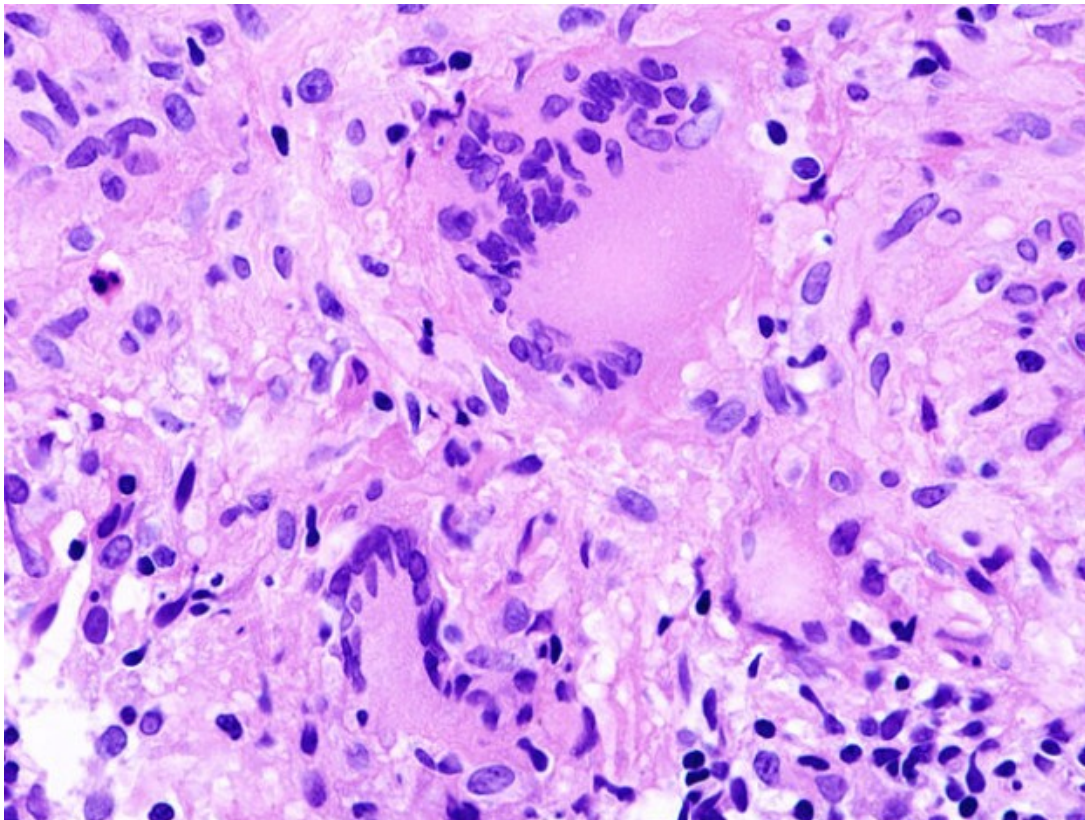


Tuberculosis (TB, Consumption) — Diagnosis and Treatment

[See online here](#)

Tuberculosis (TB) is a disease caused by *Mycobacterium tuberculosis*. The bacteria usually attack the lungs, but it can also damage other parts of the body. Approximately 30% of humankind is infected with this pathogen. TB spreads through the air when a person infected with TB of the lungs or throat talks, sneezes or coughs. *M. tuberculosis* is very acid-fast, grows very slowly, and can survive in macrophages. This poses a great challenge to physicians and scientists involved in developing therapy and prevention for this infectious disease.



