Chapter 1
Epidemiology

Abstract This chapter will describe the pathogen which causes tuberculosis: *Mycobacterium tuberculosis*. It will give an overview of the historical context, the molecular and clinical epidemiology of tuberculosis in adults and children globally and describes how other epidemics, such as HIV and diabetes, influence disease control. It also summarizes the current efforts of the WHO to curtail the pandemic.

Keywords Tuberculosis · Mycobacterium tuberculosis · Lineage · Virulence · Drug-resistance · Epidemiology · HIV · Prognosis

1.1 Tuberculosis in History

Tuberculosis (TB) has caused more deaths through the last 200 years than any other infectious disease, and has been with us since ancient times (Paulson 2013). Evidence of tuberculosis has been found in 9,000 year old mummies. There are conflicting theories of the timing of the emergence of *Mycobacterium tuberculosis* (*M.tuberculosis*) as a human pathogen with two recent theories proposing 70,000 years ago (Comas et al. 2013) or 6,000 years ago. The later study proposed that seals first transmitted the disease to humans (Bos et al. 2014).

Tuberculosis (TB) is a chronic granulomatous disease caused by the bacterium *M. tuberculosis*, and more rarely, other species of the Mycobacterium tuberculosis complex including Mycobacterium bovis and Mycobacterium africanum. The term "tubercle" in the context of consumptive ("wasting") disease was first coined by Fransiscus de la Boë (also known as Sylvius of Leyden), a Dutch anatomist in the 17th century. He found tubercles (from: tuberculum, "small lump" in Latin) in the lungs of most consumptives. Before the discovery of the pathogen in 1882 by Robert Koch, the spectrum of diseases caused by the mycobacteria were known by many names including: consumption, phtisis (from Greek "phtinein" to waste away), scrofula (swelling of lymphnodes, especially in the neck), Pott's disease (tuberculous spondylitis, named after a British orthopedic surgeon Percivall Pott, in

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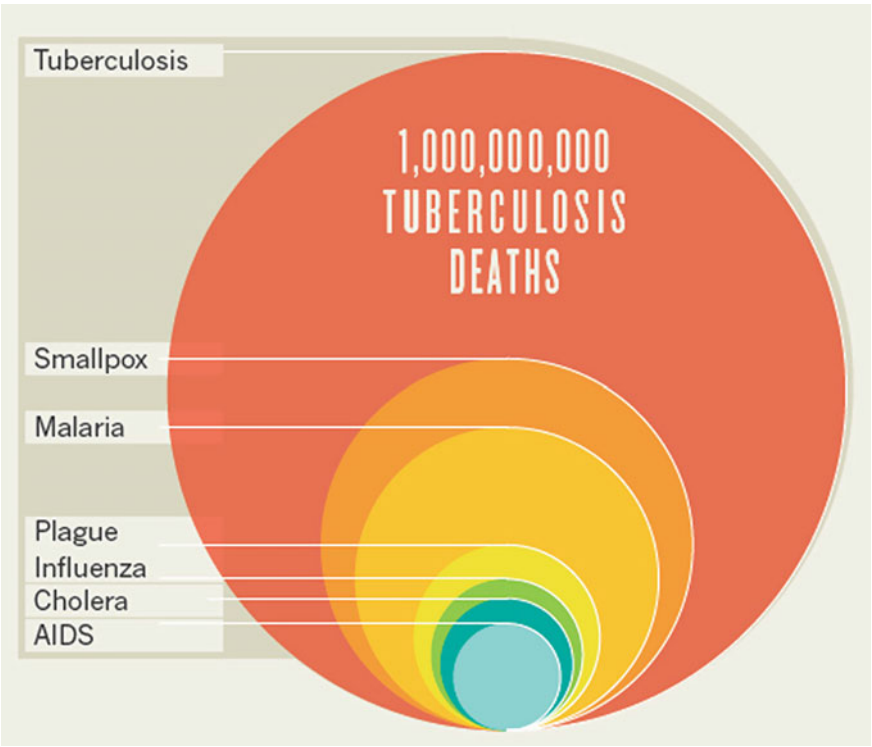

Fig. 1.1 The burden of tuberculosis. *From* Paulson T. Nature, 2013. Reprinted with permission

the 18th century, but found in Egyptian mummies and art as early as 1000 BC), yaksma (from Sanskrit: gradual destruction) and shaky oncay (Incan), balasa (Hindu: swelling). The European epidemic in the 17th century was known as "the white plague" (Fig. 1.1).

