures may be positive
Should consider treatment for LTBI to prevent TB disease	Needs treatment for TB disease
Does **not** require respiratory isolation	May require respiratory isolation
Not a TB case	A TB case

39

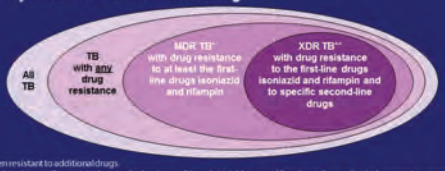
Drug-Resistant TB

- **Caused by organisms resistant to one or more TB drugs**
- **Transmitted same way as drug-susceptible TB, and no more infectious**
- **Delay in detecting drug resistance may prolong period of infectiousness because of delay in starting correct treatment**

40

Multidrug-Resistant (MDR) and Extensively Drug-Resistant (XDR) TB

- **MDR TB caused by bacteria resistant to best TB drugs, isoniazid and rifampin**
- **XDR TB caused by organisms resistant to isoniazid and rifampin, plus fluoroquinolones and ≥1 of the 3 injectable second-line drugs**



*Often resistant to additional drugs.
**Resistant to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).

41

Types of Drug Resistance

Drug resistance develops in two ways:

- **Primary resistance develops in persons initially infected with resistant organisms**
- **Secondary (acquired) resistance develops during TB therapy**

42

Circumstances Increasing the Risk of Drug-Resistant TB

Risk of drug-resistant TB is increased with exposure to a person who

- Has confirmed drug-resistant TB
- Had prior unsuccessful treatment for TB, and drug susceptibility results not known
- Originated in a drug-resistant TB prevalent country
- Has positive smear and culture 2 months after treatment start

43

Classification System for TB

- Based on TB pathogenesis (stage of disease)
- Helps clinician track the development of TB in patients
- Persons with class 3 or 5 TB should be reported to health department
- Patients should not have class 5 classification for more than 3 months

44

TB Classification System

Class	Stage of Disease
0	No exposure, no infection
1	Exposure, no evidence of infection
2	TB infection, no disease
3	TB, clinically active
4	TB, not clinically active
5	TB suspect

45

Chapter 3. Testing for TB Infection and Disease

46

Identifying High-Risk Groups for *M. tb* Testing

- Health-care providers should find and test
  - Uninfected persons at high risk for LTBI, and/or
  - Persons at high risk for progression to TB disease
- Flexibility needed in defining high-risk groups
- Risk for TB or LTBI in current high-risk groups may decrease over time, and groups currently *not* at risk may subsequently become high risk

47

Evaluation of Persons with Positive TB Tests

- Facilities should consult with local health department before starting testing program to ensure evaluation and treatment resources are available
- Persons with positive TST or IGRA should be evaluated for disease
- If disease is ruled out, consider for LTBI treatment
- If patient not willing or able to take treatment, educate on TB signs and symptoms

48

Methods for Detecting *M. tb* Infection in U.S.

- Mantoux tuberculin skin test (TST)
- IGRAs:
  - QuantiFERON-TB Gold In-Tube (QFT-GIT)®, and
  - T-Spot.*TB*®
- These tests do not exclude LTBI or TB disease
- Decisions about medical/public health management should include other info/data, and not rely only on TST/IGRA results

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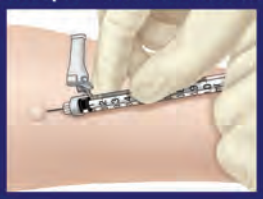
Mantoux Tuberculin Skin Test (TST)

- Purified protein derivative (PPD), derived from tuberculin, is injected between skin layers using the Mantoux technique
- Infected person's immune cells recognize TB proteins in PPD, respond to site, causing wheal to rise
- Takes 2-8 weeks after exposure and infection for the immune system to react to PPD
- Reading and interpretation of TST reaction must be done within 48–72 hours

50

Administering the TST

- Inject 0.1 ml of PPD (5 tuberculin units) into forearm between skin layers
- Produce wheal (raised area) 6–10 mm in diameter
- Follow universal precautions for infection control



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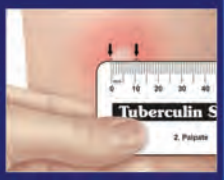
Reading the TST

- Trained health care worker assesses reaction 48–72 hours after injection
- Palpate (feel) injection site to find raised area
- Measure diameter of induration across forearm; only measure induration, not redness
- Record size of induration in millimeters; record "0" if no induration found



52

Interpreting the TST Reaction

≥5 mm induration is classified as positive in

- HIV-infected persons
- Recent contacts of infectious TB
- Persons with fibrotic changes on chest radiograph consistent with prior TB
- Patients with organ transplants and other immunosuppressed patients

53

Interpreting the TST Reaction (cont.)

≥10 mm induration is classified as positive in

- Recent arrivals from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings

54

Interpreting the TST Reaction (cont.)

≥10 mm induration is classified as positive in

- Mycobacteriology laboratory personnel
- Persons with conditions that increase risk for progressing to TB
- Children <5 years of age, or children and youth exposed to adults at high risk

55

Interpreting the TST Reaction (cont.)

≥15 mm is classified as positive in

- Persons with no known risk factors for TB

Targeted skin testing should only be conducted among high-risk groups

56

Factors that May Affect the Skin Test Reaction

False-positive	• Nontuberculous mycobacteria • BCG vaccination • Problems with TST administration
False-negative	• Anergy • Viral, bacterial, fungal coinfection • Recent TB infection • Very young age; advanced age • Live-virus vaccination • Overwhelming TB disease • Renal failure/disease • Lymphoid disease • Low protein states • Immunosuppressive drugs • Problems with TST administration

57

Special Considerations When Using TST

Boosting

- Some may have negative (waned) TST reaction when tested years after infection (e.g., older adults)
- Initial skin test may stimulate (boost) ability to react to PPD
- Subsequent positive boosted reaction may be misinterpreted as a new infection
- May still be considered for treatment if currently at high risk for TB disease

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Special Considerations When Using TST (cont.)

Two-Step Testing

- Used for initial skin testing of adults to be retested periodically, to reduce likelihood that boosted reaction will be misinterpreted as recent infection
- If 1st test positive, consider infected; if negative, give 2nd test 1–3 weeks later
- If 2nd test positive, consider infected; if negative, consider uninfected

59

Special Considerations When Using TST (cont.)