Epidemiology of Tuberculosis

Worldwide distribution of tuberculosis

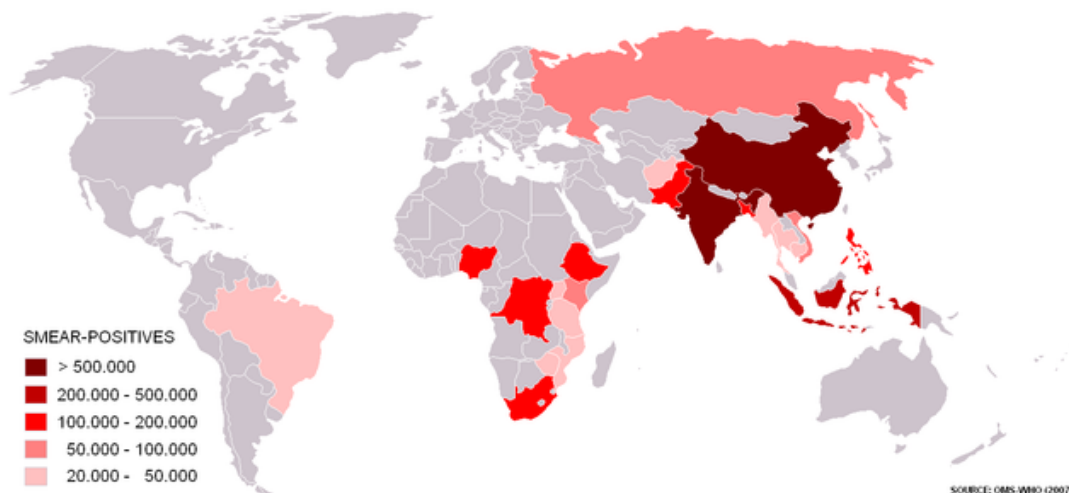


Image: Map of the 22 HBCs (high-burden countries) that account for approximately 80% of all new TB cases arising each year, by WHO Report 2009 – Global Tuberculosis Control. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

Tuberculosis is found worldwide and is one of the most frequently encountered infectious diseases along with AIDS and malaria. According to the Robert Koch Institute (RKI), 1/3rd of the world population is infected with *Mycobacterium tuberculosis*, and during their lifetime, 5% to 10 % develop tuberculosis disease that requires treatment. Worldwide, tuberculosis is the bacterial infectious disease that most frequently leads to death even though it is treatable. Tuberculosis is the leading cause of death in patients with [HIV](#).

Most individuals who are infected with *Mycobacterium tuberculosis* live in Africa, Southeast Asia, and the Western Pacific region.

Each year, almost 9 million people become sick with tuberculosis, and 1.4 million of these people die from the disease (WHO).

Risk of tuberculosis

Individuals at greater risk for tuberculosis include residents of countries with high prevalence of the disease, institutionalized patients, individuals who use intravenous drugs, and immunodeficient patients (e.g., those with [diabetes mellitus](#) or [Hodgkin disease](#)).

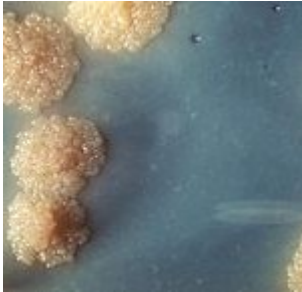
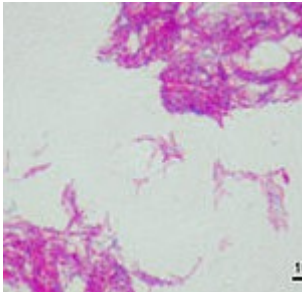
Individuals at high risk for tuberculosis include those with suspicious X-ray findings, those who have close contact with patients with active tuberculosis, and those who are HIV-infected or otherwise immunosuppressed. Countries with high risk for tuberculosis include Sub-Saharan Africa, the Indian subcontinent, and the former USSR.

Etiology and Pathogenesis of Tuberculosis

Pathogen and reservoir for tuberculosis

Tuberculosis pathogens are acid-fast, aerobic, gram-positive bacteria from the family of *Mycobacteriaceae*. In the following table, the pathogens of the *Mycobacterium tuberculosis* complex are listed with their respective reservoirs.

Tubercular Pathogen	Reservoir
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<p><i>M. tuberculosis</i> (most frequent pathogen)</p> 	<p>Humans</p>
<p><i>M. bovis</i> (ssp. <i>bovis</i> and <i>caprae</i>)</p>  <p><small>Image: <i>Mycobacterium bovis</i>, by Y tambe. Lizenz: CC BY-SA 3.0</small></p>	<p>Humans and cattle (infections via nonpasteurized milk)</p>
<p><i>M. africanum</i></p>	<p>Humans</p>
<p><i>M. microti</i></p>	<p>Small rodents</p>
<p><i>M. canetti</i></p>	<p>Patients living in the Horn of Africa</p>
<p><i>M. pinnipedii</i></p>	<p>Seals</p>

Pathogenically, these bacteria are especially effective at triggering a severe cell-mediated immune response.