1.2 Pathogen

TB is caused by bacteria of the Mycobacterium tuberculosis complex, mostly *M.tuberculosis*, but rarely also M.canetti, M.microti, M.africanum, and M.bovis (de Jong et al. 2010). Mycobacteria are non-motile, non spore-forming, aerobic, rod-shaped bacteria of 2–4 μm in length and possess a unique lipid-rich cell wall which gives the 'acid-fast' property by which they are known (acid-fast bacilli, or

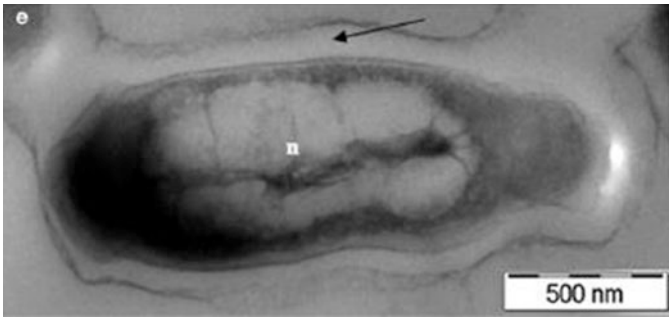

Image 1.1 Transmission electron microscope image of *Mycobacterium tuberculosis*. The *Black arrow* indicates the thick myolic acid layer. The *n*. indicates the nucleide (from Srinivasan et al., Arch Microbiol, 2014, reprinted with permission)

AFBs) and renders them resistant to many disinfectants and antibiotics. They can be divided into slow growing or rapid growing species (Image 1.1).

M. tuberculosis is slow-growing, non-pigmented and appears as cream coloured 'breadcrumbs' on culture, often also described as 'rough, tough and buff' (Collins 1997) (Image 1.2). Other mycobacteria are variously described by the synonymous terms non-tuberculous mycobacteria (NTM), mycobacteria other than tuberculosis (MOTT) and atypical mycobacteria. NTM management is complex and poorly standardized due to differences in disease presentation and available treatment options. This book will focus on TB; for guidance on NTM management refer to the American Thoracic Society (ATS) guidelines: http://www.thoracic.org/statements/resources/mtpi/nontuberculous-mycobacterial-diseases.pdf. The only other major human pathogen of the mycobacteria genus is M. leprae, which causes leprosy and is not discussed further (White and Franco-Paredes 2015).

The whole genome of *M. tuberculosis* (laboratory strain H37Rv) was sequenced in 1998 (Cole et al. 1998). Subsequent sequencing of clinical strains from around the world has illuminated pathogen diversity, evolution and spread (Comas et al. 2013). Six major geographic lineages of *M. tuberculosis* have been identified: the

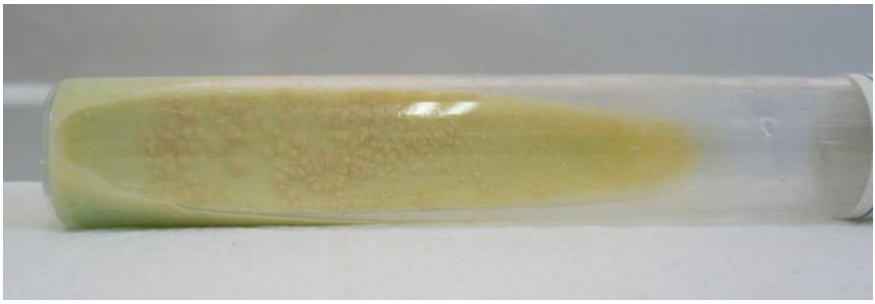

Image 1.2 *Mycobacterium tuberculosis* colonies on solid Lowenstein Jensen medium (*courtesy* of Dr. Dang Thi Minh Ha)

