

Pathogenesis

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Transmission is defined as the spread of an organism, such as *M. tuberculosis*, from one person to another.

Sources of infection

The most important source of infection is the patient with TB of the lung, or pulmonary TB and who is coughing. This person is often sputum smear-positive.

The probability of contact with a person who has an infectious form of tuberculosis, the intimacy and duration of that contact, the degree of infectiousness of the case, and the shared environment in which the contact takes place are all important determinants of the likelihood of transmission. Several studies of close-contact situations have clearly demonstrated that tuberculosis patients whose sputum contains AFB visible by microscopy are the most likely to transmit the infection. The most infectious patients have cavitary pulmonary disease and produce sputum containing as many as 10^5 – 10^7 AFB/mL. Patients with sputum smear-negative/culture-positive tuberculosis are less infectious, and those with culture-negative pulmonary disease and extrapulmonary tuberculosis are essentially noninfectious. Persons without cavitations, may be less infectious. Crowding in poorly ventilated rooms is one of the most important factors in the transmission of tubercle bacilli, since it increases the intensity of contact with a case.

In short, the risk of acquiring *M. tuberculosis* infection is determined mainly by exogenous factors. Because of delays in seeking care and in making a diagnosis, it is estimated that, in high-prevalence settings, up to 20 contacts may be infected by each AFB-positive case before the index case is found to have tuberculosis.

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Airborne transmission of the MBT

M. tuberculosis is most commonly transmitted from a person with infectious pulmonary tuberculosis to others by droplet nuclei, which are aerosolized by coughing, sneezing, or speaking. The tiny droplets dry rapidly; the smallest (<5–10 μ m in diameter) may remain suspended in the air for several hours and may reach the terminal air passages when inhaled. There may be as many as 3000 infectious nuclei per cough. Other routes of transmission of tubercle bacilli (e.g., through the skin or the placenta) are uncommon and of no epidemiologic significance.

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Infectious aerosol

Coughing produces infectious droplet nuclei (infectious particles of respiratory secretions usually less than 5 μm in diameter and containing tubercle bacilli). A single cough can produce 3000 droplet nuclei. Droplet nuclei can also be spread into the air by talking, sneezing, spitting and singing, and can remain suspended in the air for long periods. Direct sunlight kills tubercle bacilli in 5 minutes, but they can survive in the dark for long periods. Transmission therefore generally occurs indoors. Droplet nuclei are so small that they avoid the defenses of the bronchi and penetrate into the terminal alveoli of the lungs, where multiplication and infection begin. Two factors determine an individual's risk of exposure: the concentration of droplet nuclei in contaminated air and the length of time he or she breathes that air.

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Risk of infection

An individual's risk of infection depends on the extent of exposure to droplet nuclei and his or her susceptibility to infection. The risk of infection of a susceptible individual is high with close, prolonged, indoor exposure to a person with sputum smear-positive PTB. The risk of transmission of infection from a person with sputum smear-negative PTB is low, and even lower from someone with extrapulmonary TB .

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From Infection to Disease

Unlike the risk of acquiring infection with *M. tuberculosis*, the risk of developing disease after being infected depends largely on endogenous factors, such as the individual's innate immunologic and nonimmunologic defenses and level of function of cell-mediated immunity.

Infection with *M. tuberculosis* can occur at any age. Once infected with *M. tuberculosis*, a person can stay infected for many years, probably for life. The vast majority (90%) of people without HIV infection who are infected with *M. tuberculosis* do not develop TB. In these, asymptomatic but infected individuals, the only evidence of infection may be a positive tuberculin skin test. Infected persons can develop TB at any time. The disease can affect most tissues and organs, but especially the lungs. The chance of developing disease is greatest shortly after infection and steadily lessens as time goes by. Infected infants and young children are at greater risk of developing disease than older people because they have an immature immune system. The most important trigger is weakening of immune resistance, especially by HIV infection which suppresses cellular immunity. The risk that latent *M. tuberculosis* infection will

proceed to active disease is directly related to the patient's degree of immunosuppression.

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Risk factors for tuberculosis

Medical risk factors	Social risk factors
HIV	Material poor-being and poor nourishment
Diabetes	Migrants
Corticosteroid usage	Refugees
Cytostatics and chemotherapy	Prisoners
Cachexia of any genesis	Homeless
Malnutrition	Crowded and unfavorable living conditions
Non specific respiratory diseases	Alcohol addicted
Alcohol and narcotic addiction	

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Pathogenesis and Immunity

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Infection and Macrophage Invasion

The interaction of *M. tuberculosis* with the human host begins when droplet nuclei containing microorganisms from infectious patients are inhaled. While the majority of inhaled bacilli are trapped in the upper airways and expelled by ciliated mucosal cells, a fraction (usually <10%) reach the alveoli. There, alveolar macrophages that have not yet been activated phagocytize the bacilli. Invasion of macrophages by mycobacteria results largely from binding of the bacterial cell wall with a variety of macrophage cell. Phagocytosis is enhanced by complement activation leading to opsonization of bacteria. Due to inhibiting activity of the bacterial cell-wall glycolipid lipoarabinomannan, the bacilli may survive within the phagosomes. If the bacilli are successful in arresting phagosome maturation, then replication begins and the macrophage eventually ruptures and releases its bacillary contents.

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These initial stages of infection are asymptomatic.

