drugs amikacin, kanamycin, and capreomycin). Up to 10% of the MDR-TB cases worldwide may actually be XDR-TB, but the vast majority of XDR-TB cases remain undiagnosed because reliable methods for drug susceptibility testing are lacking and laboratory capacity is limited. Lately, cases deemed resistant to all anti-TB drugs have been reported from countries such as India, Italy, and Iran; however, this information must be interpreted with caution because drug susceptibility testing for several second-line drugs is neither accurate nor reproducible.

FROM EXPOSURE TO INFECTION

M. tuberculosis is most commonly transmitted from a person with infectious pulmonary TB by droplet nuclei, which are aerosolized by coughing, sneezing, or speaking. The tiny droplets dry rapidly; the smallest (<5–10 μm 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. The probability of contact with a person who has an infectious form of TB, 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 TB patients whose sputum contains AFB visible by microscopy (sputum smear–positive cases) are the most likely to transmit the infection. The most infectious patients have cavitary pulmonary disease or, much less commonly, laryngeal TB and produce sputum containing as many as 10^5–10^7 AFB/mL. Patients with sputum smear–negative/culture-positive TB are less infectious, although they have been responsible for up to 20% of transmission in some studies in the United States. Those with culture-negative pulmonary TB and extrapulmonary TB are essentially noninfectious. Because persons with both HIV infection and TB are less likely to have cavitations, they may be less infectious than persons without HIV co-infection. Crowding in poorly ventilated rooms is one of the most important factors in the transmission of tubercle bacilli because it increases the intensity of contact with a case.

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 generally estimated that, in high-prevalence settings, up to 20 contacts may be infected by each AFB-positive case before the index case is diagnosed.

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 the level at which the individual's cell-mediated immunity (CMI) is functioning. Clinical illness directly following infection is classified as *primary TB* and is common among children in the first few years of life and among immunocompromised persons. Although primary TB may be severe and disseminated, it generally is not 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. Bacilli, however, may persist for years before reactivating to produce *secondary* (or *postprimary*) *TB*, 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 TB in their lifetime—half of them during the first 18 months after infection. The risk is much higher among HIV-infected persons. Reinfection of a previously infected individual, which is common in areas with high rates of TB transmission, may also favor the development of disease. At the height of the TB resurgence in the United States in the early 1990s, molecular typing and comparison of strains of *M. tuberculosis* suggested that up to one-third of cases of active TB in some inner-city communities were due to recent transmission rather than to reactivation of old latent infection. Age is an important determinant of the risk of disease after infection. Among infected persons, the incidence of TB is highest during late adolescence and early adulthood; the reasons are unclear. The incidence among women peaks at 25–34 years of age. In this age group, rates among women may be higher than those among men, whereas at older ages the opposite is true. The risk increases in the elderly, possibly because of waning immunity and comorbidity.

TABLE 202-1 RISK FACTORS FOR ACTIVE TUBERCULOSIS IN PERSONS WHO HAVE BEEN INFECTED WITH TUBERCLE BACILLI

Factor	Relative Risk/Odds[a]
Recent infection (<1 year)	12.9
Fibrotic lesions (spontaneously healed)	2–20
Comorbidities and iatrogenic causes	
HIV infection	21–>30
Silicosis	30
Chronic renal failure/hemodialysis	10–25
Diabetes	2–4
IV drug use	10–30
Immunosuppressive treatment	10
Tumor necrosis factor α inhibitors	4–5
Gastrectomy	2–5
Jejunoileal bypass	30–60
Posttransplantation period (renal, cardiac)	20–70
Tobacco smoking	2–3
Malnutrition and severe underweight	2

[a]Old infection = 1.

A variety of diseases and conditions favor the development of active TB (Table 202-1). In absolute terms, the most potent risk factor for TB among infected individuals is clearly HIV co-infection, which suppresses cellular immunity. The risk that LTBI will proceed to active disease is directly related to the patient's degree of immunosuppression. In a study of HIV-infected, tuberculin skin test (TST)–positive persons, this risk varied from 2.6 to 13.3 cases/100 person-years and increased as the CD4+ T cell count decreased.

NATURAL HISTORY OF DISEASE

Studies conducted in various countries before the advent of chemotherapy showed that untreated TB is often fatal. About one-third of patients died within 1 year after diagnosis, and more than 50% died within 5 years. The 5-year mortality rate among sputum smear–positive cases was 65%. Of the survivors at 5 years, ~60% had undergone spontaneous remission, while the remainder were still excreting tubercle bacilli. With effective, timely, and proper chemotherapy, patients have a very high chance of being cured. However, improper use of anti-TB drugs, while reducing mortality rates, may also result in large numbers of chronic infectious cases, often with drug-resistant bacilli.

PATHOGENESIS AND IMMUNITY

INFECTION AND MACROPHAGE INVASION

The interaction of *M. tuberculosis* with the human host begins when droplet nuclei containing viable microorganisms propelled into the air by infectious patients are inhaled by a close bystander. Although the majority of inhaled bacilli are trapped in the upper airways and expelled by ciliated mucosal cells, a fraction (usually <10%) reach the alveoli, a unique immunoregulatory environment. There, alveolar macrophages that have not yet been activated (prototypic alternatively activated macrophages) phagocytose the bacilli. Adhesion of mycobacteria to macrophages results largely from binding of the bacterial cell wall to a variety of macrophage cell-surface molecules, including complement receptors, the mannose receptor, the immunoglobulin GFcγ receptor, and type A scavenger receptors. Phagocytosis is enhanced by complement activation leading to opsonization of bacilli with C3 activation products such as C3b and C3bi. (Bacilli are resistant to complement-mediated lysis.) Binding of certain receptors, such as the mannose receptor, regulates