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Tuberculosis in Adults and Children

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Tuberculosis in Adults and Children

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Preface

This monograph is written for healthcare workers in any setting who are faced with the complex care for patients with tuberculosis. Prevention, diagnosis and treatment of tuberculosis are fraught with challenges that are often reflective of problems in society as a whole. Significant progress has been made since the millennium; Global TB incidence has been reduced, access to rapid molecular diagnosis for both TB and drug resistance has been scaled up, and two new TB drugs have been approved in Europe and the USA. However, major political and socio-economic obstacles remain in the translation of these and other advances into equitable TB healthcare access for all. Access to information on developments in TB care is one such barrier, and by summarizing the most recent advances in disease epidemiology, scientific achievements in treatment and diagnosis and current recommendations for all forms of tuberculosis, we hope to improve the dissemination of access to the latest evidence base for the care of individuals with tuberculosis.

Contents

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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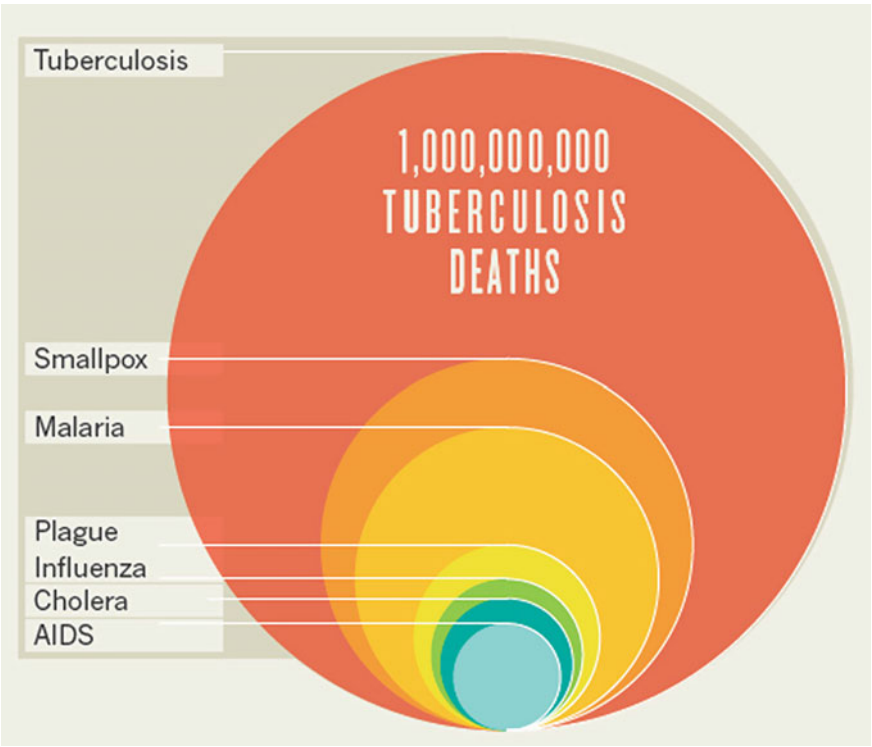

Fig. 1.1 The burden of tuberculosis. *From* Paulson T. Nature, 2013. Reprinted with permission

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

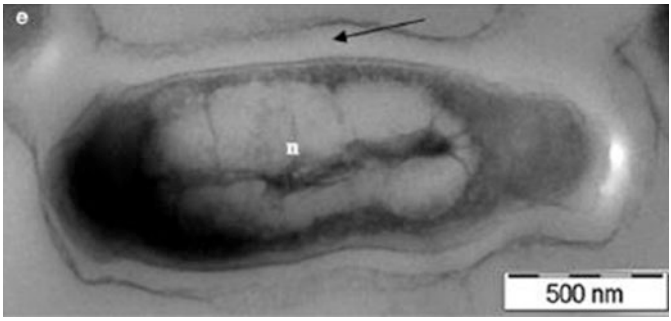

Image 1.1 Transmission electron microscope image of *Mycobacterium tuberculosis*. The *Black arrow* indicates the thick myolic acid layer. The *n*. indicates the nucleide (from Srinivasan et al., Arch Microbiol, 2014, reprinted with permission)

