Chapter 12
Tuberculosis, Epidemiology of

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Glossary

Acquired immunodeficiency syndrome (AIDS)	Clinical syndrome caused by the Human Immunodeficiency Virus (HIV). Its pathogenesis is related to a qualitative and quantitative impairment of the immune system, particularly a reduction of the CD4+cell count (surrogate marker of the disease). After an average of 10 years if untreated, HIV + individuals can develop opportunistic diseases (i.e., infections and neoplasias rarely detected in immunocompetent subjects). The natural history of the disease can be dramatically modified with administration of combination therapy composed of at least three antiretroviral (ARV) drugs.
Human immunodeficiency virus (HIV)	Virus that causes Acquired Immunodeficiency Syndrome (AIDS). It belongs to *Retroviridae* family and was discovered in 1983 by Luc Montagnier and Robert Gallo. It is transmitted mainly through

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	sexual intercourse, exchange of contaminated syringes among intravenous drug users, and contaminated blood transfusion. HIV-1 is the type most frequently detected worldwide.
Incidence	Rate describing the number of new cases of disease occurring within a unit of time in a defined cohort at risk of disease (expressed in cases per 100,000 population per year).
Latent tuberculosis infection (LTBI)	Infection caused by *Mycobacterium tuberculosis* transmitted mainly through the air. Clinical and/or radiological signs of latent tuberculosis infection cannot be detected in the majority of the cases. The infection can be presumptively diagnosed by a positive tuberculin skin testing and/or a positive interferon-γ release assay (IGRA), being able to identify a persistent adaptive immunological reactivity against mycobacterial antigens. In most individuals mycobacteria can be eliminated through chemoprophylaxis. It is estimated that one third of the human population is infected by *Mycobacterium tuberculosis* worldwide.
Mortality	Rate describing the number of deaths from a disease occurring within a unit of time in a defined cohort at risk of death (expressed in deaths per 100,000 population per year).
Mycobacterium tuberculosis	Bacterium that causes tuberculosis, discovered by Robert Koch in 1882. It is genetically closely related to other mycobacteria with which it forms a complex (*Mycobacterium africanum*, frequently detected in Western Africa, and *Mycobacterium bovis*, frequently detected in the past in cows and transmitted to human beings through unpasteurized milk).
Prevalence	Number of cases of disease in a defined population at a specific point in time; it is mainly presented as a relative frequency (i.e., proportion usually expressed per 100,000 population).
Tuberculosis	Infectious disease caused by *Mycobacterium tuberculosis*. It usually involves the lungs (pulmonary tuberculosis) but can also affect other organs (i.e., kidneys, central nervous system, lymph nodes, bones, etc.: extrapulmonary tuberculosis). Pulmonary tuberculosis, which is the most frequent clinical form, can be classified as smear-positive or smear-negative according to the result of the sputum bacteriological examination. The former is a major public

health problem being highly contagious. Only a few individuals develop tuberculosis after a mycobacterial infection, and most of them soon after infection: it is estimated that the lifetime risk is 5–10% in HIV-negatives and 5–15% yearly in HIV-positives.

Definition of the Subject and Its Importance

Tuberculosis is a disease caused by bacilli belonging to the *Mycobacterium tuberculosis* complex, which includes the species *Mycobacterium tuberculosis* (most frequently detected in human beings), *Mycobacterium africanum*, and *Mycobacterium bovis*. It is primarily an airborne disease. Mycobacteria enter into the human airways through the inhalation of droplet nuclei, i.e., particles containing mycobacteria aerosolized by coughing, sneezing, talking, or singing. Other rare, recognized ways of transmission are the ingestion of cow milk contaminated by *Mycobacterium bovis* (frequent route of transmission in the past), cutaneous inoculation in laboratory workers and pathologists, and sexual intercourse [1].

Tuberculosis is a major public health issue worldwide. Together with HIV/AIDS, it is one of the main infectious killers of individuals in their productive years in low-income countries [2]. However, tuberculosis is a highly curable disease if diagnosed and treated with combination chemotherapy. As a result of the global implementation of the World Health Organization's (WHO) STOP TB Strategy, during the period 1995–2009, 41 million tuberculosis patients were successfully treated and 6 million deaths averted compared to what would have happened if current standards were not implemented [3, 4].

Introduction

The epidemiology of tuberculosis studies the dynamics and interactions between *Mycobacterium tuberculosis* and human beings in a specific environment. Furthermore, it qualitatively and quantitatively evaluates all the covariates (for instance, the administration of antituberculosis drugs) that could interfere with the outcomes of the natural history of this interaction (i.e., exposure, infection, disease, and death) [5].

Basic and Descriptive Epidemiology of Tuberculosis

The global burden of tuberculosis is measured using epidemiological indicators (incidence, prevalence, mortality, and case fatality). Estimates of these indicators

are computed yearly by the World Health Organization which collates information obtained from surveillance systems (notification system and mortality registries), special epidemiological studies (surveys of tuberculosis prevalence and in-depth analyses of surveillance data), and experts' opinion [6].

Epidemiological Indicators

Tuberculosis incidence: number of new cases of tuberculosis occurring within a specific time period (usually 1 year) in a defined cohort. It is usually presented as a rate per 100,000 inhabitants and describes the probability of developing tuberculosis in a specific time period [6, 7].

Tuberculosis prevalence: number of cases of tuberculosis in a defined population at a specific point in time. It is presented as an absolute or a relative (usually per 100,000 inhabitants) frequency and can be considered the product of the incidence of tuberculosis by the duration of the disease. This indicator assesses the global, national, regional, and local burden of tuberculosis.

Tuberculosis mortality: number of deaths from tuberculosis occurring within a specific time period (usually 1 year) in a cohort of individuals with tuberculosis disease. It is often presented as a rate per 100,000 people and describes the probability of dying from tuberculosis in a specific time period.

Tuberculosis case fatality: number of deaths from tuberculosis occurring within a specific time period (usually 1 year) in a defined cohort of individuals with tuberculosis. It is presented as a percentage.

Incidence of sputum smear-positive pulmonary tuberculosis cases: number of new sputum smear-positive cases of pulmonary tuberculosis occurring within a specific time period (usually 1 year) in a defined cohort. It is usually presented as a rate per 100,000 population. It identifies the most contagious tuberculosis cohort, that is, the most important source of infection.

Incidence of sputum culture-positive pulmonary tuberculosis cases: number of new sputum culture-positive cases of pulmonary tuberculosis occurring within a specific time period (usually 1 year) in a defined cohort. It is usually presented as a rate per 100,000 population.

Etiologic Epidemiology of Tuberculosis

Natural History

The dynamics of the probabilistic model of tuberculosis are complex and the associated covariates, as well as their quantitative effects, are not always known. The potential interaction between a human being and the strains of *Mycobacterium tuberculosis* could result in the following non-deterministic outcomes: subclinical infection, pulmonary and/or extrapulmonary disease, and death. The incidence of

the above mentioned outcomes is regulated by the occurrence and the additive and/or the synergistic combination of multiple risk factors. Several environmental, bacterial, and human risk factors have been identified. Some of them could play an important role since the first crucial event, that is, the exposure to a source of mycobacteria [1, 5, 8].

Exposure

A critical exposure to transmission of mycobacteria from a contagious patient to a susceptible individual could be a close physical contact or permanence in a small room with limited ventilation [5].