Pregnant women

- TST is safe and reliable for mother and fetus throughout pregnancy
- Give TST to pregnant women who have risk factors for infection or disease

60

Special Considerations When Using TST (cont)

Occupational Exposure to TB

- **Cutoff for defining a positive TST reaction depends on**
  - Individual risk factors for TB
  - Prevalence of TB in the facility
- **High-risk sites should test residents and staff at entry and hire and at intervals determined by annual risk assessment**

61

Interferon Gamma Release Assays (IGRAs)

- **IGRAs detect *M. tb* infection by measuring immune response in blood**
- **Cannot differentiate between TB and LTBI; other tests needed**
- **May be used for surveillance/screening, or to find those who will benefit from treatment**
- **FDA-approved IGRAs are QFT Gold In-Tube and T-Spot.*TB* test**

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General Recommendations for Using IGRAs

- **May be used in place of, but not in addition to, TST**
- **Preferred when testing persons**
  - Who might not return for TST reading
  - Who have received BCG vaccination
- **Generally should not be used to test children <5 years of age, unless used in conjunction with TST**

63

General Recommendations for Using IGRAs (cont.)

May be used in place of TST to test recent contacts of infectious TB

- **Detect *M. tb* infection with greater specificity than TST**
- **Data are limited on ability to predict subsequent TB**
- **In contact investigations, confirm negative via retest 8–10 weeks postexposure**
- **Use same test for repeat testing to reduce misclassification errors**

64

General Recommendations for Using IGRAs (cont.)

- **May be used for periodic screening, e.g., for health-care workers**
- **IGRAs do not boost subsequent test results; administered with one patient visit**
- **Results from both IGRA and TST may be useful when initial test is**
  - Negative, and patient has high risk of TB infection or disease
  - Positive, and additional evidence is required/desired
  - Unclear or indeterminate

65

BCG Vaccination

- **Vaccine made from live, attenuated (weakened) strain of *M. bovis***
- **Early version first given to humans in 1921**
- **Many TB-prevalent countries vaccinate infants to prevent severe TB disease**

66

Recommendations for BCG Vaccination

- BCG not generally recommended in the U.S.
- However, its use may be considered in very limited circumstances
- Use BCG only after consultation with local health department and TB experts

67

Recommendations for BCG Vaccination (cont.)

Infants and Children

- Can be considered for infant or child with negative skin-test result who
  - Is continually exposed to untreated or ineffectively treated adult
  - Will be continually exposed to adult with MDR TB
- BCG vaccination *not* recommended for HIV-infected children

68

Recommendations for BCG Vaccination (cont.)

Health-Care Workers

Should be considered on individual basis for health-care workers in settings in which

- High percentage of MDR TB patients has been found,
- Transmission of drug-resistant TB strains and subsequent infection are likely, and
- Comprehensive TB infection-control precautions implemented but not successful.

69

BCG Contraindications

- Contraindicated in persons with impaired immune response from
  - HIV infection, congenital immunodeficiency
  - Leukemia, lymphoma, generalized malignancy
  - High-dose steroid therapy
  - Alkylating agents
  - Antimetabolites
  - Radiation therapy
- BCG vaccination should *not* be given to pregnant women

70

Interpretation of TB Test Results in BCG-Vaccinated Persons

- TST or IGRA not contraindicated for BCG-vaccinated persons
- Results used to support or exclude diagnosis of infection
- In BCG-vaccinated, interpret TST with same criteria used for non–BCG-vaccinated
- Booster phenomenon may occur in BCG-vaccinated persons

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Chapter 4. Diagnosis of TB Disease

72

Medical Evaluation for TB

- Medical history
- Physical examination
- Test for TB infection
- Chest radiograph
- Bacteriologic examination

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Medical Evaluation for TB
1. Medical History

- Symptoms of disease; how long
- History of TB exposure, infection, or disease
- Past TB treatment
- Demographic risk factors for TB
- Medical conditions that increase risk for TB disease

74

Medical Evaluation for TB (cont.)
1. Medical History (cont.)

Symptoms of pulmonary TB:

- Prolonged cough (3 weeks or longer), hemoptysis
- Chest pain
- Loss of appetite, unexplained weight loss
- Night sweats, fever
- Fatigue

75

Medical Evaluation for TB (cont.)
1. Medical History (cont.)

Symptoms of possible extrapulmonary TB:

- Blood in the urine (TB of the kidney)
- Headache/confusion (TB meningitis)
- Back pain (TB of the spine)
- Hoarseness (TB of the larynx)
- Loss of appetite, unexplained weight loss
- Night sweats, fever
- Fatigue

76

Medical Evaluation for TB (cont.)
2. Physical Examination

- Provides valuable information about the patient's overall condition
- Cannot be used to confirm or rule out TB disease

77

Medical Evaluation for TB (cont.)
3. Test for *M. tuberculosis* Infection

- Two methods for detecting *M. tb* infection: TST and IGRAs
- TST and IGRAs help differentiate persons with *M. tb* infection from those not infected
- Negative reaction to either does not exclude diagnosis of TB or LTBI

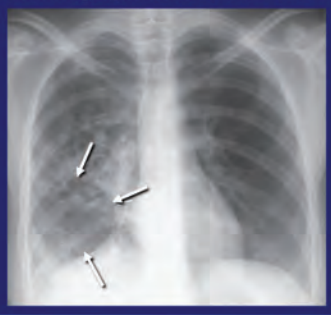
78

Medical Evaluation for TB (cont.)
4. Chest Radiograph

- Chest abnormalities suggest, but do not confirm, TB disease
- Posterior-anterior view is standard
- Apical/posterior areas of upper lobe or superior areas of lower lobe often show abnormalities
- In immunosuppressed (e.g., HIV infected), lesions may have atypical appearance

79

Chest Radiograph with Lower Lobe Cavity



80

Medical Evaluation for TB (cont.)
4. Chest Radiograph (cont.)

- Old TB can produce dense, hard nodules or lesions containing live bacilli
- Fibrotic nodules/lesions from old TB + positive TB test = high-priority candidate for LTBI treatment
- Calcified lesions pose low risk for progressing to TB
- Active versus inactive disease cannot be determined from chest radiograph alone

81

Medical Evaluation for TB (cont.)
4. Chest Radiograph (cont.)

