

Etiology and Transmission of Tuberculosis

2

Tuberculosis (TB) was once commonly called ‘consumption’ because of the wasting patients suffered. Its former medical name ‘phthisis’ also referred to the progressive wasting or consumptive condition of patients with the disease. Its current name refers instead to a histological feature of the disease: the characteristic presence of nodular lesions, or “tubercles,” in the early stages of the disease.

The infectious nature of TB and the agent responsible for its transmission from person to person have been known for over a hundred years: in 1882, the German scientist Robert Koch identified a species of bacteria, *Mycobacterium tuberculosis* (*M.b.* or tubercle bacilli), as the cause of TB (169).¹ Despite this single underlying cause, clinical manifestations of the disease vary from person to person and the ways in which the body controls the infection or allows it to progress to a destructive disease state are still not adequately understood. Furthermore, concurrent human immunodeficiency virus (HIV) infection appears to impair some of the critical immune processes involved in preventing tuberculous infection from progressing to disease, creating a somewhat different clinical course for individuals who are dually infected. Infants and young children generally manifest tuberculous infection and disease differently from adults, but have many of the characteristics of TB in HIV-infected adults.

This chapter provides background information about TB transmission and disease processes relevant to topics covered in

¹Other types of mycobacteria can cause tuberculosis in humans, but are not significant contributors to the disease in the United States. Earlier this century, *M. bovis*, which causes TB in cattle, was transmitted to human beings through unpasteurized milk and respiratory exposure to infected cattle, but now accounts for less than 1 percent of human TB cases in North America (347).



other chapters of this report. The factors involved in transmitting tuberculous infection and in developing active disease are summarized first, followed by a brief description of the clinical course of the disease in immunocompetent and immunocompromised individuals and in children.

TRANSMISSION AND INFECTIVITY

TB has two general stages relevant to its transmission and infectivity: tuberculous infection (sometimes also called “latent TB”) and active tuberculosis. As used in this report and in most of the medical literature, TB refers primarily to the active disease. Although infection with tubercle bacilli is necessary to develop TB, the majority (90 percent) of immunocompetent adults with tuberculous infection do not develop TB. The only evidence of their infection may be a positive tuberculin skin test (see chapter 4). Children and immunocompromised individuals with tuberculous infection carry a greater risk for developing active TB (see below).

Individuals with tuberculous infection are asymptomatic and not contagious to others, whereas individuals with active pulmonary disease may be symptomatic and contagious—particularly if they are untreated or inadequately treated and if the disease is manifested in the lungs (or, rarely, in the larynx). Regarding risk of transmission, the critical difference between the two types is the ability to expel (e.g., through coughing, singing, speaking, or sneezing) airborne particles containing viable tubercle bacilli.

As airborne infections go, TB is not considered the most contagious; certain airborne viral infections, such as measles and varicella (chicken pox), are more readily transmitted (66,204). However, because TB can be transmitted through casual contact (breathing) and it can be debilitating or even fatal if untreated (or untreatable, as in some cases of multidrug-resistant TB (MDR-TB)), the public’s perception of the actual risk of TB contagion has generally been magnified.

Health departments and TB centers report increased demand for tuberculin skin testing among very low risk individuals or the “worried-well” (129,243). A recent editorial in the *Washington Post* described TB as a highly contagious, deadly disease that “you can catch from the person next to you in a movie theater or classroom” (49).

According to available data, both from decades ago and the present, a single, casual contact with an infectious person in a public place (such as a subway or movie theater) is unlikely to lead to tuberculous infection, although the risk is not zero; there is a possibility, albeit remote, that inhalation of just one infectious particle containing *M.tb.* could be enough to produce infection in some cases (31). In practical terms, however, much more than a single airborne bacillus is needed to cause infection. A number of factors (outlined below) occurring simultaneously are considered critical in determining the likelihood of transmitting tubercle bacilli, of developing the infection, and of ultimately developing TB. Depending on the mix of factors in any given situation, the risk may be significant or insignificant (274).

Factors Influencing the Probability of Acquiring Tuberculous Infection

Most of the factors that determine the risk of acquiring tuberculous infection are environmental. By contrast, the risk of developing active TB after tuberculous infection is considered to be largely an individual characteristic, determined by immunologic status and other physiologic factors (described below). The main factors in determining whether the initial tuberculous infection is likely to occur are listed below:

- Probability of coming into contact with someone with infectious TB.
- Closeness or intimacy of that contact.
- Duration of contact.
- Number of viable bacilli present in the air.
- Susceptibility of the uninfected individual.