Paths of infection for tuberculosis

The mode of transmission for infection with tuberculosis is almost **exclusively airborne (droplet infection)** via aerosols with droplets < 5 µm in diameter from patients with active/infectious tuberculosis.

Note: Active tuberculosis means that pulmonary involvement is present, and airborne transmission is possible. Extrapulmonary tuberculosis normally does not pose a risk of infection for social contacts. Tuberculosis is not necessarily as contagious as other easily transmitted infectious diseases, such as [measles or chicken pox](#). Whether a person is infected when exposed to someone with active tuberculosis depends on many factors.

- Frequency, duration, and closeness of contact with a patient with infectious tuberculosis
- Amount and virulence of the inhaled pathogen
- Susceptibility of the exposed person

Signs and Symptoms of Tuberculosis

Incubation time for tuberculosis

Typically, 6–8 weeks pass between exposure to the tuberculosis pathogen and measurable immune response. The risk of tuberculosis disease is greatest in the first 2 years following infection. Infants and immunosuppressed individuals have the greatest

risk of developing the disease.

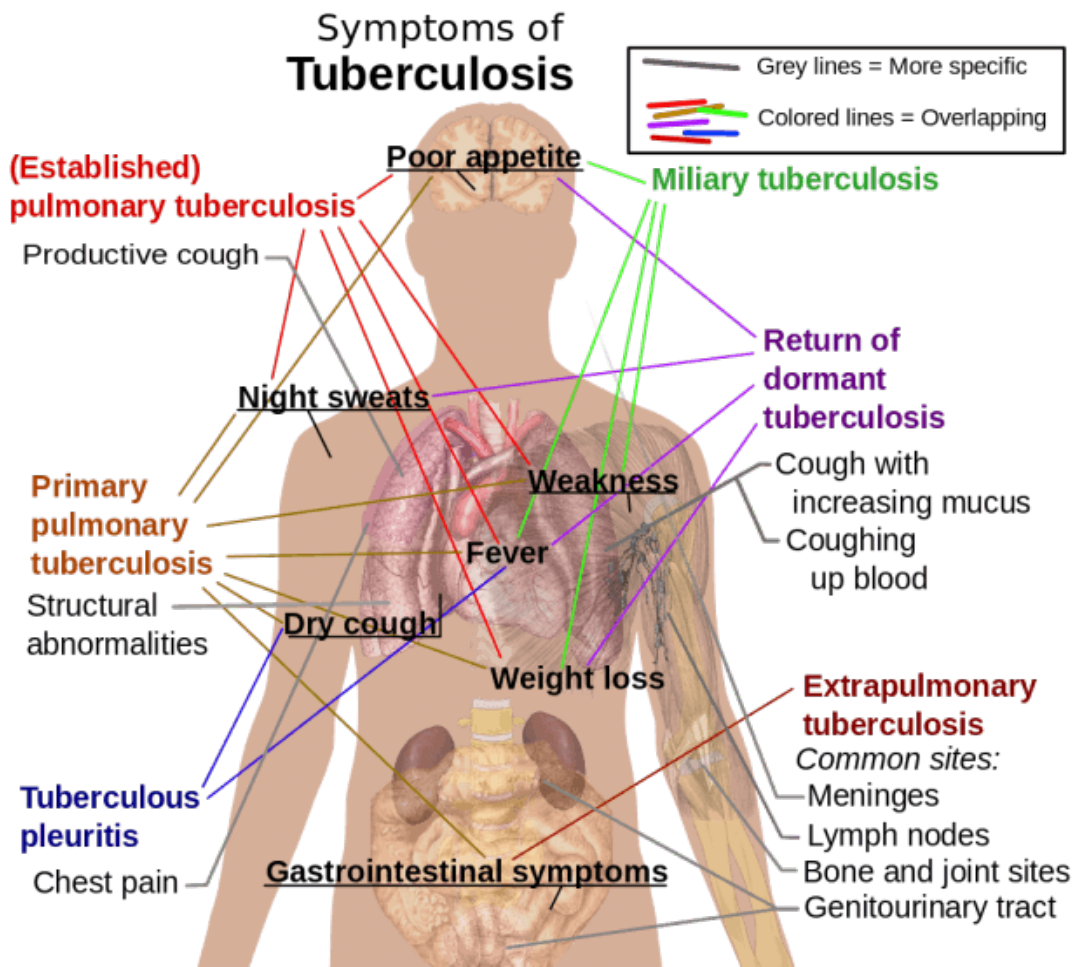


Image: Symptoms of tuberculosis

Clinical presentation of tuberculosis

Tuberculosis is not characterized by specific clinical manifestations. **Primary tuberculosis**, which is usually asymptomatic or presents as a flu, is often not recognized. In the event of the onset of the disease, most infected individuals later become ill from **post-primary tuberculosis**.

Primary tuberculosis

Primary tuberculosis is a latent infection that at first may be detected with a positive result from an indirect test for the pathogen (i.e. Mendel-Mantoux test). At this stage, there is no pathological radiological finding. The infected individual has mostly nonspecific symptoms, such as fatigue, or is asymptomatic. Pulmonary symptoms, such as a productive cough with hemoptysis, may develop.

If no radiological or other pathological changes are detectable, this stage of the disease is known as a **latent tubercular infection (LTBI)** based on a positive tuberculin reaction.

For all patients with pulmonary symptoms, one must consider tuberculosis in the differential diagnosis.

Approximately, 5-6 weeks after infection, a primary focus forms. In histology, the primary