- In HIV infected, pulmonary TB may present atypical radiograph
  - Less common: cavitary disease (with higher CD4 counts)
  - More common: infiltrates, adenopathy, or normal radiograph (with lower CD4 counts)
- With signs/symptoms, negative radiograph does not rule out disease
- With no signs/symptoms and positive TB test, negative radiograph may rule out TB in HIV-negative person

82

Medical Evaluation for TB (cont.)
5. Bacteriologic Examination of Specimens

- Specimen collection
- AFB smear classification
- NAA testing
- Culture and identification
- Drug-susceptibility testing

83

Medical Evaluation for TB (cont.)
5. Bacteriologic Examination of Specimens (cont.)

Specimen collection, processing, and review

- All persons suspected of TB disease should have sputum cultured
- Collect at least 3 sputum specimens at 8- to 24-hour intervals, at least 1 in the morning
- Follow infection control precautions during specimen collection
- Collection methods include coughing, sputum induction, bronchoscopy, gastric aspiration

84

Medical Evaluation for TB (cont.)
5. Bacteriologic Examination of Specimens (cont.)

Specimen collection methods for extrapulmonary TB

- **TB disease can occur in almost any site**
- **Variety of clinical specimens other than sputum can be submitted**
- **Before collection, ensure transport and processing procedures are in place**

85

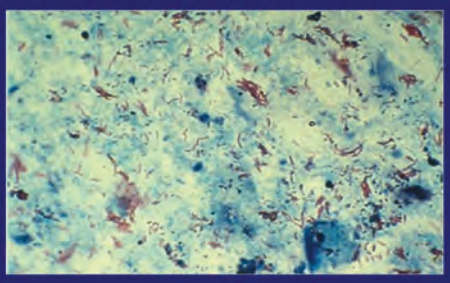
Medical Evaluation for TB (cont.)
5. Bacteriologic Examination of Specimens (cont.)

Smear examination

- **Detecting AFB in smears may be first evidence of mycobacteria**
  - Quickest (results within 24 hours) and easiest procedure
  - Provides a preliminary presumptive diagnosis of TB
  - AFB in a smear are counted and classified as 4+, 3+, 2+, or 1+

86

AFB Smear
AFB (shown in red) are tubercle bacilli



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Direct Detection Using Nucleic Acid Amplification (NAA)

- **NAA tests rapidly identify a specimen via DNA and RNA amplification**
- **Benefits may include**
  - Earlier lab confirmation of TB disease
  - Earlier respiratory isolation and treatment initiation
  - Improved patient outcomes; interruption of transmission
- **Perform at least 1 NAA test on each pulmonary TB suspect**
- **A single negative NAA test does not exclude TB**

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Nucleic Acid Amplification (NAA) Test

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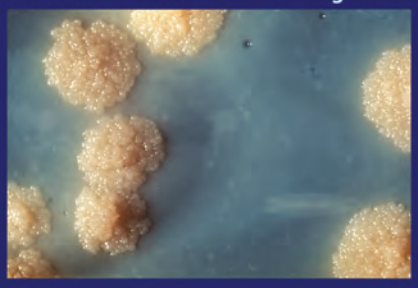
Culture

- **Remains gold standard for confirming diagnosis of TB**
- **Culture all specimens, even if smear or NAA negative**
- **Results in 4–14 days when liquid medium systems used**
- **Culture monthly until conversion, i.e., 2 consecutive negative cultures**

90

Colonies of *M. tuberculosis* Growing on Media



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Drug-Susceptibility Testing

- Conduct drug-susceptibility testing on initial *M. tb* isolate
- Promptly forward results to the health department
- Repeat for patients who
  - Do not respond to therapy or
  - Have positive cultures despite 3months of therapy

92

Drug-Susceptibility Testing

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Second-line Drug-Susceptibility Testing

Limit to persons at increased risk for drug resistance:

- Have history of treatment with TB drugs
- Had contact with a person with drug-resistant TB
- Demonstrated resistance to first-line drugs
- Has positive smears or cultures despite 3 months of TB treatment

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Molecular Detection of Drug Resistance

- Drug resistance is caused by mutations in specific *M. tb* genes
- Several molecular assays and tests can detect mutations
- Molecular detection should be used for patients with high risk for rifampin resistance (MDR TB)
- Conventional drug susceptibility testing should be done in conjunction with molecular tests

95

Genotyping

- Laboratory-based approach that analyzes the genetic material of patient isolates
- Different strains of *M. tb* have different genotype patterns
- *M. tb* isolates with identical genotypes often indicates recent transmission
- Main purpose of genotyping: add to TB controllers' understanding of TB transmission in their community

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Genotyping (cont.)

Used with traditional epi investigations, genotyping has

- Confirmed/detected transmission
- Identified risk factors for recent infection
- Demonstrated re-infection with different strains
- Identified weaknesses in conventional contact investigations
- Documented lab cross-contamination
- Identified outbreaks not previously recognized

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Chapter 5. Treatment for Latent Tuberculosis Infection

98

Treatment for Latent TB Infection (LTBI)

- Over 11 million persons in U.S. estimated to have LTBI (4% of population)
  - 5%-10% will develop TB disease if untreated
- Treatment of LTBI essential to controlling and eliminating TB disease
- Reduces risk of LTBI to TB disease progression
- Use targeted testing to find persons at high risk for TB who would benefit from LTBI treatment
- Several treatment regimens available

99

Candidates for Treatment of LTBI

High-risk persons with positive IGRA test or TST reaction of ≥5 mm:

- HIV-infected persons
- Recent contacts of persons with infectious TB
- Persons with fibrotic changes on chest radiograph consistent with prior TB
- Patients with organ transplants and other immunosuppressed patients

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Candidates for Treatment of LTBI (cont.)

High-risk persons with positive IGRA test or TST reaction of ≥10 mm:

- Recent arrivals (<5 yrs) from high-prevalence areas (e.g., Asia, Africa, Eastern Europe, Latin America, and Russia)
- Injection drug users
- Residents and employees of high-risk congregate settings (e.g., correctional facilities, homeless shelters, hospitals, and long term care facilities)
- Mycobacteriology laboratory personnel

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Candidates for Treatment of LTBI (cont.)