9 Environmental conditions (e.g., volume of airspace, ventilation with outside air, relative humidity, presence of sunlight).

Crowding, particularly in living quarters, increases both the probability of coming into contact with an infectious individual if one is present and the closeness of that contact (66). Various types of institutional residences (e.g., nursing homes, hospitals, prisons, jails, and homeless shelters) can provide circumstances conducive to the transmission of TB. Health care workers (HCWS) are necessarily at increased risk of coming into contact with infectious patients. Performance of certain cough-inducing medical procedures, such as, bronchoscopy and administration of aerosolized pentamidine, on patients with infectious TB can increase HCWS' risk of exposure to airborne tubercle bacilli (52).

Infection occurs at the point in time when an infectious particle is inhaled. However, the likelihood of inhaling that particle is dependent on the concentration of such particles in the air and the length of time spent breathing that air; the greater the exposure, the greater the likelihood that infection will result. Frequent or prolonged exposure to an infectious source case (e.g., months) is usually necessary for transmission to occur (113). According to data derived in the mid-1980s, on average, less than 30 percent of household members become infected while living with an infectious source case, but the risk is highly variable (27,249). Under extraordinary circumstances (when the concentration of infectious particles in the air is much higher than usual), exposures as brief as 2 hours have reportedly led to infection (8).

In any given situation, the infectiousness of the source case determines whether any period of exposure could result in transmission. Individuals with untreated active pulmonary or laryngeal

TB,² an advanced stage of disease, evidence of tubercle bacilli in sputum samples, and who cough frequently without covering the mouth are considered to be prime sources of infection (180).

Those not posing a risk of infection to others include individuals with tuberculous infection (rather than active disease), individuals with active TB who have been receiving adequate treatment long enough to render them noninfectious, and individuals with extrapulmonary TB without any lung or airway involvement. Adequate antimicrobial treatment can quickly reduce and eventually eliminate the infectiousness of individuals with drug-susceptible TB (160,253). Although the exact period of time required for this change varies from one patient to another and cannot be predicted precisely, research suggests it is about 6 months or longer (211). Patients with drug-resistant TB can, in some cases, be treated effectively, although the period of infectiousness may be prolonged until an adequate combination of appropriate drugs is determined. Those with MDR-TB for whom available drugs are ineffective may remain persistently infectious to others.

There is no evidence that untreated MDR-TB is more contagious than untreated drug-susceptible TB (291). However, because of delays in diagnosing resistance patterns and initiating adequate treatment, patients with MDR-TB are more likely to remain infectious for longer periods, thereby increasing their potential to infect others (see chapter 5). In several recent outbreaks of MDR-TB in hospitals, HCWS who were exposed to undiagnosed, persistently infectious patients with MDR-TB were more likely to have shown a tuberculin skin test conversion, indicating recent tuberculous infection, than HCWS without such exposure (350). There is also no evidence that HIV-infected patients with pulmo-

² Transmission of TB from patients with extrapulmonary TB (TB in tissue other than the lung) is unusual but has been reported, e.g., through manipulation of lesions or processing of lesions in the hospital or laboratory. Transmission of TB has been traced to patients with skin ulcers, abscesses, or other open lesions containing large numbers of tubercle bacilli that may be released into the air during medical procedures such as surgical draining or wound care (106,144,310).

nary TB are more or less infectious than non-HIV-infected patients with pulmonary TB (50).

Little is known about specific host factors that influence susceptibility to tuberculous infection. At present, there is no firm evidence that HIV-infected individuals are more likely to acquire tuberculous infection, although the frequency and rapidity with which HIV-infected individuals developed active TB in several recent outbreaks raises the possibility of heightened susceptibility in some populations with HIV (69,77). Individuals who are already infected with tubercle bacilli are generally considered to be partially resistant to further infection, but reinfection has been documented (207).

The concentration of infectious particles in the air also determines the likelihood of infection. Normal indoor air currents keep such particles (referred to as “droplet nuclei”) airborne for long periods of time and disperse them throughout a room or a building (7,252). Until they dehydrate naturally, they remain infectious. These particles remain suspended until they are removed or diluted by ventilation or air filtration, or possibly inactivated by ultraviolet (*UV*) irradiation (see chapter 4). The use of these and other infection control measures can reduce the risk of transmission in the presence of infectious individuals (359).