The most important variable significantly increasing the likelihood of exposure to a source of *Mycobacterium tuberculosis* is the prevalence of contagious patients in a specific setting. This is estimated as the product of the incidence of infectious individuals by the duration of their infectiousness. The number of incident cases greatly varies between settings and depends on numerous factors.

Duration of infectiousness is strictly related to the capacity of the health system for early detection and adequate treatment of an index case [5, 8]. After a microbiological diagnosis, which should include drug-sensitivity testing, proper anti-tuberculosis treatment should be started without delay [3]. Correct drug combinations and dosages should be used to avoid sub-optimal anti-bacterial activity [5, 9, 10]. Strict clinical follow-up of patients in nosocomial or community settings should be undertaken to ensure adherence to anti-tuberculosis medications for the full duration of treatment. Compliance could be compromised by the long duration of therapy and/or the emergence of adverse events. The capacity of a patient to adhere to antituberculosis therapy depends on factors related to the health system, socioeconomic conditions of the individual, type of therapy, and the disease and patient's characteristics. The concept of early case detection and immediate treatment is supported by the evidence that on average 30–40% of the close contacts of a sputum smear-positive pulmonary case are estimated to be infected at the time of diagnosis. The public health consequences of a diagnostic and/or therapeutic delay are dramatic [5].

It is clear that quality and quantity of human relations modify the risk of critical exposures and, consequently, the risk of acquiring the infection [5]. In particular, population density is a critical element: the higher the population density, the greater the risk of interactions. High population density can be experienced in urban areas or in household crowding associated with poor housing [5, 8]. Climatic condition is an additional environmental variable that plays a relevant role in the likelihood of exposure. In cold climates, people tend to spend more time in indoor activities, increasing the risk of exposure because of the higher chances of close contact. On the other side, in warm climates people tend to spend more time outdoors, diminishing frequency and duration of case–contact interactions per unit of space. At the same time natural indoor ventilation and the effect of the solar ultraviolet rays that kill mycobacteria contribute to control the spreading of infection [5].

Other relevant non-environmental modifiers of the risk of exposure are sex and age. In several low-income countries and social groups, males and females have different opportunities of social contact and therefore a different risk of exposure. For instance, in some countries females are excluded from public activities and spend most of their time indoors. The median age of tuberculosis cases, and consequently of contagious sources of infection, is considerably different between low- and high-income countries, with elderly people representing the majority of the autochthonous patients in industrialized areas and young adults counting for the largest proportion of patients in low-income countries [5, 11–13].

Infection

The risk of infection by *Mycobacterium tuberculosis* is directly associated to the probability of exposure to infectious particles produced by a tuberculosis patient through coughing, sneezing, talking, or singing [1, 5, 8, 14]. Such risk is related to the concentration of contagious droplet nuclei containing mycobacteria and to the time of exposure [1, 5].

Infectious particles must be suspended in the air in order to be inhaled by a contact of a tuberculosis patient. The speed of falling to the ground is directly correlated to the square of their diameter. However, the tendency of liquid particles to evaporate and, consequently, to reduce their diameter, increases the speed of their descent. The effect of evaporation on very large liquid particles is less important. Furthermore, humidity and temperature could influence the evaporation: high humidity hinders the evaporation of infectious particles and, indirectly, increases the speed of dropping to the ground. Overall, the effect of the diameter of the particle is more influential than that of humidity [5].

Droplet nuclei should be 1–5 μm large to be inhaled and retained in the pulmonary alveoli. It has been demonstrated that a diameter >5 μm increases the probability of being entrapped in the upper airways through the continuous movement of both the vibrissae and the muco-ciliary system. On the other hand, contagious droplets whose diameter is <1 μm can arrive to the alveolar spaces, but the probability of retention in the peripheral pulmonary alveoli is very low [1, 5].

A crucial variable that can dramatically change the air density of contagious droplet nuclei in a specific indoor environment (for instance, in a nosocomial setting) is the natural, mixed-mode, or mechanical ventilation [15]. Several authors described transmission of mycobacterial strains in health-care settings with flawed or missing ventilation systems both in low- and high-income countries. The typology of the ventilation system should be chosen taking into account several variables: the building structure, outdoor climatic conditions and air quality, purchase and maintenance costs, and national and local regulations. However, modifiers should not alter the main principle of a ventilation system that must promote an airflow direction from the infectious source to the air exhaust area [5, 15]. Ventilation rate can be evaluated measuring the volume of the space (i.e., air changes per hour – ACH) or the number of individuals in a space (i.e., liters/second/

person): every individual should have a definite supply of fresh air to dilute the concentration of mycobacteria. The World Health Organization recommends more than 11 air changes per hour for an isolation room of 24 m^3 (i.e., at least 80 l/s/person). Natural ventilation may be improved by increasing the size of windows and positioning them on opposite walls. Well-designed fans can improve the airflow direction when natural ventilation rates are not adequate (mixed-mode ventilation). However, continuous maintenance of those fans is essential. In some circumstances it may be necessary to use upper room or shielded ultraviolet germicidal irradiation (UVGI) devices. In settings with frequent climatic changes or high risk of transmission of multi-drug resistant mycobacterial strains, UVGI devices could be helpful in addition to a mechanical ventilation system.

Several measures should be implemented in household settings to reduce the risk of transmission: improvement of natural ventilation, education on cough etiquette, and respiratory hygiene. Furthermore, a tuberculosis patient should sleep isolated in a well-ventilated room or, if his/her clinical conditions are favorable, should spend as much time as possible outdoors.

Personal protective equipment may considerably reduce the possibility of infection, especially when the ventilation system is weak. In this regard only high-efficiency particulate air-filter respirators filtering out droplet nuclei sized 1–5 μm can be protective. Particulate respirators meeting or exceeding the N95 standards set by the United States Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH) or the CE certified FFP2 standards are recommended for health-care workers (particularly during the management of multi-drug resistant tuberculosis cases and aerosol-generating procedures) and visitors. Health education on the importance of respirators in communities at risk should be carried out in order to avoid stigma, and continuous training of health-care providers on the correct use (fit testing) and on indications of respirators should be organized. Surgical masks can be worn by contacts of a patient but do not protect from exposure [15]. The probability of being infected can be decreased if the source of droplet nuclei is isolated or if both mouth and nose are covered.

The most efficient measure to stop transmission is to rapidly detect and adequately treat a tuberculosis case [3, 5, 8, 15]. Patients are normally not infectious after 2–3 weeks of effective treatment. However, not all tuberculosis patients are equally infectious and there is a correlation between the number of mycobacteria in a milliliter (ml) of sputum and the efficiency of transmission. At least 5,000 mycobacteria in 1 ml of sputum are necessary to classify a sputum smear examination as positive.

Several studies demonstrated that sputum smear-positive patients are significantly more contagious than those who are sputum smear-negative and culture-positive. Furthermore, the latter are not much more infectious than tuberculosis patients who have a negative smear and culture [5, 8].

Although sputum smear-positive patients are the most contagious population, those who are sputum smear-negative need equal attention, as 17% of mycobacterial transmissions, in some industrialized settings, are due to this group of patients [5].