focus is characterized by a **granuloma with epitheloid cells** and Langhans giant cells with central caseation. Via the lymphogenic path of infection, the primary focus spreads to regional lymph nodes.

The primary focus of infection and reactive lymph nodes = **primary complex**.

Weeks or even months can pass until this primary complex (up to 90% of which is located in the lungs) heals completely. Often, scarred and calcified tissue remains, which can be detected in X-rays. Symptoms rarely occur at this point.

Important complications of primary tuberculosis

	Miliary tuberculosis	Pleuritis exsudativa tuberculosa	Landouzy sepsis
Genesis	Via hematogenous, lymphatic spread of tubercular bacilli from the primary complex	From foci close to the pleura	
People affected	Children, immunodeficient adults	Teenagers and adults older than 40 years	Immunodeficient individuals
Symptoms	High fever, severe malaise	Systemic symptoms (e.g., fever, fatigue), thoracic pain, pleural effusion	Septic course of primary tuberculosis, high fever, spleen swelling, headache
Diagnosis	Chest X-ray: miliary spot shadowing; lumbar puncture: tubercular meningitis; ocular fundus: choroidal tubercles	Pleural puncture: exudation with low sugar concentration and increased adenosine-deaminase (ADA-test), chest X-ray	
Therapy	Early, intensive parenteral chemotherapy	Tuberculosis standard therapy	Mostly lethal course

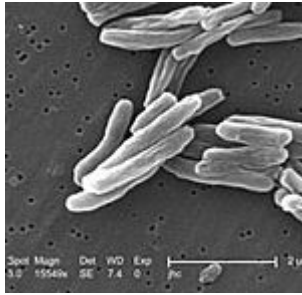
Post-primary tuberculosis

Post-primary tuberculosis (chronic tuberculosis) refers to all forms of tuberculosis that follow primary infection. In most cases, the onset of disease is based on re-infection, not a new infection.

Features and symptoms of post-primary tuberculosis

- Apical pulmonary foci
- **Simon foci**: fuzzy, small, infraclavicular or supraclavicular spots
- **Assmann's early infiltrations**
- A completely asymptomatic course is also possible

Without therapy:



■ Image: *Mycobacterium tuberculosis*

Great probability for detection of tubercular bacteria in sputum >> active, infectious tuberculosis

- Destruction and cavernization of growing areas of lung ⇒ hemoptysis

Extrapulmonary tuberculosis

Tuberculosis can affect every organ system and trigger an unlimited variety of symptoms and complications. The following table gives an overview of the most important extrapulmonary manifestations of tuberculosis.