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

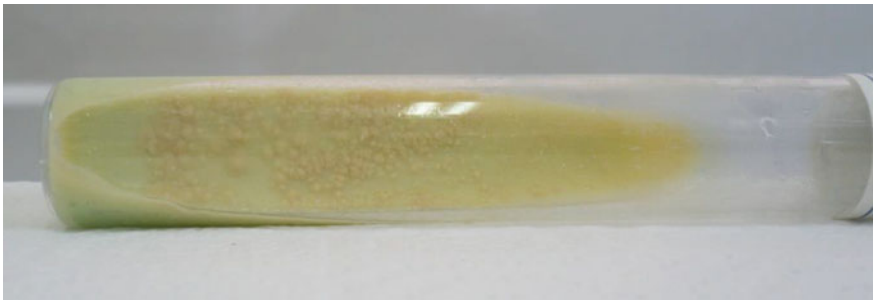

Image 1.2 *Mycobacterium tuberculosis* colonies on solid Lowenstein Jensen medium (*courtesy* of Dr. Dang Thi Minh Ha)

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

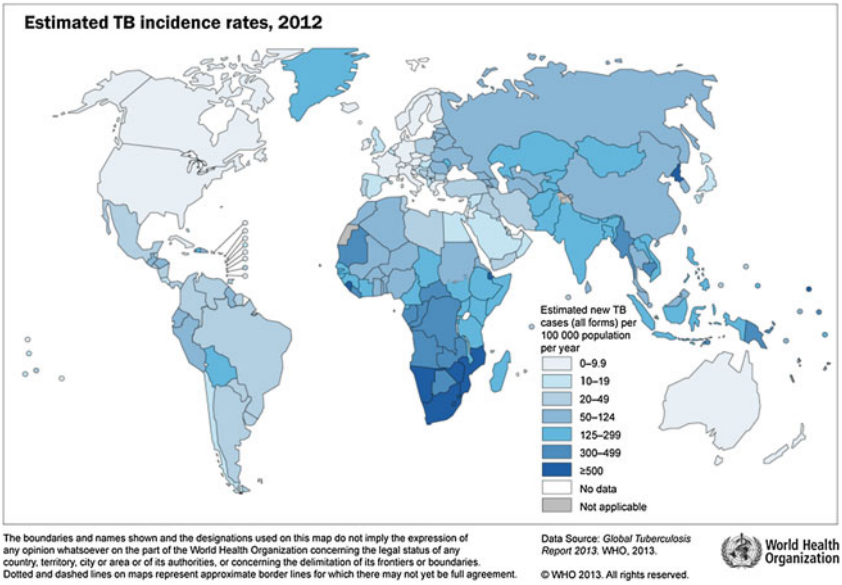

Fig. 1.2 Estimated TB incidence rates. *Source* WHO, reprinted with permission

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).

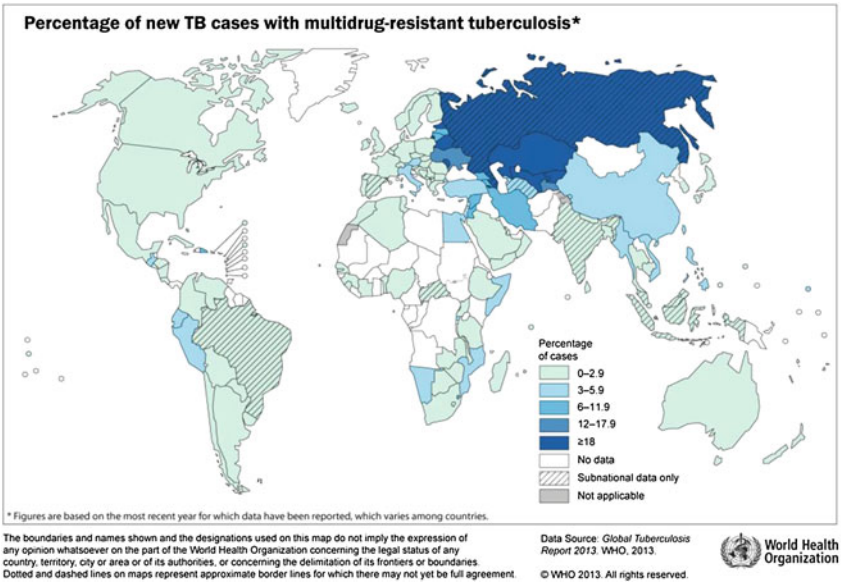

Fig. 1.3 Percentage of new TB cases with MDR-TB. *Source* WHO, reprinted with permission

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.