High-risk persons with positive IGRA test or TST reaction of ≥10 mm (cont.):

- Persons with conditions that increase risk for TB:
  - Silicosis
  - Diabetes mellitus
  - Chronic renal failure
  - Certain cancers (e.g., leukemia and lymphomas, or cancer of the head, neck, or lung)
  - Gastrectomy or jejunoileal bypass
  - Weight loss of at least 10% below ideal body weight
  - Young children <5 years of age; children/adolescents exposed to adults in high-risk categories

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Candidates for Treatment of LTBI (cont.)

- **Low-risk persons with positive IGRA test or TST reaction of ≥15 mm:**
  - Persons with no known risk factors for TB generally should not be tested
- **Targeted testing programs should only be conducted among high-risk groups**
- **If low-risk persons are tested and have positive IGRA test or TST reaction ≥15 mm, evaluate for LTBI treatment**

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Close Contacts with Negative IGRA or TST Result

- **Some contacts should be evaluated and treated for LTBI even with negative TB test results:**
  - Young children <5 years of age
  - Immunosuppressed persons
  - Others at risk for rapid progression to TB disease once infected
- **Always rule out TB disease with chest radiograph and medical evaluation before treating for LTBI**
- **Give LTBI treatment (window prophylaxis) regardless of test result**
- **Retest 8–10 weeks after last exposure to allow for delayed immune response**

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LTBI Treatment Regimens

Isoniazid (INH)

- **9-month daily regimen is preferred: 270 doses within 12 months**
  - Effective for HIV-infected as well as HIV-uninfected persons
  - Can be given twice weekly via DOT: 76 doses within 12 months
  - Preferred for children 2–11 years of age

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LTBI Treatment Regimens

INH (cont.)

- **6-month regimen also generally acceptable: 180 doses within 9 months**
  - Can be given twice weekly via DOT: 52 doses within 9 months
  - Shorter regimen not recommended for children, immunosuppressed persons, persons whose x-rays suggest previous TB

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LTBI Treatment Regimens

INH-rifapentine (RPT) regimen (12-dose regimen)

- **INH and RPT given in 12 once-weekly doses under DOT**
- **Offers equal option to 9 months daily INH, but does not replace other treatment options for LTBI (Table 5.3)**
- **Recommended for treating LTBI in otherwise healthy people ≥12 years of age who had recent contact with infectious TB, or who had a tuberculin skin test conversion or a positive blood test for TB infection**

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LTBI Treatment Regimens

INH-RPT regimen (12-dose regimen) (cont.)

- **Can be considered for specific groups that would benefit (e.g., need to complete treatment in short time)**
- **12-dose regimen is *not* recommended for children <2 years, HIV-infected persons on ART drugs, patients with presumed INH or RIF resistance, women who are or might become pregnant during treatment**
- **Patients should be monitored monthly; ask about side effects and assess for signs of adverse effects**

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LTBI Treatment Regimens

Dosage for 12-dose INH and RPT:

- **Isoniazid: 15 mg/kg rounded up to the nearest 50 or 100 mg, with a 900 mg maximum**
- **Rifapentine:**
  - 10.0-14.0 kg: 300 mg
  - 14.1-25.0 kg: 450 mg
  - 25.1-32.0 kg: 600 mg
  - 32.1-49.9 kg: 750 mg
  - ≥ 50.0 kg: 900 mg maximum
- **Keep RPT sealed until it is used**

109

Adverse Reactions to INH

Use of INH is associated with some adverse reactions:

- **Peripheral neuropathy – give vitamin B_6 if patient has risk factors, or if signs/symptoms develop**
- **Fatal hepatitis – pregnant/postpartum women at increased risk; monitor closely**
- **Elevated liver enzymes – discontinue INH if liver enzyme levels exceed 3X normal with symptoms, or 5X upper limit of normal with no symptoms**
  - Closely monitor if signs/symptoms of liver injury, or liver enzyme levels are elevated but less than above

110

Rifampin (RIF)

- **Alternative to INH is 4 months daily RIF: 120 doses within 6 months**
- **Should not be used in HIV-infected persons being treated with some antiretroviral therapy(ART)**
- **In some instances where RIF cannot be used, rifabutin can be substituted**

111

Recommendation Against the RIF/PZA Regimen

- **LTBI regimen of 2 months of RIF/PZA is no longer recommended owing to associated severe liver injury.**
- **PZA should *not* be offered to persons with LTBI, but should continue to be included in multidrug regimens for treatment of TB disease.**

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LTBI Treatment Regimens for Specific Situations

HIV-Infected Persons

- **Consult an expert in managing HIV and TB**
- **INH daily for 9 mos, rather than 6 mos, is optimal: 270 doses within 12 months**
- **HIV-infected persons on ART drugs should not take the 12-dose regimen; drug interactions not known**
- **HIV-infected persons on some ART drugs, such as protease inhibitors or delavirdine, should not take RIF**
- **Rifabutin with dose adjustments can sometimes be substituted for RIF**

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LTBI Treatment Regimens for Specific Situations (cont.)

Persons with Fibrotic Lesions Suggesting Previous TB

- **Should be treated for LTBI if they have**
  - A positive TST reaction (at least 5 mm) or IGRA result
  - No symptoms of infectious TB disease
  - No history of treatment for TB disease
- **Evaluate with sputum smear and culture, and treat only after TB disease excluded by negative culture**
- **Acceptable regimens include**
  - 9 months of INH
  - 4 months of RIF (with or without INH)
- **Persons with evidence of primary, healed TB not at increased risk for TB**

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LTBI Treatment Regimens for Specific Situations (cont.)

Contacts of Persons with Multidrug-Resistant (MDR) TB

- Consider risk for progressing to MDR disease before recommending LTBI treatment
- When prescribing treatment for these contacts, consult an MDR TB expert

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LTBI Treatment Regimens for Specific Situations (cont.)

Pregnancy and Breast-Feeding

- 9 months of INH daily or twice weekly; give with vitamin B_6
- If cannot take INH, consult with TB expert
- 12-dose INH-RPT regimen not recommended for pregnant women; its safety in pregnancy is not known
- Women at high risk for progression to TB disease, especially HIV infected or diabetic, should not delay LTBI treatment; monitor carefully
- Breast-feeding not contraindicated

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Patient Monitoring

Before starting treatment for LTBI, clinicians should

- Exclude possibility of disease (symptoms, chest radiograph)
- Determine if patient has history of prior treatment for LTBI or disease
- Determine if any contraindications to treatment
- Obtain information about current and previous drug therapy, including adverse reactions
- Recommend HIV testing, unless the patient declines (opt-out screening)

117

Patient Monitoring (cont.)