Adrenal gland	Mostly bilateral, adrenal gland insufficiency (Addison's disease)
CNS	Tubercular meningitis with typical nerve damage of the brain
Bones, joints, and cartilage	Spondylitis tuberculosa, depression abscesses, laryngeal tuberculosis
Kidney	5 years after the infection at the earliest, hematuria with sterile pyuria
Pericardium	Pericardial effusion , pericarditis , constrictive pericarditis
Abdomen	Vomiting, diarrhea , abdominal pain , weight loss
Lymph nodes	Complications of primary tuberculosis, cervical lymph nodes are commonly involved, generalized lymphadenopathy
Skin	Lupus vulgaris (typically, in the cheek region of women), tuberculids

Diagnosis of Tuberculosis

Medical history of tuberculosis

It is important to ask questions about previous infections, trips, and factors that increase risk of tuberculosis (e.g., HIV infection, alcohol abuse).

Tuberculin skin test and interferon-gamma test



Image: Tuberculin skin test according to Mendel-Mantoux

The **tuberculin skin test according to Mendel-Mantoux** is positive if a palpable node of at least 15 mm is visible after 72-96 hours. For at-risk patients, an induration > 10 mm is sufficient to confirm an infection. For high-risk patients, an induration > 5 mm is sufficient to confirm infection.

The currently more established **interferon-gamma test** is based on the in-vitro stimulation of memory cells via antigens of *Mycobacterium tuberculosis*. Hereby, the lymphocytes of the patients are stimulated with a mixture of antigens of *M. tuberculosis*. If the patient was already affected by a tuberculosis infection or had contact with the pathogen, more interferon-gamma is produced.

Note: The results of screening tests for tuberculosis are often positive. Positive test results indicate exposure of the immune system to the mycobacteria, but they do not distinguish between active and inactive (latent) tuberculosis.

Imaging of tuberculosis

Chest X-ray can help guide the diagnosis of tuberculosis, but findings may not be specific. The following might be visible on chest X-ray:

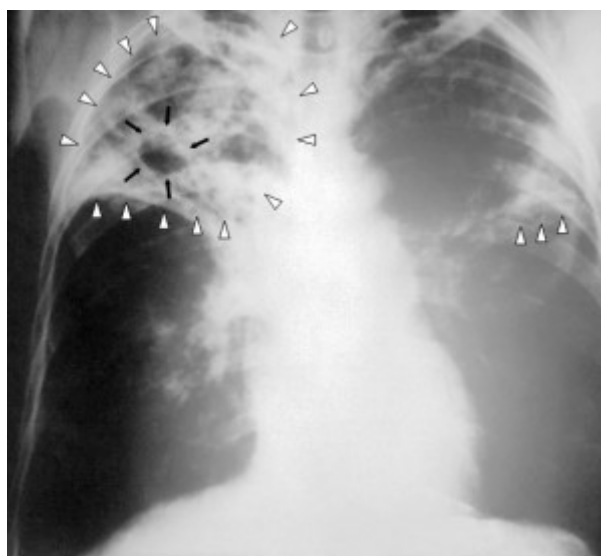


Image: X-ray of a patient with tuberculosis

■ **Primary complex:** enlarged hilar lymph node, local shadowing

- **Post-primary tuberculosis:** Simon foci, Assmann's infiltrations
- **Nonspecific:** Shadowing, calcification, caverns, pleural effusion, round foci (tuberculoma), the distinction between smooth (new) and hard infiltrations (old), foci mostly in the cranial lung regions.

CT scans may show hilar lymph nodes and retroclavicular infiltrations.

Diagnostic testing for tuberculosis

Diagnostic tests for tuberculosis include the threefold culture of **morning sputum samples**, one-time stomach fasting secretion, or invasive procedures, such as bronchoscopy, pleural puncture, or thoracoscopy with biopsy.

In patients with HIV infection, **blood cultures** are also performed because the hematogenous spread of tuberculosis (bacillemia) often occurs.