Euro-American, Indo-Oceanic, East-Asian (including Beijing strains), West-African 1 and 2, and East-African-Indian. Many studies have attempted to identify lineage-specific differences in clinical virulence and/or transmissibility, but results have been conflicting. These different findings may be the result of differences in the particular strains used for comparison, variation in host genetics, environmental influences or different study methodologies.

Some strains (e.g. Beijing and Haarlem strains) have been associated with increased drug resistance. This may result from intrinsic factors such as increased genetic mutation rates, intrinsic drug tolerance, lower fitness cost associated with resistance-conferring mutations (Ford et al. 2013), or from environmental factors that facilitated its emergence and spread. Current typing methods such as spoligotyping, IS6110 restriction fragment length polymorphism (RFLP) and variable number tandem repeat (VNTR) have value for outbreak investigations and studies of population transmission, but do not offer any information to guide treatment. Advances in the speed and cost of whole genome sequencing will soon supersede other typing techniques and would be far more informative, facilitating detailed transmission mapping and proving information on likely drug-resistance to guide clinical management (Anderson et al. 2014; Comas et al. 2013; Barry et al. 2012; Borrell and Gagneux 2009; Borrell et al. 2013; Cohen et al. 2011; Coll et al. 2013; Steiner et al. 2014).

1.3 Epidemiology

Although TB is often thought of as a historical disease in the developed world, this is not the case. Globally in 2012 there were an estimated 8.6 million new cases of active TB and 1.3 million deaths; therefore there is one new TB case every 4 s and more than two TB deaths every minute. Twenty-two high-burden countries account for 80 % of all TB cases, with India and China alone contributing almost 40 % (26 and 12 % respectively). The TB incidence per 100,000 population varies dramatically, from less than 10 per 100,000 in developed countries such as Japan, the United States, Western Europe and Australia, to rates exceeding 1000 per 100,000 in South Africa and Swaziland (WHO 2014). Overall, it is estimated that just 64 % of incident TB cases were notified to National TB Programmes in 2013 (WHO 2014).

In high burden settings, TB has its peak incidence in early adulthood, affecting the most economically productive age-groups. Whilst in low burden countries, TB is more common in the elderly; also in immigrant populations and the socially destitute. In the United States 63 % of the 9945 TB cases (a rate of 3.2 cases per 100,000 persons) reported in 2012 were among immigrants; with case rates 11 times higher than among US-born citizens (http://www.cdc.gov/tb/statistics/reports/2012/default.htm). In a Dutch study on long-term travellers to TB endemic countries the overall TB was estimated to be 3.5 per 1000 person-months of travel (Cobelens et al. 2000). TB notifications are usually higher among men than women in a ratio of approximately 2:1. Despite this, TB is a leading non-obstetric cause of