Factors Influencing the Development of Active TB After Infection

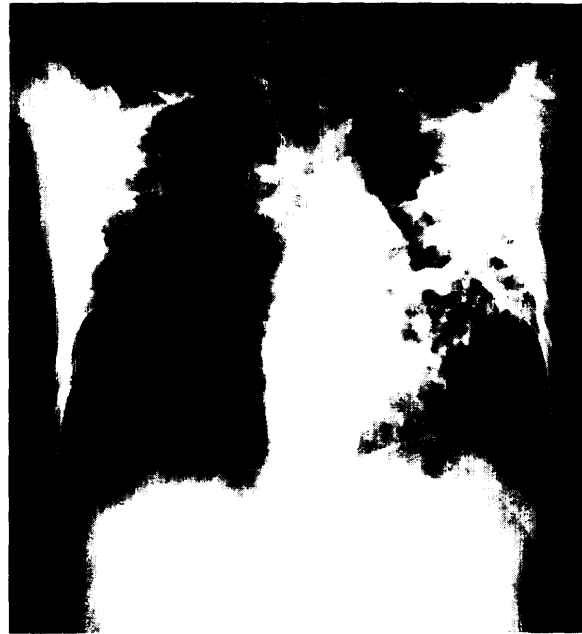
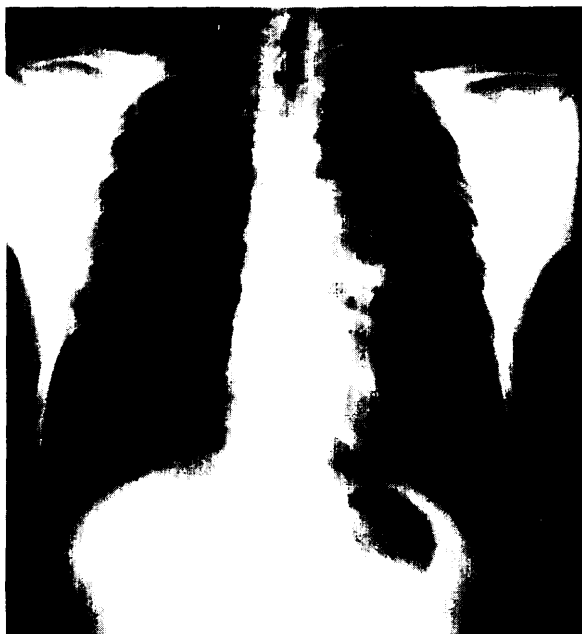
The risk of developing active TB is highest shortly after tuberculous infection occurs and declines thereafter. Accordingly, the risk of disease is highest in the most recently infected individuals, who can be identified through contact investigation. The observed incidence of TB among those with positive tuberculin skin tests differs widely among populations studied, for reasons that are still unclear (66). Some evidence also indicates that the risk of infection is higher among those exposed to the most infectious cases

and those with the closest contact to such cases (66).

Ninety percent of adults with tuberculous infection do not develop active TB, apparently due to the ability of their immune systems to hold the infection in check. Impairment of immune function (as in acquired immune deficiency syndrome (AIDS), by treatment with glucocorticoid or immunosuppressive drugs, malnutrition, various infections, or chronic conditions such as asthma and emphysema) tips the balance in favor of development of active TB among those with tuberculous infection (278,378). Whereas only 3 to 5 percent of immunocompetent individuals who acquire new tuberculous infection are thought to develop active TB within the first year after infection (97), the percent of HIV-infected individuals who acquire new infection and go on to develop active TB within the first year is estimated to be far greater (77). In a recent report, approximately one-third of the HIV-infected individuals sharing a residential facility who became infected with tubercle bacilli developed TB within 120 days (69). Most cases of TB among HIV-infected individuals are believed, however, to result from reactivation of latent tuberculous infection, rather than progression of recently acquired infection (278), although recent data from New York City indicates that the latter is increasing.

DEVELOPMENT OF TUBERCULOSIS AND ITS CLINICAL MANIFESTATIONS

Active TB manifests in a variety of ways, depending in part on the primary site of infection in the body. Pulmonary TB is the most common form of the disease, leading to cavity formation and progressive destruction of lung tissue. Pathologic and inflammatory processes associated with the disease produce weakness, fever, chest pain, cough, and when a small blood vessel is eroded, bloody sputum (31).



AMERICAN LUNG ASSOCIATION

TB, caused by an airborne bacillus, primarily affects the lungs. If untreated, it can destroy lung tissue and spread to other parts of the body and to the outside air. Pictured above are x-rays of a slightly diseased lung (left) and an extremely diseased lung (right).