According to estimates computed in the pre-antibiotic era and used to model the tuberculosis epidemic, an undiagnosed sputum smear-positive patient can infect 10–12 contacts annually. Since after 2 years, the probability of death or spontaneous conversion to sputum smear-negativity is high, the average number of contacts infected by a single smear-positive case was estimated to be 20–24 [5, 8, 16]. The delay of diagnosis and/or of treatment of just 2–3 months could result in infection of several contacts [5].

Numerous factors determine patient's delay to diagnosis: these include alcohol or substance abuse, low income, difficult access to health care facilities, disabilities, and beliefs about tuberculosis. On the other hand, other concomitant pulmonary diseases, sputum smear-negative or extra-pulmonary tuberculosis, inexperience of health care workers, weak health care infrastructure, and absence of respiratory symptoms are all factors associated with healthcare delay [17, 18].

The annual burden of the most relevant source of tuberculosis infections is assessed through an epidemiological indicator: the incidence of sputum smear-positive pulmonary tuberculosis cases. This describes the number of new sputum smear-positive cases of pulmonary tuberculosis occurring within 1 year in a defined population at risk of tuberculosis [5, 6, 8]. The average annual risk of latent tuberculosis infection is an important epidemiological indicator that assesses the probability of becoming infected with *Mycobacterium tuberculosis* in a period of 1 year [5, 8].

Clinical and/or radiological signs of latent tuberculosis infection cannot be detected in the majority of the cases. However, it can only be presumptively diagnosed through a tuberculin skin testing (TST) and/or an interferon-γ release assay (IGRA), which identifies a persistent adaptive immunological reactivity against mycobacterial antigens [14, 19–22]. The tuberculin skin test, performed with an intradermal injection of purified protein derivative (PPD) obtained from *Mycobacterium tuberculosis* culture filtrate, has been considered as the gold standard diagnostic tool for identifying individuals latently infected with *Mycobacterium tuberculosis*. The main limitation of this technique is the low specificity, due to antigenic similarities between PPD, Bacille Calmette-Guerin (BCG) strains, and nontuberculous mycobacterial strains. Furthermore, its application and interpretation significantly depend on the health worker responsible for the test [14, 19, 22].

Interferon Gamma Release Assays (IGRA), available in two different commercial forms, that is, QuantiFERON-TB Gold In Tube (QFT-IT; Cellestis Ltd., Chadstone, Australia) and T-SPOT.TB (Oxford Immunotec, Abingdon, UK), are tools for the in vitro diagnosis of latent tuberculosis infection. They detect cellular immune reactivity toward *Mycobacterium tuberculosis*–specific antigens (ESAT-6, CFP-10, and TB7.7). As such, contrary to PPD, they can discriminate between people previously immunized with Bacille Calmette-Guerin vaccination or those infected by non-tuberculous mycobacteria from tuberculosis patients [14, 19–22].

The average annual risk of tuberculosis infection can be estimated with direct or indirect methods:

– The direct evaluation assesses the proportion of individuals who convert to tuberculin skin test in a defined period of time. The main limitations are related

to the sample size, which should be large enough in order to obtain an adequate statistical power, and to the boosting phenomenon (an apparent conversion related to repeated tests).
– The indirect evaluation relies on the relationship between the prevalence of tuberculosis infection in a specific time-point and the average annual risks of infection.

The probability of being infected is estimated to be very low in high-income countries (from 0.1% to 0.01%) especially among the young. On the other hand, the prevalence of infection is high in most developing countries, due to ongoing transmission [5, 8]. Overall, one third of the global population is estimated to be infected by *Mycobacterium tuberculosis* [5, 6, 8].

Disease

Active tuberculosis is the outcome of infection with *Mycobacterium tuberculosis* [1, 5, 8, 23]. As for exposure and infection, the likelihood of clinical tuberculosis is strictly dependent on risk factors, the impact of which is not only related to their effect on the pathogenesis of the disease but also to their prevalence in the general population [5, 8].

After the establishment of tuberculosis infection the probability of developing a disease is higher in the first 12–24 months after the entry of *Mycobacterium tuberculosis* into the human body, and decreases as time elapses from the infection. It is generally estimated that the risk of disease is about 5% in the first 1–2 years after infection, and up to 5% in the subsequent years [1, 5, 8]. The age of primary infection is an important determinant of the cumulative risk, as this is the highest in young individuals (from 35% to 50% in children aged less than 15 years and those who are in close contact with a sputum smear-positive patient) [5, 8].

The key pathogenic factor favoring the development of tuberculosis is the quantitative and/or functional deficiency of the innate and/or adaptive immune system, which is responsible for the control of tuberculosis infection [2, 5, 8, 23]. The host cellular and molecular mechanisms triggered by mycobacterial infections are only partially known. After reaching the lower respiratory tract, the mycobacteria grow, partially controlled for the first few weeks by nonspecific immunity. CD4+ lymphocytes producing interferon-γ are recruited after 2 weeks but their number is not sufficient to activate the pool of alveolar macrophages. Their priming in the draining lymph nodes occurs only after the first 7–10 days because mycobacteria are initially phagocytosed by non-motile phagocytic cells. T-cell priming and accumulation could additionally be delayed through the activation of regulatory T lymphocytes. Continuous activation of T lymphocytes is vital to control mycobacteria in the granuloma; nevertheless, several experimental data demonstrated that once exposed to chronic mycobacterial stimulation, T lymphocytes can experience a functional collapse [1, 23]. Numerous medical conditions can modify one or more components of the immune response against *Mycobacterium tuberculosis*, compromising the control of the infection, and, then,

increasing the probability of development of disease [1, 5, 8]. For these reasons and due to its global burden, HIV/AIDS is recognized as the most important risk factor for the development of tuberculosis [1, 2, 5, 8, 24, 25]. Numerous studies demonstrated that the lower the CD4+ lymphocytes counts the higher the risk of developing pulmonary as well as extrapulmonary disease. The qualitative and quantitative role of CD4+ lymphocytes in the adaptive immune response against mycobacteria is crucial, particularly their interaction with macrophages, which need to be activated in order to be effective. The risk of development of tuberculosis disease is 5–15% per year if the mycobacterial infection precedes HIV transmission. On the contrary, such risk could be significantly higher if mycobacterial infection develops in a seriously immunocompromised host. Generally, the probability of developing tuberculosis is 20–37-fold higher in HIV-infected compared to HIV-negative individuals. The relative risk is 20.6 in countries with a generalized HIV epidemic, 26.7 in countries with concentrated epidemics, and 36.7 in low HIV-prevalence countries [1, 2, 5, 8, 26].

Another medical condition that could compromise the immune key players against mycobacterial strains is diabetes mellitus. The estimated prevalence of diabetes is 180 million individuals globally, a figure expected to increase to 360 million by 2030 [5, 27]. The probability of developing tuberculosis is 1.5–8 times higher among individuals with diabetes compared to healthy subjects. No significant differences in terms of risk of disease have been detected between low- and high-income countries [28–32]. Experimental studies showed that hyperglycemic mice have higher mycobacterial loads, impaired production of interferon-γ and interleukin-12 together with an impaired T helper 1 response. Leukocyte bactericidal activity is reduced in diabetic patients compared to healthy individuals. Diabetic patients have an altered chemotaxis and oxidative killing of neutrophils. Furthermore, impaired immunity is frequently associated with other relevant risk factors like chronic renal failure, malnutrition, and pulmonary microangiopathy [28, 33, 34]. Nevertheless, several epidemiological analytical studies assessing the relative risk or the odds ratio of diabetic patients are biased because routine data sources were used, which do not allow controlling for all confounders. The population-attributable risk for diabetes is similar to that of HIV/AIDS; although the relative risk related to HIV/AIDS is highest, ranging from 6.5 to 26 (i.e., 2–9 times higher than the relative risk of diabetes), it is less prevalent than diabetes [28–33, 35].