Chapter 2
Pathogenesis

Abstract In this section the different phases of infection with *Mycobacterium tuberculosis* will be reviewed. Starting from transmission by inhalation, to the innate and adaptive immune response and the dual role of tuberculoma formation in walling off infection, but also providing an advantageous environment for bacilli to survive and multiply. Recent data has shown the role of Tumour Necrosis Factor alpha (TNF-α) in tuberculoma maintenance and its genetic control is more complex than previously thought. The role of vitamin D in susceptibility to tuberculosis also an area which has seen a resurgence of interest and new evidence emerging that targeted vitamin D therapy may have a role in improving TB outcomes.

Keywords Transmission · Innate immune response · Aadaptive immune response · Tumor necrosis factor (TNF) · Tuberculoma · Granuloma · Vitamin D · Susceptibility · Interferron gamma (IFN)

2.1 Transmission

Transmission of TB is by inhalation of infectious droplet nuclei containing viable bacilli (aerosol spread). Mycobacteria-laden droplet nuclei are formed when a patient with active pulmonary TB coughs and can remain suspended in the air for several hours. Sneezing or singing may also expel bacilli. Factors influencing the chance of transmission include the bacillary load of the source case (sputum smear-positive or lung cavities on chest radiograph), as well as the proximity and duration of exposure (Escombe et al. 2008). Transmission is dramatically and rapidly reduced with effective treatment (Dharmadhikari et al. 2014). In general, the risk of infection among household contacts of TB patients is ∼30 % (Singh et al. 2005) (Fig. 2.1).

For reasons not clearly understood, the majority of individuals infected with *M. tuberculosis* (∼90 %) do not develop disease. Following inhalation of *M. tuberculosis* an individual may have one of the following outcomes: (1) fail to

D. Heemskerk et al., *Tuberculosis in Adults and Children*,
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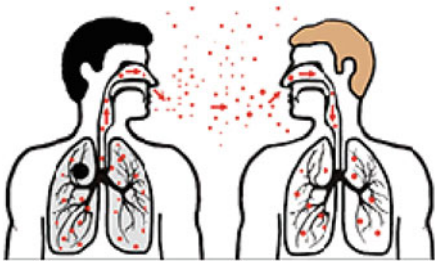

Fig. 2.1 Transmission of TB bacilli. *Source* CDC

register an infection, (2) become infected but then clear the infection, (3) successfully contain the infection but continue to harbour bacilli in the absence of symptomatic disease (latent TB infection), or (4) develop progressive TB disease (Saenz et al. 2013). It has been estimated that one-third of the world population have latent TB infection and may be at risk to develop TB disease as they age, or become immunocompromised in the future. The factors resulting in reactivation of latent TB infection in the absence of overt immune suppression are not well understood, but the huge reservoir of individuals with latent TB infection represents a major barrier to TB elimination (Dye and Williams 2010).

Susceptibility to TB is influenced by environmental, host and pathogen factors. Innate immune responses play a crucial role in host defense against mycobacteria (Fig. 2.2). Although numerous gene polymorphisms have been identified which influence host susceptibility to TB, it is apparent that in the vast majority of cases susceptibility is polygenetic (Fitness et al. 2004). The complex interplay of multiple genetic variants has yet to be fully elucidated. On-going genome wide association studies (GWAS) studies should better illuminate genetic determinants of TB susceptibility and disease severity (O'Garra et al. 2013). In children immune maturation is a major determinant of risk with infants (<2 years of age) being at highest risk of disease development and potential dissemination (Perez-Velez and Marais 2012).

2.2 The Innate Immune Response

The key players in the innate defence against *M. tuberculosis* are the alveolar macrophages and dendritic cells. Macrophages, dendritic cells and other immune cells recognize mycobacterial structures, pathogen associated molecular patterns (PAMPs) with membrane associated pattern recognition receptors (PRRs), of which the most studied are the Toll-like receptors (TLR2, TLR4, TLR9). PAMPs such as lipoarabinomannan, phosphatidylinositol and heat shock proteins (Hsp65 and Hsp70), and mycobacterial nucleic acids, such as the CpG motif, are recognized by TLRs. On interaction with the TLRs, signalling pathways are activated which lead to the production of predominantly proinflammatory cytokines, such as TNF, IL-1B, IL-12 and nitric oxide (Kleinnijenhuis et al. 2009; van Crevel et al. 2002).