About 2–4 weeks after infection, two host responses to *M. tuberculosis* develop: a macrophage-activating cell mediated immune response and a tissue-damaging response. The *macrophage-activating response* is a T cell-mediated phenomenon resulting in the activation of macrophages that are capable of killing and digesting

tubercle bacilli. The *tissue-damaging response* is the result of a delayed-type hypersensitivity (DTH) reaction to various bacillary antigens; it destroys unactivated macrophages that contain multiplying bacilli but also causes caseous necrosis of the involved tissues. Although both of these responses can inhibit MBT growth, it is the balance between the two that determines the form of tuberculosis that will develop subsequently. Cell mediated immunity is critical at this early stage. In the majority of infected individuals, local macrophages are activated when bacillary antigens, processed by macrophages, stimulate T lymphocytes to release a variety of lymphokines. These activated macrophages aggregate around the lesion's center and effectively neutralize MBT without causing further tissue destruction. In the central part of the lesion, the necrotic material resembles soft cheese (*caseous necrosis*). Even when healing takes place, viable bacilli may remain dormant within macrophages or in the necrotic material for many years. These "healed" lesions in the lung parenchyma and hilar lymph nodes may later undergo calcification.

While cell mediated immunity confers partial protection against *M. tuberculosis*, humoral immunity plays a less well-defined role in protection. It is considered that antibodies may prevent dissemination of infection. In the case of CMI, two types of cells are essential: macrophages, which directly phagocytize tubercle bacilli, and T cells (mainly CD4+ T lymphocytes), which induce protection through the production of cytokines, especially IFN-. The role of cytokines in promoting intracellular killing of mycobacteria, however, has not been entirely studied.

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The Delayed-Type Hypersensitivity Reaction (DTH reaction)

In a minority of cases, the macrophage-activating response is weak, and mycobacterial growth can be inhibited only by intensified DTH reactions, which lead to lung tissue destruction. The lesion tends to enlarge further, and the surrounding tissue is progressively damaged and cavities are formed.

Skin Test Reactivity

DTH reaction is the basis of the TST, which is used primarily for the detection of *M. tuberculosis* infection in persons without symptoms. The cellular mechanisms responsible for TST reactivity are related mainly to previously sensitized CD4+ T lymphocytes, which are attracted to the skin-test site. There, they proliferate and produce cytokines. While DTH is associated with protective immunity (TST-positive persons being less susceptible to a new *M. tuberculosis* infection than TST-negative persons), it does not guarantee protection against reactivation. In fact, cases of active tuberculosis are often accompanied by strongly positive skin-test reactions.

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Granuloma Formation

With the development of specific immunity and the accumulation of large numbers of activated macrophages at the site of the primary lesion tubercles are formed. These lesions consist of accumulations of lymphocytes and activated macrophages that evolve toward epithelioid and giant cell morphologies. Initially, the tissue-damaging response can limit mycobacterial growth within macrophages. Although *M. tuberculosis* can survive, its growth is inhibited within this necrotic environment by low oxygen tension and low pH. At this point, some lesions may heal by fibrosis, with subsequent calcification, whereas inflammation and necrosis occur in other lesions.

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The hallmarks are the presence of (1) granulomas (collections of activated blood and tissue-derived macrophages termed epithelioid histiocytes surrounded by a rim of lymphocytes), and (2) caseous necrosis (foci of necrosis and softening at the center of a granuloma). Within the region of caseous necrosis, the contents can liquefy and slough, leaving behind a cavity, another hallmark of tuberculosis. Other features of the granulomas include multinucleated giant cells

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Primary tuberculosis

Clinical illness directly following infection is classified as *primary tuberculosis* and is common among children and among immunocompromised persons. Although primary tuberculosis may be severe and disseminated, it is not generally associated with high-level transmissibility. When infection is acquired later in life, the chance is greater that the mature immune system will contain it at least temporarily. The majority of infected individuals who ultimately develop primary tuberculosis do so within the first year or two after infection. So children who develop disease usually do so within two years following exposure and infection. Most do not develop disease in childhood but may do so later in life. Dormant bacilli, however, may persist for years before reactivating to produce *secondary* (or *postprimary*) *tuberculosis*, which, because of frequent cavitation, is more often infectious than is primary disease. Overall, it is estimated that up to 10% of infected persons will eventually develop active tuberculosis in their lifetime. The risk is much higher among HIV-infected persons. Reinfection of a previously infected individual, which is common in areas with high rates of tuberculosis transmission, may also favor the development of disease. Molecular typing and comparison of strains of *M. tuberculosis* suggested that up to one-third of cases of active tuberculosis were due to recent transmission rather than to reactivation of latent

infection. In the majority of cases, the lesion heals spontaneously and may later be evident as a small calcified nodule (*Ghon lesion*).

Although healing frequently takes place, immunocompromised persons (e.g., patients with HIV infection) may develop miliary tuberculosis and/or tuberculous meningitis.

Postprimary Disease

Also called *adult-type*, *reactivation*, or *secondary tuberculosis*, postprimary disease results from endogenous reactivation of latent infection and is usually localized to the apical and posterior segments of the upper lobes, where the substantially higher mean oxygen tension (compared with that in the lower zones) favors mycobacterial growth. In addition, the superior segments of the lower lobes are frequently involved. The extent of lung parenchymal involvement varies greatly, from small infiltrates to extensive cavitory disease. While up to one-third of untreated patients develop severe pulmonary tuberculosis within a few weeks or months after onset (the classical "galloping consumption" of the past), others undergo a process of spontaneous remission or proceed along a chronic, progressively debilitating course ("consumption"). Individuals with such chronic disease continue to discharge tubercle bacilli into the environment. Most patients respond to treatment decreasing cough, weight gain, and a general improvement in well-being within several weeks.