

CHAPTER 1

THE GLOBAL BURDEN OF TUBERCULOSIS

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Introduction

Tuberculosis has long ranked among the most feared and dreaded of all of the many afflictions of the human race and names for the disease such as John Bunyan's 'Captain of all of these Men of Death' truly reflect its unenviable reputation in days gone by. Tragically, though, the disease is still so prevalent that, in 1993, 111 years after the causative organism was identified and half a century after the introduction of effective therapy, the World Health Organization (WHO) deemed it necessary to take the unprecedented step of declaring it a Global Emergency (World Health Organization, 1994a).

Although being among the most widespread and prevalent of the chronic diseases that plague mankind, the precise impact of tuberculosis on human health worldwide can only be estimated indirectly. Even in some developed nations, notification and record-keeping are far from being optimal (Sheldon *et al.*, 1992), while in many regions where the burden of tuberculosis is high disease surveillance is rudimentary. Surveys of the prevalence of the disease based on case-finding and bacteriological surveys are notoriously unreliable as they are critically dependent on the quality of medical services and diagnostic facilities. In 1994, 3.3 million cases of tuberculosis worldwide were notified whereas, as outlined below, the estimated total number of cases was between two and three times higher.

A major problem faced by epidemiologists is the complex ‘timetable’ of human tuberculosis. Infection by the tubercle bacillus induces certain immunological changes, notably a conversion to dermal reactivity to tuberculin. From the results of tuberculin testing surveys, it has been estimated that about one third of the human population has been infected by the tubercle bacillus: approximately 2,000 million people (Kochi, 1991; Raviglione *et al.*, 1995; Raviglione and Luelmo, 1996; Raviglione and Nunn, 1997). It is assumed, though never formally proven, that all infected persons who convert to tuberculin positivity develop the so-called primary complex, consisting of a small lesion at the site of bacillary implantation (usually the lung) and enlarged regional lymph nodes. Dissemination of bacilli to other organs may occur via the lymphatic system or blood stream. In most cases, though, the primary complex remains undetected and the infected person never experiences the clinical features of tuberculosis.

There is indirect evidence that, in infected persons who do not succumb to primary tuberculosis, the disease enters a latent state and that bacilli remain within the tissues in a poorly understood ‘persister’ form (Grange, 1992). These quiescent foci of infection can potentially reactivate at any time during the remainder of the infected person’s life. For many years it was dogmatically asserted that, once infected, a person was protected against exogenous reinfection so that all tuberculosis developing later in life was due to endogenous reactivation. There is now, however, considerable evidence — some of it provided by the application of highly discriminative DNA ‘fingerprinting’ techniques — that exogenous reinfection does indeed occur in both immunosuppressed and non-immunosuppressed persons (Dwyer *et al.*, 1993; Small *et al.*, 1994; Marchal, 1997).

Not all those infected by the tubercle bacillus develop overt disease. Indeed, only a minority do so. The ratio of infection to development of overt tuberculosis is termed the *disease ratio*. As a general rule, about 5% of those infected develop so-called primary tuberculosis within five years of infection and a further 5% subsequently develop post-primary disease, giving a total of 10% (Raviglione and Nunn, 1997). The actual

risk of developing tuberculosis after infection varies throughout life, but on average the annual risk is about 0.2%.

The disease ratio shows some regional variation and, as discussed below, it is much higher in the presence of certain predisposing factors, notably human immunodeficiency virus (HIV) infection. In addition, neonates and infants are more likely to develop overt tuberculosis following infection. There have been many attempts to link susceptibility to tuberculosis to race and ethnicity, but numerous confounding factors such as differing socio-economical and environmental conditions render such analyses very difficult. Although this issue awaits clarification, it appears that genetic factors play only a minor role in determining susceptibility to this disease.

Overt primary tuberculosis is the result of either local complications of the primary complex or of non-pulmonary lesions resulting from blood-borne dissemination to other organs. In both cases, the bacilli are unable to escape from the lesions so that the patients are usually not infectious.

Post-primary disease, by contrast, usually involves the lung, irrespective of the site of the initial infection, and the gross tissue destruction characteristic of this form of the disease causes the formation of well-oxygenated cavities that favour the growth of bacilli and facilitate their access to the sputum. Thus, patients with post-primary lesions are often infectious and are said to have 'open' tuberculosis. There is a close relationship between 'smear positivity', i.e. the presence of enough acid-fast bacilli in the sputum (at least 5,000 bacilli per ml) for them to be detected microscopically, and infectivity (Rouillon *et al.*, 1976). The relative infectivity of smear-positive and negative-patients is shown in Table 1. Sputum microscopy therefore plays a key role in disease control by providing a rapid, robust, sensitive and specific means of detecting infectious patients in a community.

As infection by the tubercle bacillus leads to conversion to tuberculin positivity, skin testing surveys are used to determine the *annual infection rate*, or *annual risk of infection*, in a community (Enarson and Rouillon, 1998). Ideally, representative groups from the population

Table 1. Prevalence of infection by the tubercle bacillus according to closeness of contact. Data from a study in the Netherlands. Data from Rouillon *et al.* (1976).

Microscopical status of source case sputum	% subjects infected among contacts of source case		
	At home (<i>n</i> = 858)	Near relative or friend (<i>n</i> = 4207)	Colleague at work (<i>n</i> = 3931)
Smear positive	20.2	3.7	0.3
Smear negative	1.1	0.2	0.0

should be tested at yearly intervals in order to determine the number of persons who actually convert from negative to positive in a given year. This approach is, however, usually impractical and indirect estimates of the annual infection rate are arrived at by testing a group of similar age range, such as military recruits, or even a population of mixed ages, provided the average age is known. Owing to serious methodological problems, such estimates must be interpreted with caution (Rieder, 1995).

The Global Burden of Tuberculosis

As the annual risk of a tuberculin-positive person developing active tuberculosis is about 0.2%, data on the annual infection rate from many countries can be used, subject to the methodological problems discussed above, to calculate the total number of new cases of tuberculosis developing from the infected pool each year. According to the WHO, the numbers of new cases in 1990 and 1995 were 7.5 million and 8.8 million respectively and the numbers are predicted to rise to 10.2 million by the year 2000, a 37% increase from the 1990 estimate (Dolin *et al.* 1994; Raviglione and Nunn, 1977). Some authorities, such as Enarson and Rouillon (1998), regard the WHO figures for incidence and deaths as an overestimate. Using modified methods, the WHO estimate for 1997 was