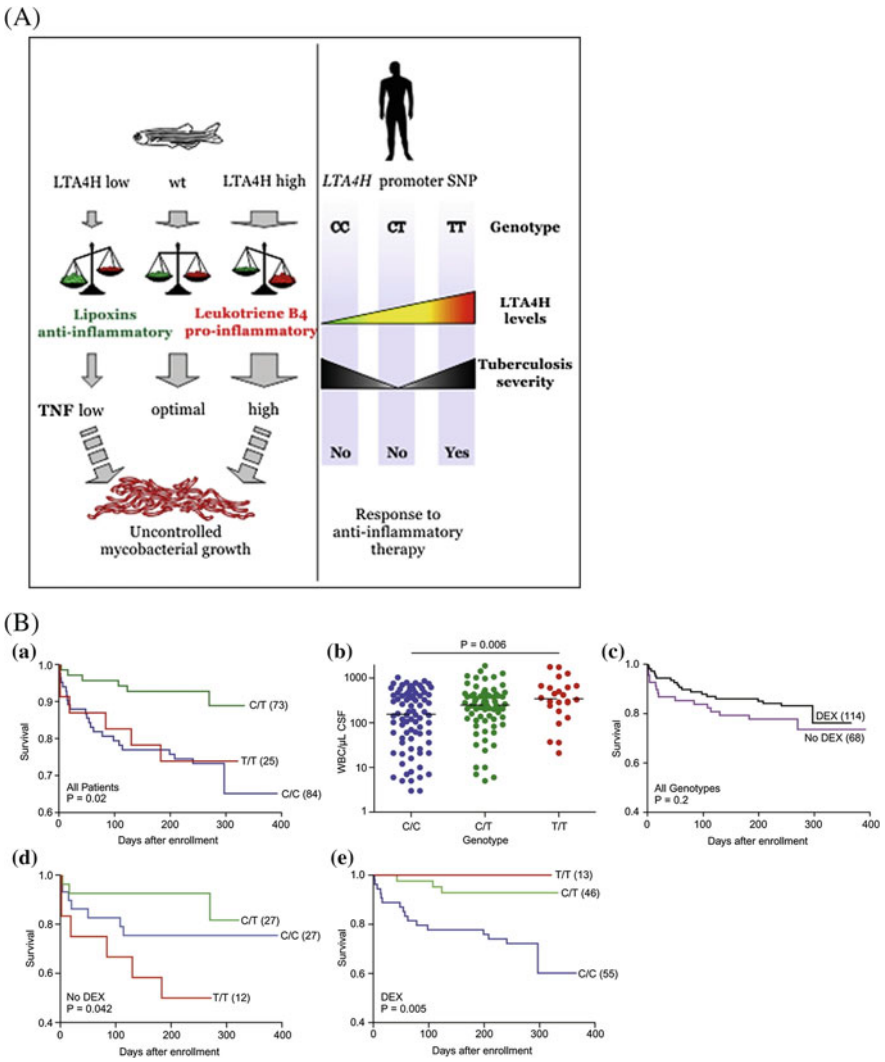

Fig. 2.2 Host genotype influences response to treatment with adjunctive steroids in Vietnamese patients with TB meningitis. **A** Humans may have polymorphisms in the LTA4H gene locus, which influence the severity of the inflammatory response. A process which is thought to be analogous to the susceptibility of zebrafish to *Mycobacterium marinum* infection. **B** Patients with the TT (high inflammatory) genotype, respond well to adjunctive treatment with dexamethasone. *From* Tobin et al., Cell, 2012, reprinted with permission

PRR-mediated phagocytosis of the pathogen by macrophages is an essential feature of the innate immune response. Ingested bacteria are then destroyed through phagosome-lysosome fusion and acidification (by H_2O_2 and other reactive oxygen intermediates) however *M. tuberculosis* may subvert this process and evade

destruction (Sullivan et al. 2012). Essentially the innate immune response mediated through macrophages can have three major results; (1) cell necrosis, (2) apoptosis (3) survival of the infected macrophages. If the cell undergoes necrosis, mycobacteria are released and may infect new macrophages or disseminate whereas an apoptotic cell membrane is not compromised and the bacteria are destroyed with the macrophage. Survival of infected macrophages enables the mycobacteria to persist and even proliferate before the adaptive immune response is activated by specific T-cells that have been selected in the regional lymph nodes; generally 2–3 weeks after primary infection (Saenz et al. 2013).