Chronic renal failure and the hemodialytic treatment increase the risk of developing tuberculosis from 6.9 to 52.5 times compared to the general population [5, 36]. Some epidemiological studies highlight a greater incidence of tuberculosis in the first year of dialysis due to the occurrence of a severe immune depression. It is difficult to understand the role of chronic renal failure because the majority of the studies enrolled principally hemodialytic patients. The crucial pathogenetic feature is the impaired immune response to mycobacterial isolates, in particular type 1 helper T-cell responses involving interleukin-12 and interferon-γ production and co-stimulatory function of antigen-presenting cells. In the final stages of a chronic renal failure, a high rate of anergy to mycobacterial antigens administered intracutaneously has been documented (i.e., from 32% to 40%). Other relevant elements

are the continual inflammatory phase of monocytes/macrophages due to the uremia and to the dialysis, malnutrition (mainly related to vitamin D intake), and hyperparathyroidism [5, 36–38].

Silicosis increases the likelihood of pulmonary tuberculosis from 2.8 to 39 times if compared to healthy controls whereas the probability of developing extra-pulmonary tuberculosis is 3.7-fold greater (the pleural form is the most common form, 61% of cases) [1, 5, 24, 39–41]. The average time elapsing between the diagnosis of silicosis and the development of tuberculosis is 6.8 years. The incidence of tuberculosis seems to be proportional to the severity of silicosis and the intensity of exposure to crystalline silica dust. Occupational activities in the mines seem to modify considerably the risk of developing tuberculosis: in particular, drilling has been associated with a greater intensity of exposure. Some studies identified a higher relative risk (i.e., 1.1–4.0) of developing tuberculosis in miners exposed to silica but without silicosis. These epidemiological findings support the results of experimental studies demonstrating that silica modifies the pulmonary immune response, and impairs the metabolism and the function of pulmonary macrophages till their apoptosis after long exposure [5, 24, 39–41]. The incidence of silica-related tuberculosis has been increased by the increased prevalence of HIV infection in resource-limited countries. The incidence of pulmonary tuberculosis in South African gold miners is 3,000 per 100,000 population. For this reason, several authors strongly recommend the treatment for latent tuberculosis infection in individuals with and without silicosis (especially for HIV-infected people) [5, 39–41].

Smoking is another relevant modifier, being associated to a relative risk of developing tuberculosis ranging from 2.3 to 2.7 [1, 5, 24, 42, 43]. Furthermore, it increases the risk of infection (relative risk of 1.7). The relative risk for latent tuberculosis infection and disease is not independent: the increase of the risk of infection directly increases the proportion of individuals at risk of disease. Therefore, the independent relative risk for tuberculosis in an infected population is obtained computing the ratio of the two relative risks (i.e., 1.4–1.6). Smoking reduces adaptive immune responses, decreasing CD4+ cell counts, altering macrophages, and mechanically disrupting the cilia in the upper respiratory airways. A dose–response effect has been documented: the likelihood of tuberculosis is directly linked to the number of cigarettes smoked daily.

Being treated with immunosuppressive drugs could increase the risk of tuberculosis, as recently demonstrated with the anti-TNFα therapies for the treatment of chronic inflammatory diseases (for instance, rheumatoid arthritis, psoriasis and psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, and inflammatory bowel disease) [44]. TNF is a protein crucial for granuloma initiation and stability in the lungs. It fosters the phagocytic and killing activities of the alveolar macrophages and favors the gathering of cells at the inflammatory site inducing adhesion molecules. Four monoclonal anti-TNF antibodies are currently available and are used for the treatment of chronic inflammatory diseases: adalimumab, certolizumab pegol, golimumab, and infliximab. The risk of developing tuberculosis is amplified by 1.6–25.1 times and varies depending on the clinical setting and type of anti-TNF therapy prescribed [44–46].

The role of a corticosteroid treatment in the pathogenesis of tuberculosis is debated [5]. Daily dose of 10 mg or higher of corticosteroids, prescribed for a few days, appears to not be associated with an increased risk of developing tuberculosis but experimental studies on rabbits documented their role in increasing the risk of disease.

Numerous studies evaluated the impact of several tumors as risk factors for tuberculosis, but only lymphomas, pulmonary neoplasia, and head/neck cancers seem associated to the development of the disease [5]. Other relevant diseases and medical events that could increase the risk of tuberculosis are malnutrition, substance abuse, gastrectomy, and jejunoileal by-pass [5, 24]. Intravenous drug and alcohol abuse could increase the risk of tuberculosis by compromising the immune system. Malnutrition, meat and fish deficiencies, or a vegetarian diet are epidemiologically associated to increased probability of tuberculosis [5, 24].

Mortality

The wide availability of anti-tuberculosis drugs has decreased mortality from tuberculosis and case fatality in developed countries. In the pre-antibiotic era, 30% and 66% of patients with tuberculosis died after 1 and 5 years from the notification of the disease, respectively [5, 8]. The most important prognostic variables are the site and type of tuberculosis, the early and adequate administration of anti-tuberculosis treatment, and adherence to treatment [3, 5, 8]. The majority of deaths caused by tuberculosis are attributable to sputum smear-positive tuberculosis [5, 8].

Patient's delay and/or health-care system's delay are associated to increased mortality. Patient's delay can be reduced with health education measures, decreasing tuberculosis stigma, and improving the health-care network. The delay of the health-care system could be related to several factors, particularly poor availability of diagnostic means and misdiagnosis; furthermore, negative prognostic health-care–associated factors are poor accessibility to antituberculosis drugs, incorrect prescription of anti-tuberculosis regimens in terms of dosages, time of exposure, and drug susceptibility of the infecting mycobacterial strains.

Tuberculosis/HIV Coinfection

HIV infection has dramatically changed the epidemiology of tuberculosis in high- and low-income countries, mostly in sub-Saharan Africa, Southeast Asia, and Eastern Europe. It was estimated that tuberculosis incidence in 2008, if compared with the rate computed in 1990, increased by 11% due to the HIV pandemic. In sub-Saharan Africa, tuberculosis mortality has tripled in the last two decades and 29% of tuberculosis-related deaths are associated to HIV infection [1, 2, 5, 8, 47, 48]. The increase in tuberculosis notification rates mirrored the increase in the HIV prevalence with a delay of 4–7 years [2, 48–50].

By the end of 2008, 33.2 million individuals were estimated to be living with HIV. Incidence and mortality in 2007 were 2.7 million and 2.1 million, respectively [48, 49]. Tuberculosis is estimated to be the cause of 26% of the deaths in people living with HIV. The majority of TB/HIV patients is located in sub-Saharan Africa but in numerous high HIV prevalence areas only 20% HIV-infected individuals know their HIV status. The infection is principally transmitted through sexual relationships, exchange of contaminated syringes among intravenous drug users, and transfusion of infected blood. The risk of developing tuberculosis ranges from 3% to 15% per year in HIV coinfected patients, while the cumulative lifelong risk in non-HIV-infected individuals is 10%. However, surveys carried out in high HIV prevalence areas estimated an annual probability of developing tuberculosis up to 30% in advanced immunocompromised patients [1, 2, 5, 8, 48–50].