Establish rapport with patient and emphasize

- Benefits of treatment
- Importance of adherence to treatment regimen
- Possible adverse side effects of regimen
- Establishment of optimal follow-up plan

118

Patient Monitoring (cont.)

- Baseline laboratory testing not routinely indicated for all patients
- Baseline hepatic measurements are indicated for
  - Patients with a liver disorder or liver disease
  - Patients with HIV infection
  - Pregnant women and those in immediate postpartum period
- Patients with abnormal baseline tests should be monitored regularly

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Patient Monitoring (cont.)

At least monthly, evaluate for

- Adherence to prescribed regimen
- Signs and symptoms of TB disease
- Signs and symptoms of adverse effects, especially hepatitis
  - Jaundice, loss of appetite, fatigue, and/or muscle and joint aches

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Chapter 6.
Treatment of TB Disease

121

Major Goals of TB Treatment

- Cure patient, minimize risk of death/disability, prevent transmission to others
- Provide safest, most effective therapy in shortest time
- Prescribe multiple drugs to which the organisms are susceptible
- Never treat with a single drug or add single drug to failing regimen
- Ensure adherence and completion of therapy

122

Develop Treatment and Monitoring Plan

Plan should include

- Description of treatment regimen
- Methods for assessing/ensuring adherence
- Monitoring methods for treatment response and adverse events

123

Adherence

- Nonadherence results in inadequate treatment
- Can lead to treatment failure, relapse, ongoing transmission, and drug resistance
- Clinician responsible for completion of therapy
- To ensure adherence, provide education, case management, DOT, incentives and enablers, and combination pills
- If these fail, take more restrictive action

124

Case Management

Strategy to ensure patients complete treatment. Three elements:

- Assigning responsibility
- Conducting regular systematic review
- Developing plans to address barriers to adherence

Case managers must ensure patients are educated about TB, therapy is continuous, and contacts are evaluated properly

125

Directly Observed Therapy (DOT)

- Health-care worker watches patient swallow each dose
- DOT is preferred management strategy for all patients
- Can reduce acquired drug resistance, treatment failure, and relapse
- Nearly all regimens can be intermittent if given as DOT
- DOT reduces total number of doses and encounters
- For drug-resistant TB, use daily regimen and DOT

126

Current Anti-TB Drugs

10 drugs FDA-approved for treatment of TB

- Isoniazid (INH)
- Rifampin (RIF)
- Pyrazinamide (PZA)
- Ethambutol (EMB)
- Rifapentine (RPT)
- Streptomycin (SM)
- Cycloserine
- Capreomycin
- *p*-Aminosalicylic acid
- Ethionamide

127

Current Anti-TB Drugs (cont.)

- **Four first-line drugs considered standard treatment:**
  - Isoniazid (INH)
  - Rifampin (RIF)
  - Pyrazinamide (PZA)
  - Ethambutol (EMB)

- **Rifabutin and rifapentine also considered first-line drugs in some circumstances**
- **Streptomycin (SM) formerly first-line drug, but now less useful owing to increased SM resistance**

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TB Disease Treatment Regimens

- **Four regimens recommended for treatment of drug-susceptible TB, with different options for number of doses and for length of continuation phase**
- **Initial phase: standard four drugs (INH, RIF, PZA, EMB) for 2 months (one excludes PZA)**
- **Continuation phase: additional 4 months; 7 months for some patients**

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TB Disease Treatment Regimens (cont.)

- **When to use 7-month continuation phase:**
  - Disease is cavitary and sputum culture is positive at end of initial phase;
  - Initial phase excluded PZA; or
  - Once-weekly INH and RPT used in continuation phase, and culture is positive at end of initial phase.

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Regimen 1 for Treatment of Pulmonary, Drug-Susceptible TB 6-Month Standard Regimen for Most Patients

Initial phase

INH, RIF, PZA, EMB daily (7 or 5 days/week) for 8 weeks

4-month continuation phase options

1) INH, RIF daily (7 or 5 days/week) for 18 weeks

2) INH, RIF intermittently (2 days/week or 1 day/week for INH, rifapentine) for 18 weeks

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Regimen 2 for Treatment of Pulmonary, Drug-Susceptible TB 6-Month Daily + Intermittent Dosing Options

Initial phase

INH, RIF, PZA, EMB daily (7 or 5 days/week) for 2 weeks, *then* 2 days/week for 6 weeks

4-month continuation phase options

1) INH, RIF intermittently (2 days/week) for 18 weeks

2) INH, RPT intermittently (1 day/week) for 18 weeks

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Regimen 3 for Treatment of Pulmonary, Drug-Susceptible TB 6-Month Intermittent Dosing Options

Initial phase

INH, RIF, PZA, EMB intermittently (3 days/week) for 8 weeks

4-month continuation phase

INH, RIF intermittently (3 days/week) for 18 weeks

133

Regimen 4 for Treatment of Pulmonary, Drug-Susceptible TB 7-Month Regimen without Pyrazinamide

Initial phase

INH, RIF, EMB daily (7 or 5 days/week) for 8 weeks

7-month continuation phase options

1) INH, RIF daily (7 or 5 days/week) for 31 weeks
2) INH, RIF intermittently (2 days/week) for 31 weeks

134

Treatment Completion

- Defined as ingesting prescribed number of doses within specified time
- Duration depends on drugs used, isolate's susceptibility, and patient's response to drugs
- Most patients can be treated with 6-mo or 9-mo therapy; 6 mo is used for most patients

135

Follow-up After Treatment

- Not necessary for patients with satisfactory response
- Patients with susceptible TB should report symptoms
- Patients with resistant organisms must have individualized follow-up evaluation

136

Treatment Interruptions

- Treatment interruption is common
- Restart or continue therapy based on when interruption occurred and duration of interruption

137

Treatment Interruption During Initial Phase

- If lapse ≥14 days, restart treatment
- If lapse <14 days, continue treatment to completion as long as all doses completed within 3 months

138

Treatment Interruption During Continuation Phase

- **If patient received ≥80% of doses and**
  - Sputum smear was negative on initial testing, further therapy may not be needed
  - Sputum smear was positive on initial test, continue therapy
- **If patient received <80% of doses, and lapse is**
  - <3 months long, continue therapy
  - >3 months long, restart therapy from beginning of initial phase

139

Treating Culture-Negative Disease

- **Some patients may have culture-negative pulmonary TB disease**
- **Start culture-negative patient on four-drug therapy if high clinical suspicion for TB**

140

Treatment Regimens for Specific Situations

Pregnant Women

- **Initial regimen should consist of INH, RIF, and EMB**
  - SM is contraindicated; PZA not contraindicated, but detailed data on teratogenicity not available
  - If PZA not used, duration of therapy is 9 months
  - If treating MDR TB in pregnancy, consult MDR TB expert
- **Breast-feeding not contraindicated for women being treated for TB disease**
- **Vitamin B_6 supplementation recommended if taking INH**

141

Treatment Regimens for Specific Situations (cont.)