2.3 The Adaptive Immune Reponse

Dendritic cells are an important mediator between the innate and adaptive immune response which in addition to phagocytosis, present live mycobacteria to naïve T cells after migrating to regional lymph nodes. After antigen presentation in lymph nodes, CD4+ T cells are activated, and migrate to the lungs to impede mycobacterial progressive growth. The crucial role of T-cells in immunity to mycobacteria is evidenced by the dramatically increased susceptibility of individuals with HIV infection. Susceptibility to TB increases as the CD4 cell count decreases. IFN-γ, produced by activated T-cells, has a crucial role in protection against TB. IFN-knock-out mice, and humans with impaired IFN-γ genes are highly susceptible to severe TB disease (van Crevel et al. 2002). IFN-γ is essential in macrophage activation and intracellular mycobacterial killing (Flynn et al. 1993). TNF-α is another key cytokine produced by macrophages, dendritic cells and T cells and plays a central role in granuloma formation, macrophage induction and has immunoregulatory properties. Patients using TNF suppressing agent are at increased risk of infection and reactivation. A Cochrane review of TNF-α inhibitors given for any indication found a summary risk estimate odds ratio [OR] of 4.68, [95 %CI: 1.18–18.60] for reactivation of TB compared to control groups (Singh et al. 2011). However, TNF may also contribute to deleterious inflammatory responses in patients with progressive disease.

2.4 The Complex Role of TNF and Its Genetic Control

Although it is observed that TNF suppression can cause more rapid progression to TB disease, many aspects of the diverse functions of this proinflammatory factor have yet to be elucidated (Souto et al. 2014; Murdaca et al. 2015). Currently it is proposed that the effect of TNF on containment of mycobacterial infection is achieved by mediating the maintenance of granuloma integrity by regulating cell-adhesion proteins, chemokine attraction, and preventing T-cell dependent granuloma disintegration and inflammatory destruction by regulating IFN

producing CD4+ and CD8+ T cells. A second mechanism is by promoting apoptosis of mycobacteria containing macrophages, rather than non-apoptotic death, thus preventing intercellular spread of bacteria (Miller and Ernst 2008).

It has been shown that in a Vietnamese population with TB meningitis that a polymorphism in the LTA4H gene which leads to either excessive or deficient TNF-α production can determine the response to adjunctive dexamethasone therapy. This polymorphism was initially identified in a zebrafish model of mycobacterial infection (Cronan and Tobin 2014). TB meningitis patients with an excessive TNF-α genotype appeared to benefit from adjunctive corticosteroids, with decreased mortality. While for those with a low TNF-genotype, steroids may actually be harmful, with increased mortality observed in this group when receiving steroids. It is possible that similar naturally occurring variants in the LTA4H genotype in all individuals exposed to TB may influence susceptibility and disease progression. It is now becoming apparent that rather than a simplistic model of high pro-inflammatory response being protective, the most protective response is balanced between pro-and anti-inflammatory mediators, or 'just right', which has led to the term 'Goldilocks' gene (Tobin et al. 2013).

2.5 The Tuberculoma

The hallmark of mycobacterial infection is the tuberculoma or granuloma. Our current knowledge on granuloma development in the human in the different stages of disease stems from meticulous post-mortem studies performed more than a century ago. Granulomas are described by gross pathological appearance: solid or non-necrotic, caseous or necrotic, or end-stage cavitary. Depending on the degree of liquefaction, the caseum (from Latin, cheese-like), can be referred to as liquid/soft or solid/hard. It is thought that in solid necrosis, the mycobacteria are more efficiently contained, and generally less viable mycobacterium are found in hard caseum. If sufficiently large, the granulomas may drain their (liquid) content into the bronchial tree, releasing viable bacilli into the airways, to be aspirated into other parts of the lung or coughed up and transmitted. If associated with parenchymal destruction it heralds the onset of lung cavities, where extra-cellular bacilli multiply exponentially. It has long been assumed that the granuloma formation serves the host in containing the bacilli and preventing bacterial spread but it may also be exploited by the bacilli to proliferate (Ramakrishnan 2012). Indeed many people have evidence of healed granulomas, without having experienced active tuberculous disease. However, it is evident that control of infection within granulomas are not necessarily homogeneous within the same individual and ineffective in a substantial proportion of the global population.