The risk of developing tuberculosis is directly correlated to the degree of immunodeficiency, particularly with the quantitative impairment of CD4+ cell counts, which are considered a relevant surrogate marker of infection together with the HIV-viral load. For this reason tuberculosis is the main opportunistic disease and cause of death in HIV + individuals globally [1, 2, 5, 8, 48, 50].

It is crucial to detect HIV-positive individuals and to start antiretroviral therapy (ART) to decrease the probability of developing tuberculosis and, consequently, the probability of transmitting mycobacterial strains to susceptible individuals. The risk of developing tuberculosis is reduced by 70–90% in patients treated with ART if compared with untreated HIV-positive individuals. In 2008, more than four million individuals were treated with antiretroviral drugs [1, 2, 5, 8, 48–54].

The role of HIV infection on tuberculosis incidence is strictly related to the prevalence of latent tuberculosis infection in the population, particularly in those aged 15–54 years. In industrialized countries, where the prevalence of the mycobacterial infection is low in all age groups, incidence and prevalence of tuberculosis in HIV + individuals are also low. However, in some metropolitan areas an epidemiological scenario comparable to that described in some low-income countries, with high proportions of coinfected individuals has been documented [2, 5, 8, 47, 48].

It is estimated that 30% of HIV + individuals are infected by mycobacterial strains worldwide, with a wide variability from 14% in Europe to 46% in Southeast Asia.

A series of tuberculosis/HIV collaborative activities have been developed to address tuberculosis/HIV coinfection (Table 12.1) [2, 3, 48, 49, 51, 55, 56]:

- Establishment of a tuberculosis/HIV coordinating body to plan and carry out common activities, such as monitoring and evaluation of the epidemiological indicators and clinical outcomes.
- Surveillance of the prevalence of HIV infection in patients with tuberculosis.
- Intensified tuberculosis case finding aimed at identifying tuberculosis symptoms and clinical signs in HIV-positive individuals attending specialized health-care settings (HIV clinics, sexually transmitted diseases, clinics, etc.).

Table 12.1 Tuberculosis/HIV collaborative activities [3]

1. *Establishment of the mechanisms for collaboration*
   - Set up a coordinating body for tuberculosis/HIV collaborative activities that could be effective at all levels
   - Carry out surveillance of HIV-prevalence among tuberculosis cases
   - Carry out joint tuberculosis/HIV planning
   - Conduct monitoring and evaluation
2. *To decrease the burden of tuberculosis in people with HIV/AIDS*
   - Implement intensified tuberculosis case finding
   - Introduce isoniazid preventive therapy
   - Ensure the control of latent tuberculosis infection in health-care and congregate settings
3. *To decrease the burden of HIV in patients with tuberculosis*
   - Provide HIV testing and counseling
   - Introduce HIV-prevention methods
   - Introduce cotrimoxazole preventive therapy
   - Ensure care and support for people with HIV/AIDS
   - Introduce antiretroviral therapy

– Isoniazid preventive therapy (IPT) in HIV-positive individuals latently infected by mycobacterial strains. In these cases, it is strongly recommended to microbiologically exclude tuberculosis before the administration of the anti-tuberculosis drug.
– Infection control measures in health care and congregate settings to avoid the spread of mycobacterial strains.
– HIV counseling together with HIV rapid testing in tuberculosis patients.
– Introduction of HIV-prevention methods.
– Cotrimoxazole preventive therapy.
– Wide availability of antiretroviral (ARV) drugs.

Delivery of ART to HIV-positive patients with tuberculosis is deemed one of the most important measures for a successful DOTS strategy as it can prevent the shift from latent tuberculosis infection to active tuberculosis following the immunological recovery. However, several issues can hamper the efficacy of ART in tuberculosis patients: pharmacokinetic interactions between anti-HIV drugs and anti-tuberculosis drugs and immune-reconstitution syndrome (IRIS) could increase morbidity and mortality, for instance, decreasing the adherence and, then, the clinical efficacy of the specific treatment regimens [2, 48, 50–54].

The combination of three of the above mentioned tuberculosis/HIV activities, that is, Intensified Case Finding, Isoniazid Preventive Therapy and Infection Control measures, known as the “Three I’s”, can have a significant role in the prevention of mycobacterial infections and tuberculosis, and in the early identification of tuberculosis cases [2, 3, 55, 56].

Intensified Case Finding helps to rapidly identify tuberculosis suspects using questionnaires focused on symptoms and clinical signs of tuberculosis. Individuals with or at high risk of HIV infection or in congregate settings (such as mines, prisons, etc.) are regularly screened and counseled by HIV services and/or by community-based organizations supporting HIV-positive patients.

Isoniazid Preventive Therapy can be administered to HIV-positives without tuberculosis, reducing the risk of developing the disease by 33–67% for up to 4 years. The criteria for treatment include HIV-positive individuals living in areas with a proportion of latent tuberculosis infection above 30% or HIV-positives with documented latent tuberculosis infection or exposure to a contagious tuberculosis index case. The efficacy of its combination with the ART in preventing the development of tuberculosis has been proven.

Tuberculosis Infection Control measures can prevent the spread of mycobacterial strains to vulnerable patients, health-care workers, the community, and those living in congregate settings.

However, slow implementation of the "Three I's" has been documented because of the difficulty faced by some national programs to integrate these components in the framework of HIV care. Some national tuberculosis programs do not support the implementation of some activities (for instance, the use of isoniazid preventive therapy) and gaps in policy and operational guidance remain a major obstacle in some settings. Infection control still represents a serious challenge at national-, regional-, and facility-level for the absence of a coordinating body or for multiple coordinating bodies, lack of technical expertise, trained health care workers, and laboratory biosafety. Furthermore, inadequate diagnostic tools for latent tuberculosis infection and tuberculosis have hampered the implementation of intensified tuberculosis case finding and the delivery of isoniazid preventive therapy predominantly in resource-limited settings [2, 48, 55, 56]. Nevertheless, it was estimated that 1.4 million tuberculosis cases were tested globally for HIV infection in 2008, which is a 64-fold increase if compared with the estimates in 2002. The increase was significant in sub-Saharan Africa (from 4% to 45% in 2004 and 2008, respectively). A significant improvement has been documented in the number of HIV-infected people screened for tuberculosis: from 600,000 in 2007 to 1.4 million in 2008. Improvements were also recently recorded on the provision of preventive and therapeutic drugs, particularly trimethoprim-sulfamethoxazole preventive treatment (200,000 HIV-positives with tuberculosis in 2008), isoniazid preventive therapy (50,000 HIV-positives in 2008), and ART (100,000 HIV-positives with tuberculosis in 2008) [2, 48, 49].

All countries with a high HIV prevalence should be committed to rapidly implement and scale-up all tuberculosis/HIV collaborative activities.

Future investments in the translational research aimed at identifying new diagnostics and therapeutics as well as international and national political commitment could improve the epidemiology of tuberculosis/HIV coinfection [2, 5, 8, 48, 50, 53].