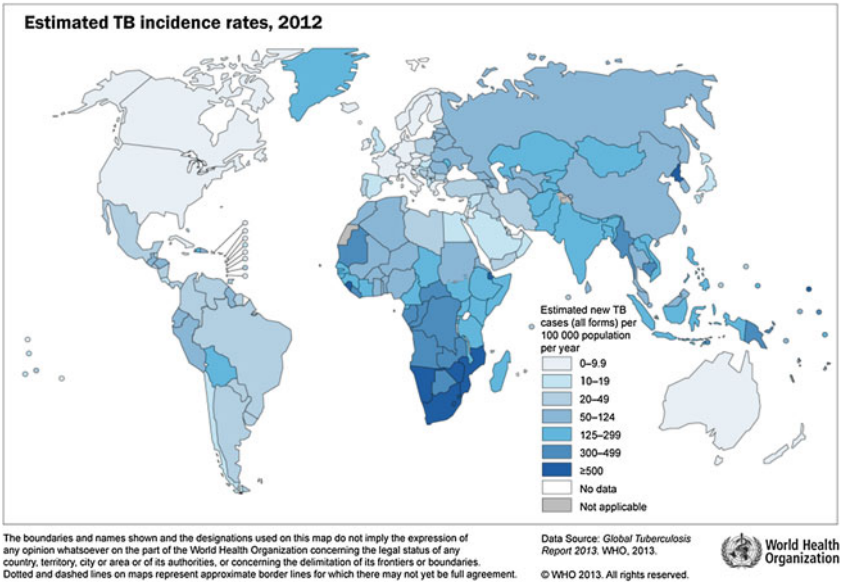

Fig. 1.2 Estimated TB incidence rates. *Source* WHO, reprinted with permission

death in women from TB endemic areas (WHO 2002). Various theories have been proposed to account for this difference including differences in smoking rates, occupational lung damage, social networking patterns and immune function. It is likely that the causes are multifactorial and include potential detection bias in settings where women have greater difficulty in accessing health care.

Infection with human-immunodeficiency virus (HIV) greatly increases the chances of an individual developing active TB following exposure, or of having reactivation of latent disease, with the probability increasing as immunosuppression advances (Lin and Flynn 2010). For an HIV uninfected individual with latent TB there is a 10 % lifetime risk of developing active TB disease, while for those with HIV there is a 10 % annual risk (WHO 2008). 1.1 million (13 %) of the incident TB cases in 2012 were in people living with HIV/AIDS and 75 % of these were in sub-Saharan Africa. TB is the leading cause of death among HIV-infected patients, with an estimated one in four HIV-related deaths attributed to TB (WHO 2008) (Fig. 1.2).

Young children with TB are generally less infectious and due to the difficulty of confirming a TB diagnosis in this age group, data has not been systematically collected on the TB disease burden suffered by children and many are treated without notification. However, since 2010 countries have been encouraged to report age disaggregated data to WHO for children less than 5 years and 5–14 years of age. Despite being limited by poor case ascertainment and incomplete reporting, WHO estimates that 530,000 children developed TB during 2012; resulting in 74,000 deaths among HIV-uninfected (and many more among HIV-infected) children (WHO 2013). The contribution of TB to child mortality is undetermined, particularly

in TB endemic areas. More recent estimates are that ~1 million incident cases occur among children every year (Jenkins et al. 2014), while the contribution of TB to under-5 mortality is likely to be underestimated in TB endemic areas, especially among children dying from pneumonia, malnutrition and meningitis (Graham et al. 2014). Pooled analysis of autopsy studies identified TB in ~10 % of 811 children (both HIV-infected and -uninfected) who died from respiratory disease in five African countries (Marais et al. 2014). Of the estimated 1.3 million deaths in children attributed to pneumonia in 2011, most occurred among young children living in TB endemic areas (Zar et al. 2013). Apart from its contribution to "pneumonia deaths", TB may also be the underlying cause in a substantial number of children dying from meningitis, presumed sepsis, HIV/AIDS or severe malnutrition.

Smoking, diabetes and other co-morbidities increase susceptibility to active TB. The increasing prevalence of diabetes, particularly in developing Asian countries such as India and China has focused attention on the link between diabetes and TB susceptibility and in 2011 WHO issued guidelines for the integrated management of TB among diabetes patients (WHO 2011). It has been predicted that global diabetes prevalence will increase by 69 % by 2030, with 80 % of prevalent cases in the developing world (Shaw et al. 2009). Individuals living with diabetes have a 2–3 times higher risk of developing active TB; around 10 % of TB cases globally are now linked to diabetes (WHO 2011). The Stop TB Strategy was launched in 2006 and now aims to eliminate TB (defined as <1 case/million population) by 2050 (http://www.who.int/tb/features_archive/global_plan_to_stop_tb/en/). Efforts towards elimination are challenged by the HIV pandemic and the increasing prevalence of drug resistant strains of M. tuberculosis (Fig. 1.3).