On microscopic level the tuberculous granuloma is an organized aggregation of immune cells and debris. It contains macrophages that have undergone morphological change into epithelioid cells which form into zipper-like arrays around the necrotic centre. They retain the ability to phagocytise mycobacteria. Macrophages

can also fuse to form multinucleated giant cells and foam cells, which have high lipid contents, but only few bacteria and their protective role is uncertain. Other cell types surrounding the granuloma are dendritic cells, neutrophils, B cells, T cells, natural killer (NK) cells, fibroblasts. Epithelial cells often are found in the outer layer of the granuloma. Mycobacteria are concentrated in the periphery of the central necrotic area.

2.6 Vitamin D and the Immune Response

In the pre-antibiotic era TB patients were often treated with cod-liver oil and sunshine, both sources of 25-hydroxyvitamin-D, which has immunomodulatory properties. Currently the interest in the role of vitamin D-status in susceptibility to TB and the use of vitamin D adjunctive to antimycobacterial treatment has been re-ignited (Nunn et al. 2013). Particularly in the context of multi drug resistance, adjunctive treatment with vitamin D may be of importance in TB patients as, second-line treatment regimens are less bactericidal and should be paired with an optimal immune response in order to effectively eliminate infection.

2.6.1 Vitamin D Metabolism

Vitamin D is historically associated with bone disease for its role in maintenance of calcium homeostasis by promoting calcium absorption in the intestines and bone resorption, processes which are regulated by parathyroid hormone. However, the anti-inflammatory properties of vitamin D are increasingly being investigated by researchers globally in the context of other conditions, such as diabetes, infectious and autoimmune diseases and cardiovascular disease (Theodoratou et al. 2014).

Dietary sources of vitamin D are limited, however fish liver oils and fatty fish naturally contain vitamin D. It is difficult however to get the acquired intake of vitamin D solely from natural dietary sources. Sunlight is a another source of Vitamin D, as after exposure to ultraviolet B, 7-dehydrocholesterol in the plasma membrane of human keratinocytes is converted to previtamin D3, from which vitamin D3 (cholecalciferol) is formed. Vitamin D is fat soluble and is carried in the circulation by hepatically produced vitamin D-binding protein. In the liver, vitamin D is hydroxylated to form 25-hydroxyvitamin (25(OH)D) (also known as calcidiol, the serum measure of vitamin D), which is converted to the steroid hormone 1,25-dihydroxyvitamin D (calcitriol, the biologically active metabolite) in the kidneys. The actions of the hormone are mediated either through ligation with a nuclear vitamin D-receptor (VDR) to regulate gene transcription, resulting in genomic responses, or via membrane rapid-response receptors (Ralph et al. 2013; Coussens et al. 2014).

2.6.2 Antimicrobial Effects of Vitamin D

Several mechanisms are proposed by which vitamin D may exert antimycobacterial properties and enhances the immune response. In particular the transcription of cathelecidin is completely dependant on sufficient levels of 1,25-hydroxyvitamin D (Aranow 2011). Cathelecidin destroys microbial membranes in the phagolysosome in macrophages.

2.6.3 Vitamin D Deficiency and Susceptibility to Tuberculosis

Vitamin D deficiency has been implicated to play a role in increased susceptibility to active TB disease in numerous studies.

25-hydroxyvitamin-D receptors are present on all immune cells, including macrophages, and are upregulated after stimulation of Toll-like receptors, which play a central role in mycobacterial recognition. Polymorphisms in the VDR receptor potentially modulate the activity of the receptor and thus the action of Vitamin D. A meta-analysis of the most widely studied polymorphisms in the VDR (*Fok*I, *Taq*I, *Apa*Iand *Bsm*I) and susceptibility to TB, showed that among Asians, the *Fok*Iff genotype had a positive association (OR 2.0, 95 %CI 1.3–3.2) with TB, whereas, a significant inverse association was observed for the *Bsm*I bb genotype (OR 0.5, 95 %CI 0.4–0.8). Marginal significant associations were found for *Taq*I and *Apa*I polymorphisms (Gao et al. 2010).