Drug-Resistant Tuberculosis

Development of resistance to anti-tuberculosis drugs has been documented since the early years of introduction of chemotherapy for the treatment of tuberculosis. The large majority of patients treated with streptomycin in the first Medical

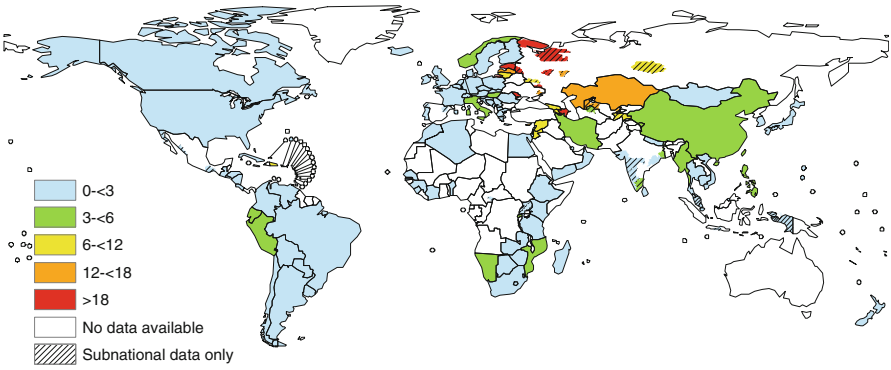

Fig. 12.1 Distribution of MDR-TB among new TB cases, 1994–2010

Research Council randomized clinical trial in the 1940s acquired resistance to that drug [57]. The spread of drug-resistant strains was soon recognized, and a survey of clinics in England in the 1950s found that over 5% of patients with tuberculosis without a history of previous treatment had strains resistant to at least one of the three major drugs in use at that time [58]. If even once the three effective drugs are used in combination, the development of drug resistance is theoretically impossible [59]. However, despite the introduction of combination regimens throughout the world many years ago, drug resistance has been progressively documented [60].

In the early 1990s, several reports were published on the emergence of multidrug resistant TB (MDR-TB), but the populations surveyed were not comparable, and methods used to quantify the problem were not standardized thus making it difficult to estimate the global magnitude of drug-resistant TB [61–64].

In 1994, the Global Project on Anti-tuberculosis Drug Resistance Surveillance was established in order to estimate the global burden of drug-resistant TB worldwide using standardized methodologies so that data could be compared across and within regions [65]. The Project aimed to monitor trends in resistance, evaluate the performance of TB control programs, and advise on drug regimens. The Supranational TB Reference Laboratory Network (SRLN), a network now consisting of 29 laboratories globally, was developed in order to provide quality assurance to drug resistance surveys including panel testing before the start of a survey and rechecking of isolates during the survey [66]. Since 1994 drug resistance data have been systematically collected and analyzed from 119 countries worldwide (62% of all countries of the world). Out of them, 48 countries can rely on continuous surveillance systems based on routine diagnostic drug susceptibility testing of all patients. The remaining 71 countries have relied on special surveys of representative samples of patients.

The distributions of multidrug-resistant TB (MDR-TB), defined as TB caused by strains of *Mycobacterium tuberculosis* that are resistant to at least isoniazid and rifampicin, are given in Figs. 12.1 and 12.2, for new and previously treated TB cases, respectively. Proportions of MDR-TB exceeding 18% among new TB cases

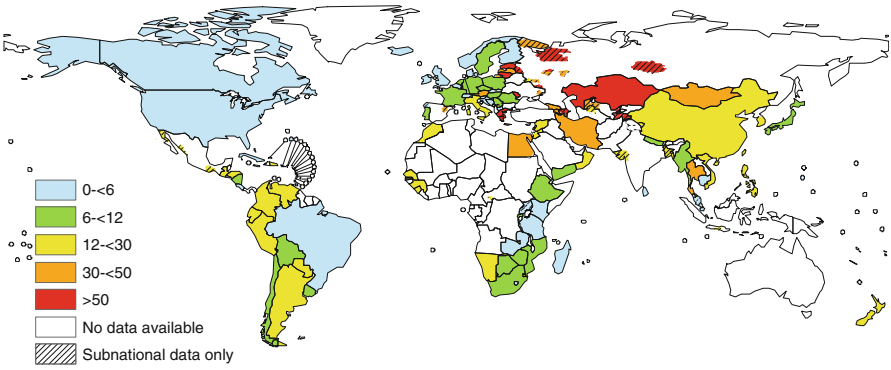

Fig. 12.2 Distribution of MDR-TB among previously treated TB cases, 1994–2010

(in countries reporting more than ten MDR-TB cases) have been documented in Estonia (22.0%), Russian Federation (Arkhangelsk Oblast, 25.7%, Belgorod Oblast, 19.8%, Ivanovo Oblast, 20.3%, Kaliningrad Oblast, 22.3%, Murmansk Oblast, 28.9%, Pskov Oblast, 24.3%, and Vladimir Oblast, 20.9%). Proportions of MDR-TB exceeding 50% among previously treated TB cases (for countries reporting more than ten MDR-TB cases) are found in Estonia (51.6%), Lithuania (51.5%), Russian Federation (Arkhangelsk Oblast, 58.8%, Belgorod Oblast, 51.6%, Ivanovo Oblast, 57.7%, and Tomsk Oblast, 53.8%), and Tajikistan (Dushanbe city and Rudaki district, 61.6%, 95% CI: 52.5–70.2) [67, 68].

Since 2006, WHO has also been collecting and analyzing data on resistance to second-line anti-TB drugs. Extensively drug-resistant TB (XDR-TB), defined as MDR-TB plus resistance to a fluoroquinolone and at least 1 second-line injectable agent – amikacin, kanamycin, and/or capreomycin-, has been documented in 69 countries globally [67].

Overall, there were an estimated 390,000–510,000 cases of MDR-TB (primary and acquired) arising in 2008, with the best estimate at 440,000 cases. Among all incident TB cases globally, 3.6% (95% CI: 3.0–4.4) are estimated to have MDR-TB.

The estimated global number of incident MDR-TB episodes among new and relapse TB cases in 2008 was between 310,000 and 430,000 episodes, with the best estimate at 360,000 episodes. The estimated global number of incident acquired MDR-TB episodes was between 83,000 and 110,000 episodes, with the best estimate at 94,000 episodes. Almost 50% of MDR-TB cases worldwide are estimated to occur in China and India. These estimates refer to cases of MDR-TB that arose in 2008 and do not reflect the number of prevalent cases of MDR-TB. The number of prevalent cases of MDR-TB in many parts of the world is estimated to be much higher than the number arising annually.

An estimated 150,000 deaths caused by MDR-TB occurred globally in 2008, including those with HIV infection (range: 53,000–270,000). The estimated number of MDR-TB deaths excluding those with HIV infection was 97,000 (range: 6,000–220,000) [69].

Although the association of HIV and MDR-TB has been widely documented in hospital outbreaks of drug-resistant TB among people living with HIV, based on the population-based data gathered till now, it is not possible to conclude whether an overall association between MDR-TB and HIV epidemics exists [70–72].

More work is needed to understand global trends of the MDR-TB epidemic but in a group of countries and settings, decreasing trends in absolute numbers of MDR-TB are documented (Estonia, Latvia, China, Hong Kong, United States of America, and two Oblasts in the Russian Federation, Tomsk and Orel) [69].

Control of Tuberculosis

In the second half of the nineteenth century more than one third of deaths globally were due to infectious diseases and 15% were due to tuberculosis. In particular, more than 30% of men and women during their productive years died of tuberculosis.