Infants and Children

- **Treat with same regimens recommended for adults, with exception that EMB not used routinely in children**
- **Treat as soon as diagnosis suspected**
- **For disseminated TB or TB meningitis in children, treat for 9–12 months**

142

Treatment Regimens for Specific Situations (cont.)

HIV-Infected Persons

- **Management of HIV-related TB is complex**
- **Should be provided in consultation with experts in treatment of both HIV and TB**
- **Can be treated with standard regimens except:**
  - Do not use once-weekly continuation-phase INH and RPT
  - In patients with advanced HIV, use daily or 3x weekly therapy

143

Treatment Regimens for Specific Situations (cont.)

HIV-Infected Persons (cont.)

- **If possible, use a rifamycin for the entire course of therapy, along with ART**
- **A major concern: RIF interacts with some PIs and NNRTIs**
- **Rifabutin has fewer drug interactions and may be used instead of RIF**
- **Drug dosages may need adjusting; consult expert**

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Treatment Regimens for Specific Situations (cont.)

HIV-Infected Persons (cont.)

- These guidelines are likely to change over time
- For more information, see Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis at: http://www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/default.htm

145

Pregnancy in HIV-Infected Women

- Treatment is complicated in HIV-infected pregnant women with TB
- Pregnancy alters distribution/metabolism of some drugs, including ART
- Protease inhibitor concentrations reduced in pregnancy

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HIV-Infected Children

HIV-infected children with TB at greater risk for severe forms of disease

- For more information, see Managing Drug Interactions in the Treatment of HIV-Related Tuberculosis at: http://www.cdc.gov/tb/publications/guidelines/TB_HIV_Drugs/default.htm

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Conditions Requiring Additional Considerations

- Renal insufficiency/end-stage renal disease
  - Some TB drugs are cleared by the kidneys; thus the dosing must be altered with renal disease
  - Rather than decrease dosage size, increase dosing interval
- Hepatic disease - consider regimens with fewer hepatotoxic agents
- Extrapulmonary TB - In most cases, treat with same regimens used for pulmonary TB

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Conditions Requiring Additional Considerations (cont.)

Drug-resistant TB: can develop as primary or secondary resistance

- Primary resistance is caused by initial infection with resistant organisms
- Secondary or acquired resistance develops during therapy owing to
  - Patient being treated with inadequate regimen,
  - Patient not taking drugs as prescribed, or
  - Other conditions such as drug malabsorption or drug-drug interactions.

149

Conditions Requiring Additional Considerations (cont.)

Multidrug-resistant TB (MDR TB)

- Presents high risk for treatment failure, relapse, further acquired resistance, and/or death
- Clinicians unfamiliar with its treatment should seek expert consultation
- Always use DOT to ensure adherence

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Conditions Requiring Additional Considerations (cont.)

Culture-negative TB

- **Failure to isolate TB bacilli from person with clinical evidence does not exclude TB**
- **At minimum, TB suspects should have 3 specimens for smear and culture**
- **If high likelihood of TB, initiate therapy with INH, RIF, PZA, and EMB**

151

Patient Monitoring

Recommended Examinations for Baseline Monitoring

Patient	Recommended Test
All patients	Measure aminotransferases (i.e., AST, ALT), bilirubin, alkaline phosphatase, and serum creatinine and a platelet count
Patients at risk for hepatitis B or C (e.g., injection drug user, born in Asia or , or HIV infected)	Conduct serologic tests
Patients who are taking EMB	Test visual acuity (Snellen chart) and color vision (Ishihara)
HIV-infected patients	Obtain CD4+ lymphocyte count

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Patient Monitoring (cont.)

Monitoring During Treatment

Patient	Recommendations
All patients	Repeat at least monthly clinical evaluations to • Identify possible adverse reactions to medications • Assess adherence
Patients who are taking EMB	• Question monthly regarding visual disturbances • Repeat monthly testing for visual acuity (Snellen chart) and color vision (Ishihara) for patients whose dose exceeds 15-20 mg/kg and those who have been receiving EMB for >2 months
Patients who have extrapulmonary TB disease	Evaluation depends on • Sites involved • Ease with which specimens can be obtained

153

Evaluating Response to Treatment

- **Assess patient's response to treatment using three methods:**
  - Clinical evaluation, bacteriological examination, chest radiograph
- **Conduct clinical evaluations at least monthly; after 2 months of therapy, if symptoms do not resolve, reevaluate for**
  - Potential drug-resistant disease
  - Nonadherence to drug regimen

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Evaluating Response to Treatment (cont.)

- **Bacteriological examination**

If cultures do not convert to negative after 3 months of therapy, evaluate patient for drug resistance or adherence issues; after 4 months, consider treatment failed

- **Chest radiograph**

Patients with initially negative cultures should have chest radiograph after 2 months of treatment and at completion of therapy

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Evaluating Response to Treatment (cont.)

- **Monitor for adverse reactions**
- **Common adverse reactions include**
  - Gastrointestinal problems
  - Hepatitis
  - Rash
  - Fever

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Chapter 7.
TB Infection Control

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Introduction

- *M. tb* can be transmitted in any setting
- Transmission has been documented in health-care settings where there is exposure to persons with infectious TB who
  - Have unsuspected TB disease,
  - Have not received adequate treatment, or
  - Have not been isolated from others.