A meta analysis of 7 studies on vitamin D status and susceptibility to TB, including 531 individuals found that patients with tuberculosis have lower average pre-treatment serum levels of vitamin D than healthy controls matched on sex, age, ethnicity, diet and geographical location. The pooled effect size in random effects meta-analysis was 0.68 (95 %CI 0.43–0.93) (Nnoaham and Clarke 2008).

A systematic Cochrane review in 2011 found no consistent evidence of beneficial impact on TB treatment outcomes for micronutrient supplementation, including vitamin D (Sinclair et al. 2011). Supplementation of patients on treatment for pulmonary TB has been associated with accelerated resolution of inflammatory responses (Coussens et al. 2012). Supplementation led to accelerated clinical and radiological recovery as well as an enhanced immune response in those with deficient serum vitamin D at diagnosis in a recent trial (Salahuddin et al. 2013) (Fig. 2.3).

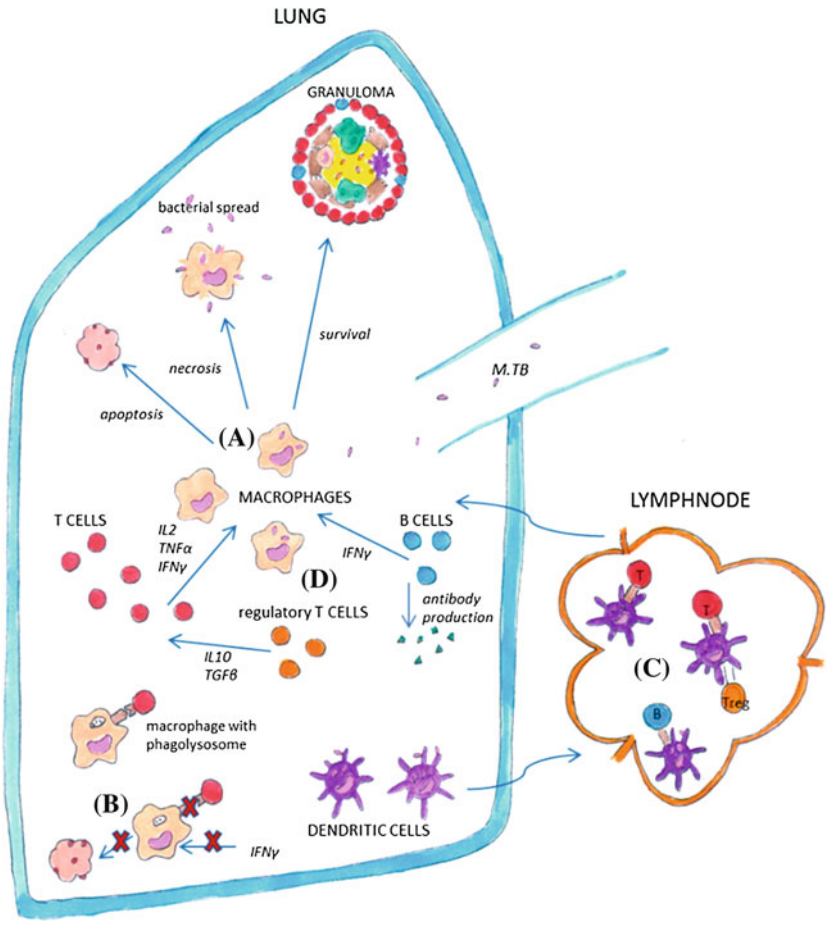

Fig. 2.3 Schematic representation of basic immunological antimycobacterial mechanisms in the lung and lymphnode. Macrophages and dendritic cells initially encounter Mycobacterium tuberculosis (M.TB) in the lung. *A* After ingestion, macrophages can undergo apoptosis or necrosis. After necrosis, bacterial spread may ensue. Surviving macrophages assist in early granuloma formation, either leading to elimination or clinical latency. *B* The mycobacteria can evade the immune response by inhibiting phagolysosome formation and apoptosis, as well as blocking the response of macrophages to IFNγ. *C* Resident dendritic cells of the lung can travel to regional lymphnodes, presenting live mycobacteria and mycobacterial antigen, activating naïve T-cells, B-cells and regulatory T-cells. *D* In the lung, activated T-cells and B-cells (attracted to the lung by chemokines) control bacterial growth by production of cytokines and antibodies. Regulatory T-cells control the inflammation through the production of IL-10 and TGF-β. Adapted from Saenz et al. Tuberculosis, 2013, adapted and reprinted with permission

Chapter 3
Clinical Manifestations

Abstract In this chapter we will review the clinical manifestations of tuberculosis disease.