Acid-fast bacilli may be detected by using Ziehl-Neelsen stain or immunofluorescence stain with auramine. However, a negative finding does not exclude active pulmonary tuberculosis.

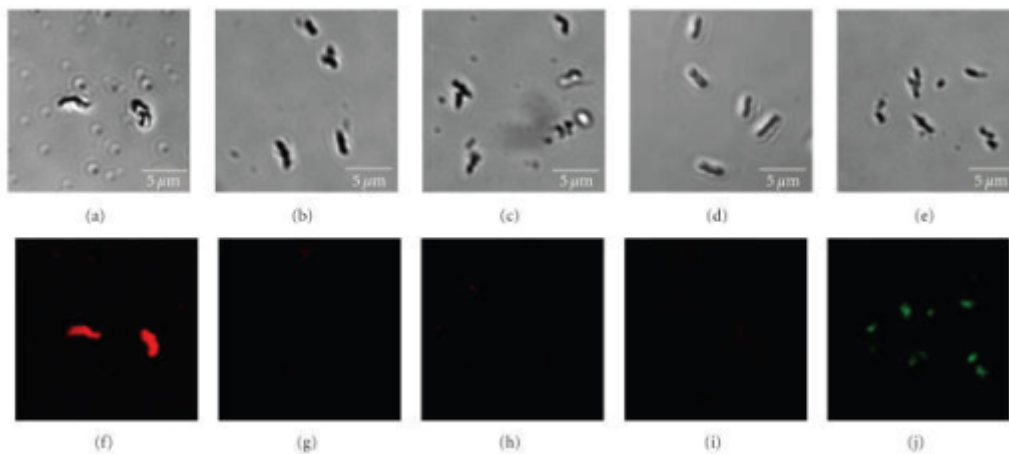


Image: Immune fluorescence stain

Note: A positive culture identifies *Mycobacterium tuberculosis* and provides evidence of active pulmonary tuberculosis.

With **polymerase chain reaction (PCR) analysis**, mycobacteria can be detected within 48 hours. Additionally, this measure is characterized by very high sensitivity and specificity. However, PCR testing cannot distinguish between previous inflammation and active infection.

Differential Diagnosis for Tuberculosis

The most important differential diagnoses for pulmonary tuberculosis are:

- [Chronic bronchitis](#)
- [Pneumonia](#)
- Viral diseases
- Lung mycosis
- [Bronchial carcinoma](#)

Therapy for Tuberculosis

Drug therapy for tuberculosis

In 97% of cases, tuberculosis is curable. Every case of active tuberculosis requires treatment. The patient must be isolated until there is no more risk for infection. Normally, this state is reached at 4–6 weeks after initiation of therapy.

Note: Almost every board examination asks questions about treatments for tuberculosis and their side effects.

Anti-tuberculosis drugs	Effect	Side effects
Isoniazid	Strongest anti-tuberculosis drug, bactericidal effect	Hepatotoxic, neurotoxic (polyneuropathy)
Rifampicin	Bactericidal (inhibition of DNA-dependent RNA-polymerase)	Hepatotoxic, reddish discoloration of bodily secretions
Pyrazinamide	Bactericidal	Hepatotoxic (transaminases, uric acid)
Ethambutol	Bacteriostatic or bactericidal, depending on the dose	Risk for optic neuritis with loss of vision, central scotoma (therefore an ophthalmological examination is required before initiation of therapy)
Streptomycin	Bactericidal	Lesion of the vestibular nerve with balance disorders, ototoxicity; renal insufficiency

Administration of medications for tuberculosis

- **Overall duration:** at least 6 months
- **Initial phase:** 2 months of standard therapy with isoniazid, rifampicin, pyrazinamide, and ethambutol
- **Stabilization phase:** 4 months of treatment with isoniazid and rifampicin, then monitoring of sputum over a period of 2 years
- **Once daily:** Mycobacteria have very slow growth kinetics. Thus, the medications must be administered every day all at once to reach synergistic peak levels
- **Control of side effects:** monitoring of liver function, kidney function, auditory function, X-rays, visual acuity testing
- **Maximum doses** must not be exceeded