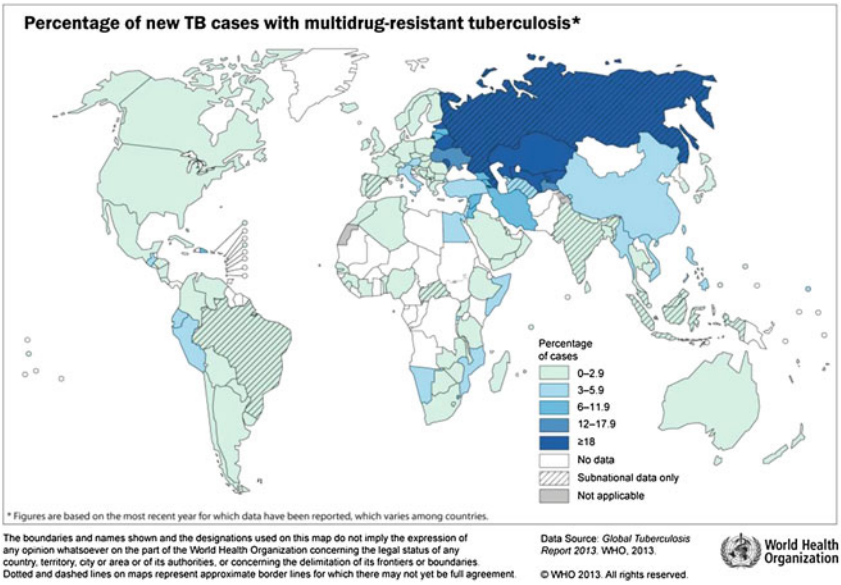

Fig. 1.3 Percentage of new TB cases with MDR-TB. *Source* WHO, reprinted with permission

1.4 Prognosis

TB is a curable disease. The fact that it remains the most pressing public health problem for a significant proportion of the world, despite the availability of a cure and knowledge on prevention of transmission shows how medicine can fail without commitment at all levels of the community. The distribution of the TB pandemic painfully demonstrates the inequalities in health care delivery globally. Over 95 % of cases and deaths are in low and middle income countries. In general, prognosis of outcome is dependent on a multitude of factors: host factors (genetic variance, co-morbidities, HIV-coinfection, treatment adherence, access to healthcare) and pathogen factors (pathogen virulence, drug-resistance) and the site of the infection (pulmonary or extrapulmonary). The principle factors in a favourable outcome are early recognition, drug susceptibility and appropriate treatment. Without treatment, the case fatality for sputum culture positive (HIV negative) patients is estimated to be 70 %, in contrast with sputum culture negative patients for whom it is estimated to be 20 % (Tiemersma et al. 2011). The treatment success rate (either cured or finished a full course of treatment) for newly diagnosed sputum positive TB patients reported for the US in 2011 (according to WHO) was 78 %. For new smear negative and extrapulmonary TB, treatment success rate is 85 % (http://www.who.int/gho/tb/epidemic/treatment/en/).

TB is the most common cause of death among HIV patients, estimated to cause 26 % of AIDS related deaths. The treatment success rate globally for all new TB patients without HIV was 87 %, in contrast with a 73 % success rate for new TB patients with HIV (Getahun et al. 2010). The most lethal form of TB is TB meningitis, which, when treated, has a mortality of approximately 25 % in HIV negative patients and can exceed 60 % in HIV positive patients. Half of TB meningitis survivors will suffer neurological sequelae (Thwaites et al. 2004; Torok et al. 2011).

Drug resistant TB carries a higher mortality than drug susceptible TB. Of the 34,000 MDR patients enrolled on treatment in 2010, only 48 % successfully completed treatment and 15 % died. Among 795 XDR cases, mortality was approximately 50 %.

The key to maintaining the momentum towards achieving the STOPTB target of global TB eradication by 2050 will be sustained commitment from donors, governments, national TB programmes, researchers and other stakeholders at all levels of society.