In industrialized nations, before the availability of the first anti-mycobacterial antibiotics in the second half of 1900, the incidence of tuberculosis notification dramatically decreased because of the reduction or elimination of some risk factors favoring the spread of mycobacterial strains in the community (for instance, improvement of the social and economic conditions of many families) and the implementation of public health interventions, such as the identification and isolation of contagious tuberculosis patients [1, 5, 8, 16, 73].

The first sanatorium was built in Germany in 1857 in order to isolate contagious tuberculosis patients and to provide them with adequate food, rest, sunlight, and fresh air. The dispensary system was introduced in 1897 in Scotland, England, following the basic German principle of the separation of an infectious patient from the community. After the Italian, Forlanini proved the efficacy of artificial pneumothorax to increase the likelihood of cure in tuberculosis cases in 1907, sanatoria increased their surgical activities to create pulmonary collapse (for instance, plombage and thoracoplasty) [1, 5, 8, 16, 74, 75].

The wide distribution of antituberculosis drugs and the scale-up of therapeutic combination, together with the establishment of the first National Tuberculosis Programs (NTPs) and the further improvement of the socio-economic situation, have been significantly associated with a rapid decline of tuberculosis incidence and prevalence in the USA and in numerous European countries [1, 5, 8, 16]. However, in the mid-1980s the erroneous feeling of imminent elimination of tuberculosis, supported by the persistent decline of incidence and prevalence, has led to a reduction of tuberculosis control measures with numerous sanatoria closed or converted into non-tuberculosis specialized facilities. The escalation of the HIV/AIDS epidemic, the increasing number of migrants from high tuberculosis incidence countries, socioeconomic changes due to the collapse of the Soviet Union contributed to the rapid increase of tuberculosis incidence in low-incidence countries [1, 5, 8, 16, 76, 77]. Epidemiological trends in low-income countries are partially known but in the

last decades the improvement of surveillance systems has increased the confidence on morbidity and mortality estimates [5, 8].

The World Health Organization has played a crucial role in the fight against tuberculosis worldwide. In 1993, tuberculosis was declared a global public health emergency and reiterated in 2000 by the United Nations Millennium Development Goals (MDGs). The Millennium Development Goal mainly focused on the tuberculosis issue aims at combating HIV, malaria, and other infectious diseases.

In the last 20 years, two public health strategies have changed the natural history of tuberculosis worldwide: DOTS strategy since 1996 and Stop TB Strategy since 2006. Both of them were launched after interactive and proactive debates and discussions between governmental and non-governmental organizations and national representatives of high tuberculosis incidence countries (tuberculosis control program managers and their staffs) [8, 78–82].

DOTS strategy is based on finding and treating contagious cases. It consists of five components: government commitment to tuberculosis control, bacteriological diagnosis through smear microscopy (mainly on individuals complaining of characteristic tuberculosis symptoms), short-course antituberculosis therapy that has to be standardized and supervised (i.e., directly observed, at least during the initial phase), uninterrupted high-quality drug supply, and individual outcome evaluation through a standardized recording and reporting system. Its targets were to detect 70% of sputum smear-positive tuberculosis cases and to successfully treat 85% of them by 2005. DOTS can reduce annual tuberculosis notifications from 6% to 8%, decreasing the incidence, the prevalence, and the mortality.

In 2005, the World Health Organization launched the new Stop TB Strategy (Table 12.2) [82]. The former strategy was revisited to pursue DOTS expansion, adding six other components to be implemented to reach the 2015 Millennium Development Goal related to tuberculosis control, that is, to reduce prevalence of and mortality due to tuberculosis by 50% relative to those of 1990.

The new Stop TB Strategy can be summarized in the following elements [82]: (1) pursuing high-quality DOTS expansion and enhancement; (2) addressing tuberculosis/HIV coinfection, multi-drug resistant tuberculosis, and other challenges; (3) contributing to the strengthening of health-care systems; (4) engaging all care providers; (5) empowering people and communities with tuberculosis; and (6) enabling and promoting research.

This new Strategy addresses several issues that emerged during the implementation and scale-up of the DOTS strategy: spread of tuberculosis/HIV coinfection and increased rates of multi-drug resistant tuberculosis, weak health care systems, exclusion of the private sector from national tuberculosis control strategies (often managing poor and marginalized individuals), passive involvement of tuberculosis patients and communities, few resources in research and development of new diagnostics, drugs, and vaccines.

The first component, that is, "to pursue quality DOTS expansion and enhancement" is aimed at improving the previous strategy: political commitment should be strong in terms of financial resources available for tuberculosis control at national- and regional-level as well as for strengthening of health system. National laboratory

Table 12.2 WHO-recommended Stop TB Strategy [82]

1. *Pursue high-quality DOTS expansion and enhancement*
   - Secure political commitment, with adequate and sustained financing
   - Ensure early case detection, and diagnosis through quality-assured bacteriology
   - Provide standardized treatment with supervision, and patient support
   - Ensure effective drug supply and management
   - Monitor and evaluate performance and impact
2. *Address TB/HIV, MDR-TB, and the needs of poor and vulnerable populations*
   - Scale up collaborative TB/HIV activities
   - Scale up prevention and management of multidrug-resistant TB (MDR-TB)
   - Address the needs of TB contacts, and of poor and vulnerable populations, including women, children, prisoners, refugees, migrants, and ethnic minorities
3. *Contribute to health system strengthening based on primary health care*
   - Help improve health policies, human resource development financing, supplies, service delivery, and information
   - Strengthen infection control in health services, other congregate settings, and households
   - Upgrade laboratory networks, and implement the Practical Approach to Lung Health (PAL)
   - Adapt successful approaches from other fields and sectors, and foster action on the social determinants of health
4. *Engage all care providers*
   - Involve all public, voluntary, corporate, and private providers through Public–Private Mix (PPM) approaches
   - Promote use of the International Standards for TB Care (ISTC)
5. *Empower people with TB, and communities through partnership*
   - Pursue advocacy, communication, and social mobilization
   - Foster community participation in TB care
   - Promote use of the Patients' Charter for TB care
6. *Enable and promote research*
   - Conduct program-based operational research, and introduce new tools into practice
   - Advocate for and participate in research to develop new diagnostics, drugs, and vaccines

networks should be improved with the introduction of culture methods and drug susceptibility testing as well as new effective evidence-based diagnostic technologies. In order to obtain high-treatment rates and to avoid the emergence and spread of drug-resistant strains treatment support should be provided through a patient-centered approach. A national body should manage the continuous supply of quality-assured anti-tuberculosis drugs. Continuous monitoring of the national TB program and evaluation of the tuberculosis control activities should be regularly implemented.

The second component of the strategy describes all the interventions that should be implemented to control and avoid further emergence of the rising issues: tuberculosis/HIV coinfection and multi-drug resistant tuberculosis. Tuberculosis and HIV national programs should implement collaborative activities. Patients with drug-resistant tuberculosis should have access to diagnosis and proper treatment with second-line anti-TB drugs. More attention should be given to groups at highest risk of developing tuberculosis (such as prisoners, immigrants, etc.).

The third component is focused on strengthening of health system, highlighting all the elements necessary to improve a national health system: human and financial resources, information systems, and national policies.