Problems of treatment

1. **Diagnosis:** culture is slow (4 weeks+)
2. **Compliance:** no one likes taking tablets for several months
3. **Toxicity:** especially the liver; raised LFTs common, may need to change treatment
4. **Drug resistance:**

- Occurs if a patient is given single-agent therapy
- Need for extended treatment (12 months+)
- Extensively resistant disease is often fatal

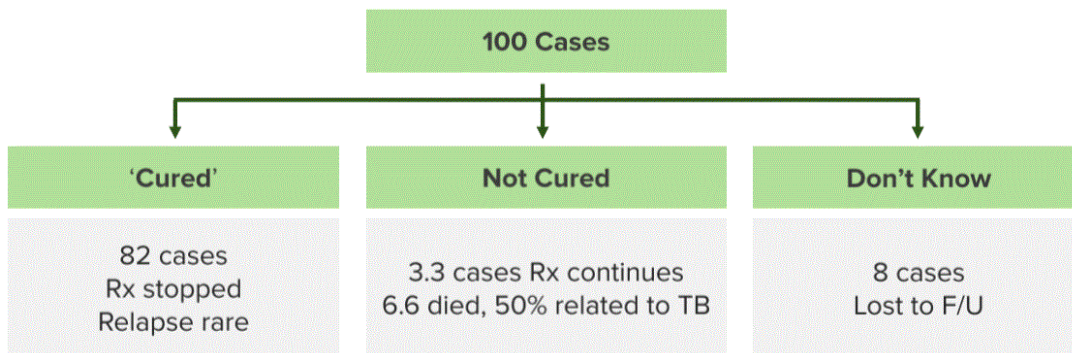


Image: Non-resistant *M. tuberculosis* is readily curable, by Lecturio

Prophylaxis for Tuberculosis

Screening programs for tuberculosis

M. tuberculosis is exclusively transmitted among humans. Screening programs in areas with high risk for infection include tuberculin tests and X-ray images of the [lungs](#).

In areas with low risk for infection, administration of the **BCG (Bacille Calmette-Guérin) vaccination** is not generally recommended. This vaccination is indicated for individuals at high risk of exposure (e.g., employees in shelters for homeless people).

Note: Administration of the BCG vaccine is contraindicated in individuals with positive tuberculin reactions, immunosuppression, or AIDS.

Chemoprophylaxis for tuberculosis

Chemoprophylaxis should be considered if...

- A new occurrence of positive tuberculin reaction is present in a patient at risk for tuberculosis. Treatment is conducted with isoniazid for 9 months. In healthy individuals, initial management consists of X-ray monitoring ('watchful waiting').
- A child younger than 1 year is definitely exposed; monotherapy with isoniazid should be administered for 3 months.
- The interferon-gamma-test is positive and bacteriology is negative.

Review Questions

The correct answers can be found below the references.

1. A medical student working in the emergency department of a large city hospital sees a patient from Eastern Europe. During the physical examination, the patient coughs several times. On the following day, the medical student learns that this patient is suspected to have tuberculosis. Which of the following statements is most likely true?

- A. Incidence of multidrug-resistant tuberculosis in Eastern Europe is similar to the incidence in the United States.
- B. Microscopy of respiratory material stained according to the Ziehl-Neelsen technique has the greatest diagnostic sensitivity of routine methods for the detection of tuberculosis bacteria.
- C. The treating physician has an obligation to report clinical suspicion of tuberculosis to the state or local health department.
- D. The laboratory director has an obligation to report the detection of *Mycobacterium tuberculosis* to the state or local health department.
- E. The medical student should immediately be treated with a fourfold combination of post-exposure prophylaxis.

2. Anti-tuberculosis drugs are administered in combination. Which is the most likely regimen to be used during the stabilization phase?

- A. 4 months isoniazid and rifampicin
- B. 4 months isoniazid and ethambutol
- C. 4 months rifampicin and pyrazinamide
- D. 8 months isoniazid and rifampicin
- E. 8 months isoniazid and pyrazinamide

3. Which is the most typical X-ray finding for post-primary tuberculosis?

- A. Schaumann bodies
- B. Simon foci
- C. Asteroid bodies
- D. Kerley lines
- E. Jet phenomenon

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Correct answers: 1D, 2A, 3B

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