The disease can affect other sites in the body (“extrapulmonary TB”), although only pulmonary and laryngeal TB are contagious through the airborne route. Various forms of extrapulmonary TB are more likely to occur in HIV-infected individuals and in children. These disseminated forms of the disease can result in the formation of small miliary (seed-like) lesions or life-threatening meningitis (inflammation of the membranes surrounding the brain and spinal cord). Such dissemination begins in the lung, which is the initial site of infection, and travels through the bloodstream to other parts of the body or through lymphatic to regional lymph nodes. Some organs take up and allow the multiplication of bacilli more readily than others, e.g., upper lung, kidneys, bone, and brain. Long-term damage can result, even in cured cases of TB, including impaired breathing due to lung damage, mental impairment from meningitis, and spinal deformity and leg weakness due to vertebral involvement (152),

Immune Responses to Tuberculous Infection and Disease

The cellular immune system is believed to play a central role in the development of TB in the body. While some of the relevant immunologic processes have been identified, fundamental questions remain concerning the interplay and regulation of immunologic forces that both inhibit the progress of the disease and actually contribute to the destructive disease process itself (31,74).

Airborne particles containing tubercle bacilli that are inhaled (and that manage to reach the lower parts of the lung) are initially engulfed by macrophages (a type of scavenger cell) in the alveoli (terminal air sacs in the lung). If the bacilli are not destroyed by the alveolar macrophages, the bacilli multiply, killing the cell and attracting nonactivated macrophages from the bloodstream. In these new macrophages, the bacilli multiply logarithmically. Antigenic substances present within or secreted by tubercle bacilli stimulate T-lymphocytes (CD4 cells) to produce chemical

substances (lymphokines), which activate these new macrophages, enabling them to destroy or inhibit the bacilli. The process by which macrophages are armed to destroy the bacilli they ingest is called cell-mediated immunity (CMI) and forms one part of the body's immune response to TB.

Another interrelated immune process that occurs in response to tuberculous infection is called delayed-type hypersensitivity (DTH), an inflammatory response that destroys bacilli-laden inactivated macrophages. An overabundance of DTH is blamed for most of tissue damage characteristic of pulmonary tuberculosis: caseous necrosis (death of tissues, leading to caseating granulomas and liquefaction of solid caseous tissue, producing cavities in the tissue) (71,72,73,74). Within the liquefied caseum, tubercle bacilli multiply outside of the cells, reaching tremendous numbers. Host resistance may be overwhelmed and the bacilli may develop resistance to antimicrobial drugs. Liquefaction and cavity formation allow the disease to become contagious, because the bacilli spread via the airways to other parts of the body and to the outside air.

Clinical Course in HIV-Seropositive Individuals

HIV-related immunodeficiency impairs both parts (DTH and CMI) of the immunologic response to tuberculous infection, leaving individuals with HIV more vulnerable to the development of clinical TB. Recent evidence suggests that TB tends to occur early in the course of HIV infection (321) often as the first overt manifestation of HIV infection. Infection with (non-contagious) non

tuberculous mycobacteria, e.g., *Mycobacterium avium* complex, occurs frequently in individuals with AIDS, often leading to serious complications and earlier death. The surveillance definition of AIDS was recently expanded to include TB as an AIDS-defining condition among those with HIV infection (364).

The clinical course of TB in individuals with AIDS is dramatically different from TB in immunocompetent adults. Pulmonary TB in individuals with AIDS resembles that of TB in infants. The bacilli disseminate (via the bloodstream and lymphatic), producing extrapulmonary lesions, including tuberculous lymphadenitis or meningitis. Characteristic features of TB in individuals with HIV infection include a high prevalence of anergy to tuberculin skin testing (see chapter 4), atypical x-ray presentation of the disease in the lung, and frequency of extrapulmonary disease (162).

Clinical Course in Children

Infants and young children also manifest TB differently from immunocompetent adults, but the specific reasons for this are not yet clearly defined. Infants and young children can or are more likely to develop severe, life-threatening TB as an immediate complication of the primary infection, without the long latent period common in adults. They are more likely to develop extrapulmonary forms of the disease, especially lymphadenitis, osteotuberculosis, and meningitis (25 1,301). Active TB in such children typically is manifested by caseous lesions that do not liquefy or cavitate, so they are less likely to transmit the disease to others.