The fourth component underlines the importance of the engagement of all health-care providers, including those outside national health system (public–private mix approach) and those working in prisons, general hospitals, and medical colleges.

The fifth component is aimed at describing the empowerment of people with tuberculosis and of communities, sharing some tuberculosis activities like treatment support. Furthermore, communities could have a role in reducing tuberculosis stigma.

The sixth component highlights the importance of the operational and biomedical research aimed at improving program performance and at developing new diagnostic, therapeutic, and preventive tools.

The Stop TB Strategy addresses all the risk factors associated to the development of mycobacterial infection and tuberculosis, including the reduction of the social and economic consequences of the disease. It supports the Global Plan to Stop TB (2011–2015), developed by the Stop TB Partnership [81]. The plan is aimed at identifying political and public health strategies to be implemented, and financial needs and existing gaps to address in order to scale up the Stop TB Strategy. Finally, International Standards of Tuberculosis Care (ISTC) have been issued to help both public and private health care providers to deliver quality DOTS services [83–85]. The aim is to describe an evidence-based standard of care for health-care workers managing confirmed or suspected tuberculosis individuals. The following principles of care are highlighted: early and accurate bacteriological diagnosis; administration of standardized and effective anti-tuberculosis drug regimens as well as appropriate treatment support and supervision; and monitoring of treatment outcomes.

Global Epidemiological Situation

Incidence

According to the last global estimates the number of new cases of tuberculosis in 2009 was 9.4 million, ranging from 8.9 million to 9.9 million (137 cases per 100,000 inhabitants). During the recent years the incidence trend has slowly decreased but the absolute frequency has increased due to population growth. The regions contributing the most to the global estimated incidence of tuberculosis are the South-east Asian region with 35% of cases (3,300,000), the Western Pacific region with 20% (1,900,000 cases), the African region with 30% (2,800,000 cases) followed by the Eastern Mediterranean region (7%), the European region (4%), and the Region of the Americas (3%) [4, 6].

The World Health Organization identified 22 so-called high burden countries (HBCs), accounting for more than 80% of the incident cases estimated globally. India accounts for 21% of all tuberculosis patients and China for 14%. The highest incidence rates in 2009 were estimated in India (range: 1.6–2.4 million), China

(range: 1.1–1.5 million), South Africa (range: 0.40–0.59 million), Nigeria (range: 0.37–0.55 million), and Indonesia (range: 0.35–0.52 million). The incident tuberculosis/HIV coinfection was estimated in 1.1/9.4 million (12%; 1.0–1.2 million, 11–13%) individuals, with the vast majority of patients in the African region. Among the incident cases estimated in 2008, 440,000 (range: 390,000–510,000) patients were infected by multi-drug resistant mycobacterial strains, that is, with resistance in vitro to at least isoniazid and rifampicin (MDR-TB).

Prevalence

The estimated tuberculosis prevalence in 2009 was 200 cases per 100,000 inhabitants as a consequence of 14 million (range: 12–16 million) prevalent patients.

Mortality

In 2009 about 1.7 million individuals (i.e., 26 cases per 100,000 inhabitants) died of tuberculosis, with 400,000 (range: 320,000–450,000) and 1.3 million (range: 1.2–1.5 million) deaths among tuberculosis/HIV coinfected and HIV-negative patients, respectively.

Case Notifications

National tuberculosis programs registered 5.8 million tuberculosis patients in 2009: most of them were new cases (94.8%) and 0.3 million were relapses (i.e., previously treated cases whose most recent anti-tuberculosis treatment outcome was "cure" or "treatment completed" but who were afterward diagnosed with sputum smear and/or culture-positive tuberculosis); 57% of the pulmonary tuberculosis cases was considered highly infectious, that is, sputum smear-positive. Among the 5.5 million new cases notified in 2009, 47.3% (2.6 million) was sputum smear-positive, 36.4% (2.0 million) sputum smear-negative while 16.4% (900,000) was affected by extrapulmonary tuberculosis.

The causes behind the global under-reporting could be linked to the patients (limited knowledge of tuberculosis; economic and/or geographical barriers to access health care; etc.) and/or to the health systems (poor clinical and laboratory capacities; few trained health care workers; poor compliance to national laws on notification after tuberculosis diagnosis).

Treatment Outcomes

The global treatment success ("cured" plus "treatment completed") rates for new sputum smear-positive cases treated during the years 2007 and 2008 were higher than the target set in 1991, that is, 85%.

In 2008 three WHO regions contributed to this result: Eastern Mediterranean Region, the South-east Asian Region, and the Western Pacific Region; the worst treatment success rate was documented in the European Region (66%), followed by the Region of the Americas (77%) and the African Region (80%).

Future Directions

Elimination of tuberculosis, or reducing the incidence of new sputum smear-positive cases below one per one million inhabitants, is the goal for the next decades. The target endorsed by Stop TB Partnership is the elimination of tuberculosis as a public health problem by 2050 [6–88].

The objectives of the tuberculosis elimination strategy are:

- Reduction of the incidence of latent tuberculosis infection.
- Reduction of the prevalence of latent tuberculosis infection.

The aim is to decrease the burden of future new tuberculosis cases.

In low tuberculosis-incidence countries, the lowest prevalence and incidence of latent tuberculosis infection are detected in the autochthonous youngest groups. The epidemiological projections indicate that each generation will be substituted by a generation with a lower risk of infection and, then, characterized by a lower prevalence of latent tuberculosis infections [5, 8, 86, 88].

Early detection and adequate treatment of contagious tuberculosis patients are of paramount importance in order to achieve a positive epidemiological trend. Moreover, the progression to tuberculosis in individuals infected by mycobacterial strains should be prevented, particularly focusing on high-risk groups (migrants, HIV-positives, ethnic minorities, prisoners, elderly people, and close contacts of tuberculosis index cases) [5, 8, 86].

This combined approach is deemed essential to reach the elimination goal, and it should be supported by international and national policies, embracing the following components [2, 5, 8, 86, 87]:

- Political commitment toward control and elimination, particularly providing human resources, facilities, and funds
- Case detection through case-finding among symptomatic individuals presenting at health services and active case finding in special groups through quality-assured laboratories and trained health-care providers
- Access to tuberculosis diagnostic and treatment services, implementing collaborative activities with health bodies or organizations working with migrants, prisoners, homelessness, etc.

– Standard approach to treatment of tuberculosis and latent tuberculosis infection, following international evidence-based recommendations
– Surveillance and treatment outcome monitoring, following standard internationally accepted definitions

However, tuberculosis indicators could potentially worsen in the next decades due to the following public health challenges:

– Drug-resistant mycobacterial strains (mostly multi/extensively drug-resistant mycobacteria)
– HIV/AIDS
– Immunocompromised individuals
– Political unrests and wars, natural disasters, and starvation

Adequate funds, constant international and national political commitment, and an effective supply of anti-tuberculosis and anti-HIV drugs and diagnostics represent relevant components for a successful strategy. In particular, the research and development of new effective anti-tuberculosis drugs with an improved toxicity, tolerability, and efficacy profile and the evaluation of the activity of potential adjunctive treatments, such as vitamin D, as well as of new primary preventive measures (i.e., vaccines) are crucial priorities for the near future. Basic and applied research would need to be followed by operational research, as new diagnostic, therapeutic, and preventive approaches must be tested at the program-level (field trials) after clinical trials [89].

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