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Infectiousness

- Directly related to number of bacilli-laden droplets expelled into the air
- Infection occurs when person inhales droplets, which travel to alveoli
- Young children with TB less likely to be infectious, but can transmit *M. tb*
- Infectiousness usually declines rapidly with treatment
  - However, some remain infectious for weeks or months

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Infectiousness (cont.)

Patient factors associated with infectiousness:

- Coughing
- Cavity in the lung
- Sputum smears positive for acid-fast bacilli (AFB)
- TB disease of the lungs, airway, or larynx
- Undergoing cough-inducing or aerosol-generating procedures
- Not receiving adequate therapy
- Culture positive

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Criteria to Be Considered Noninfectious

Patients no longer considered infectious if:

- They have 3 consecutive negative sputum smears,
- Their symptoms have improved, and
- They are adhering to an adequate treatment regimen for at least 2 weeks

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Environmental Factors that Enhance Risk of Transmission

- High concentration of droplet nuclei in the air
- Exposure in small, enclosed spaces
- Poor ventilation that inadequately dilutes or removes droplet nuclei
- Recirculation of air containing droplets
- Improper specimen handling procedures
- Positive air pressure in patient's room causing flow to other areas

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TB Infection Control Measures

- **TB infection control (IC) measures should be based on TB risk assessment for the setting**
- **The goals of IC programs are**
  - Detect TB disease early and promptly
  - Isolate persons with known/suspected TB
  - Start treatment in persons with known/suspected TB

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Detection of TB Disease

- **Primary risk in health-care settings: unsuspected persons with TB disease**
- **Protocols for detecting, isolating, and managing TB suspects should be implemented**
- **Staff admitting patients should be trained to know signs/symptoms of TB**

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Airborne Precautions

- **Separate and isolate persons with TB signs/symptoms**
  - Preferably use airborne infection isolation (AII) room
  - Single-patient room with controlled environment to minimize transmission of infection
  - Continue precautions until 3 negative smears, 2 weeks therapy, and improved symptoms
- **Start TB patients/suspects on standard TB therapy**

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Hierarchy of Controls

TB IC program should be based on three levels of controls:

- **Administrative controls to reduce risk of exposure**
- **Engineering controls to prevent spread and reduce concentration of droplet nuclei**
- **Personal respiratory protection to further reduce risk of exposure**

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Administrative Controls

To reduce risk of exposing uninfected persons to infectious disease:

- **Assign responsibility for IC in the facility**
- **Conduct annual facility risk assessment by examining**
  - Number of TB patients in the setting
  - Promptness of detecting, isolating, and evaluating TB suspects
  - Evidence of transmission in the setting
  - Community TB rate

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Administrative Controls (cont.)

- **As part of risk assessment, do risk classification to determine need for testing**
  - Low risk: Settings where persons with TB not likely to be seen
  - Medium risk: Settings where HCWs will possibly be exposed to TB
  - Potential ongoing transmission: Settings with evidence of transmission in past year

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Administrative Controls (cont.)

- Institute IC plan to ensure TB suspects found, isolated, evaluated, treated
- Ensure recommended laboratory services are available
- For HCWs, implement effective work practices and test as classification indicates
- Ensure equipment is properly cleaned, disinfected, and sterilized
- Educate, train, and counsel HCWs, patients, visitors about TB

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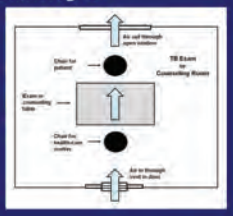
Environmental Controls

Prevent spread and reduce concentration of infectious droplet nuclei through

- Primary controls: ventilation technologies
  - Natural ventilation: relies on open doors, windows
  - Mechanical ventilation (local exhaust and general): equipment, use of AII room
- Secondary controls: HEPA filters and ultraviolet germicidal irradiation (UVGI)

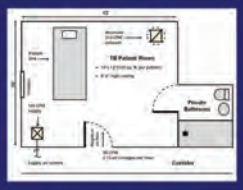


170

Environmental Controls (cont.)

AII rooms designed to prevent spread of droplet nuclei

- TB suspect/patient should be put in AII room immediately
- Facilities that see TB patients should have at least one AII room



171

Environmental Controls (cont.)

Characteristics of AII room:

- Single-patient room with private bathroom
- Negative pressure relative to hallway
- Air sent outdoors or through HEPA filter
- Six or more air changes per hour (in some settings 12 or more air changes per hour are recommended)
- Visitors should use N95 respirator

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Respiratory Protection Controls

Consists of using personal protective equipment in areas with increased risk of exposure:

- TB AII rooms
- Rooms where cough- or aerosol-producing procedures are done
- Vehicles transporting infectious patients
- Homes of infectious TB patients

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Respiratory Protection Controls (cont.)

- Settings that use respiratory protection controls should develop, implement, and maintain a respiratory protection program
- Train HCWs on respiratory protection
- Educate patients on respiratory hygiene
- Test HCWs for mask fit and functionality

174

Respirator for Health-Care Workers

Health-care worker wearing a respirator

Respirators

- Designed to filter out droplet nuclei from being inhaled by the health-care worker and other individuals.
- Should properly fit different face sizes and features.
- Should NOT be worn by the patient.

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Surgical Mask for Persons with Infectious TB Disease

Infectious TB patient wearing a surgical mask

Surgical masks

- Designed to stop droplet nuclei from being spread (exhaled) by the patient.
- Should NOT be worn by the health-care worker.

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Infection Control Programs in Nontraditional Settings

Nontraditional settings seeing TB patients must have an IC program. These include

- Correctional facilities
- Homeless shelters
- Long-term care facilities
- Home-based health-care and outreach settings
- Emergency medical services

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TB Infection Control in the Home

Patients can be sent home while still infectious if

- A follow-up plan has been made
- Patient is on standard treatment and DOT arranged
- No very young (under 5 years) or immunocompromised persons in household
- Patient willing to refrain from travel outside the home except for health-care visits

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TB Infection Control in the Home (cont.)

HCWs visiting patients at home should:

- Instruct patients to cover mouth/nose when coughing or sneezing
- Wear a respirator when visiting or transporting an infectious patient
- Collect specimens in well-ventilated area

HCWs whose responsibilities include visiting patients at home should participate in an annual TB testing program

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Chapter 8. Community TB Control

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Responsibility for TB Control

- Health departments maintain primary responsibility for TB prevention and control
- Complexity of TB control requires public health sector to collaborate with others

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Roles and Responsibilities of Public Health Sector

Public health sector plans, coordinates, and evaluates TB control efforts

Requires state and local health departments to focus on

- Planning and policy development
- Contact investigation
- Clinical/diagnostic services for TB patients and their contacts
- Training and education
- Surveillance and information management
- Monitoring and evaluation

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Roles and Responsibilities of Public Health Sector (cont.)

Planning and Policy Development

- TB control programs should collaborate with community stakeholders to develop plan
- Written plan should be based on the following:
  - Local epidemiologic data
  - Availability of clinical and support services
  - Availability of fiscal resources
  - Current legal statutes and standards of care

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Roles and Responsibilities of Public Health Sector (cont.)

Planning and Policy Development (cont.)

Plan should

- Assign specific roles and responsibilities
- Define pathways of communication
- Assign sufficient human and financial resources
- Provide for expert consultation and oversight
- Provide guidance to TB laboratories

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Roles and Responsibilities of Public Health Sector (cont.)

Planning and Policy Development (cont.)

Plan should

- Ensure complete/timely contact investigations (CIs) are done; assist local providers in CIs and providing DOT
- Provide culturally appropriate info to patients
- Minimize financial and cultural barriers to TB control
- Ensure clinicians promptly report all suspected and confirmed TB cases

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Roles and Responsibilities of Public Health Sector (cont.)

Clinical and Diagnostic Services

Health department must ensure

- TB patients can access diagnostic/treatment services
- Completeness of TB-related services and continuity of care, regardless of where patient seeks care
- Standards of care are met

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Roles and Responsibilities of Public Health Sector (cont.)

Clinical and Diagnostic Services (cont.)

Health department must ensure

- Radiology and lab services readily accessible
- Radiograph and AFB results available within 24 hours
- All TB smear, culture, and drug-susceptibility results reported promptly by laboratories

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Roles and Responsibilities of Public Health Sector (cont.)

Training and Education

TB control programs should

- Provide training for TB control program staff
- Educate other HCWs, community members, public health officials, and policy makers
- Create and implement educational activities using resources from CDC, RTMCCs, NIH-supported TB curriculum centers, NTCA, and others

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Roles and Responsibilities of Public Health Sector (cont.)

Surveillance and Information Management

- Surveillance and information management systems should be priorities of all TB control programs
- Patient care can be improved through standardized data collection and test result tracking
- Other benefits include ready access to details of treatment regimens, DOT administration, drug-drug interactions

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Roles and Responsibilities of Public Health Sector (cont.)

Monitoring and Evaluation

- Evaluation provides programs evidence-based means of improving TB control strategies
- Develop evaluation priorities based on local TB challenges and how services are organized
- First priority for evaluation should be on key TB control strategies:
  - Identify and treat all persons with infectious TB disease
  - Find contacts and others at high risk; offer therapy
  - Interrupt transmission in high-risk settings

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Roles and Responsibilities of Specific Private Sector Providers

Private sector includes

- Clinicians
- Community health centers
- Hospitals
- Academic institutions
- Medical professional organizations
- Community-based organizations
- Correctional facilities
- Civil surgeons
- Pharmaceutical and biotechnology industries

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Roles and Responsibilities of Specific Private Sector Providers (cont.)

Role of Clinicians

- Understand prevalent medical conditions of their patient populations
- Be aware of local TB reporting laws
- Know procedures for suspected TB: diagnose, hospitalize, report case, plan treatment
- Follow current guidance for screening, diagnosis, treatment of TB and LTBI
- Be able to administer TB tests, rule out TB disease, administer treatment

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Roles and Responsibilities of Specific Private Sector Providers (cont.)

Role of Community Health Centers

- Ensure staff ability to assess, diagnose, and start treatment for TB and LTBI
- Work closely with local physicians, hospitals, labs, and public health agencies
- Arrange for reporting of TB suspects; refer patients to necessary services

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Roles and Responsibilities of Specific Private Sector Providers (cont.)

Role of Community Health Centers (cont.)

- Be aware of local programs providing TB services for high-risk patients
- Educate and motivate patients about implications of TB
- Establish recommended infection control practices

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Roles and Responsibilities of Specific Private Sector Providers (cont.)

Role of Hospitals

- Develop infection control policies and plans to prevent transmission
- Promptly report suspected/confirmed TB cases
- Provide training to staff
- Ensure TB patients are discharged on a standard regimen and with follow-up plan

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Roles and Responsibilities of Specific Private Sector Providers (cont.)

Role of Academic Institutions

- Incorporate TB into their curricula
- Serve as a community resource in TB management issues
- Partner with local public health agencies in TB control activities
- Provide leadership in conducting TB-related research

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Roles and Responsibilities of Specific Private Sector Providers (cont.)

Role of Medical Professional Organizations

- Train/educate members regarding TB
- Provide professional leadership on clinical practice and control of TB
- Advocate for adequate TB control funding
- Promote global TB control; link U.S. health professionals with those outside the U.S.

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Roles and Responsibilities of Specific Private Sector Providers (cont.)

Role of Community Based Organizations

- Partner with local public health sector to facilitate access to services for target population
- Participate in advocacy/support activities
- Coordinate with public health sector to develop education materials tailored to their populations

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Roles and Responsibilities of Specific Private Sector Providers (cont.)

Role of Correctional Facilities

- Coordinate with local public health sector to develop epi profile of TB risk in inmate population
- Develop written policies and establish effective TB control program
- Ensure persons under TB treatment are linked to needed services upon discharge
- Develop infection control program
- Evaluate institution's TB control program, in collaboration with local public health sector
- Develop ongoing training/education for staff

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Roles and Responsibilities of Specific Private Sector Providers (cont.)

Role of Civil Surgeons

- Understand and follow current guidelines for diagnosis/treatment of TB and LTBI
- Work with local public health sector; report suspected and confirmed TB cases
- Develop referral mechanism for evaluation of TB in persons seeking status adjustment

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Roles and Responsibilities of Specific Private Sector Providers (cont.)

Role of Pharmaceutical and Biotechnology Industries

- Understand their role in developing tools for diagnosing, treating, preventing TB
- Review costs/markets for new product development and potential funding sources
- Join coalitions such as Global Partnership to Stop TB, Global Alliance for TB Drug Development, FIND
- Work with other stakeholders to ensure access to products for patients

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Notes

Notes