Keywords Symptoms · Primary tuberculosis · Pulmonary tuberculosis · Chest X-ray · Endobronchial tuberculosis · Lymphnode tuberculosis · Extra-pulmonary tuberculosis · Pleural tuberculosis · Miliary tuberculosis · Central nervous system tuberculosis · Tuberculous meningitis · Spinal tuberculosis

3.1 Primary Tuberculosis

Primary (initial) infection is usually indicated by tuberculin skin test (TST) or interferon-gamma release assay (IGRA) conversion, which reflects a delayed type hypersensitivity reaction to protein products of *M. tuberculosis*. TST conversion usually occurs 3–6 weeks after exposure/infection; guidelines for its correct interpretation can be found at: http://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm. Primary infection remains undiagnosed in the majority of cases, as symptoms are mild, non-specific and usually self-resolving. A primary (Ghon) complex is formed, consisting of a granuloma, typically in the middle or lower zones of the lung (primary or Ghon focus) in combination with transient hilar and/or paratracheal lymphadenopathy and some overlying pleural reaction. The primary complex usually resolves within weeks or months, leaving signs of fibrosis and calcification detectable on chest X-ray. In general the risk of disease progression following primary infection is low, but young children and immunocompromised patients are at increased risk.

The natural history of a re-infection event is not well described, since we have no good measure of its occurrence. We know it is likely to be common in TB endemic areas, since molecular epidemiological evidence suggests that many disease episodes (the vast majority in some settings) result from currently circulating strains, representing recent infection/re-infection. A re-infection event probably triggers

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very similar responses to those observed with primary (first-time) infection and the risk of subsequent disease progression seems to be substantially reduced. However, re-infection is likely to occur multiple times during the lifetime of an individual living in a TB endemic area, which explains its large contribution to the disease burden observed.

Reactivation disease or post-primary TB are often used interchangeably for TB occurrence after a period of clinical latency. However, since reactivation disease is clinically indistinguishable from progressive primary disease or re-infection disease (DNA fingerprinting is required to distinguish reactivation from re-infection) the terminology is not descriptive or clinically useful. True reactivation disease is often preceded by an immunological impetus. Patients with immunocompromise due to severe malnutrition, HIV-infection, chronic hemodialysis, immunosuppressive therapy, diabetes or silicosis etc. are at increased risk.

3.2 Pulmonary Tuberculosis

TB symptoms are usually gradual in onset and duration varying from weeks to months, although more acute onset can occur in young children or immunocompromised individuals. The typical triad of fever, nightsweats and weightloss are present in roughly 75, 45 and 55 % of patients respectively, while a persistent non-remitting cough is the most frequently reported symptom (95 %) (Davies et al. 2014). Approximately 20 % of active TB cases in the US are exclusively extrapulmonary (EPTB), with an additional 7 % of cases having concurrent pulmonary and EPTB (Peto et al. 2009).

3.2.1 Parenchymal Disease

Patients with cavitary lung disease typically present with (chronic) cough, mostly accompanied by fever and/or nightsweats and weightloss. Cough may be non-productive or the patient may have sputum, that can be mucoid, mucopurulent, blood-stained or have massive haemoptysis. Other symptoms may be chest pain, in patients with subpleural involvement, or dyspnoea, however rare. Upon auscultation, the findings in the chest may be disproportionally normal to the findings on chest X-ray. The results of the chest X-ray may be critical for treatment initiation for those patients who are sputum smear negative. In particular in low resource countries, chest X-ray interpretation is often done by non-expert medical staff, and missed diagnosis is common. Typical findings include normal chest X-ray, focal upper lobe opacities, diffuse opacities, consolidation, reticulonodular opacities, cavities (Fig. 3.1a), nodules, miliary pattern (Fig. 3.1b), intrathoracic lymphadenopathy, pleural effusion. In HIV-infected patients, smear yield is lower and radiological abnormalities may be less typical, frustrating diagnosis. Severely

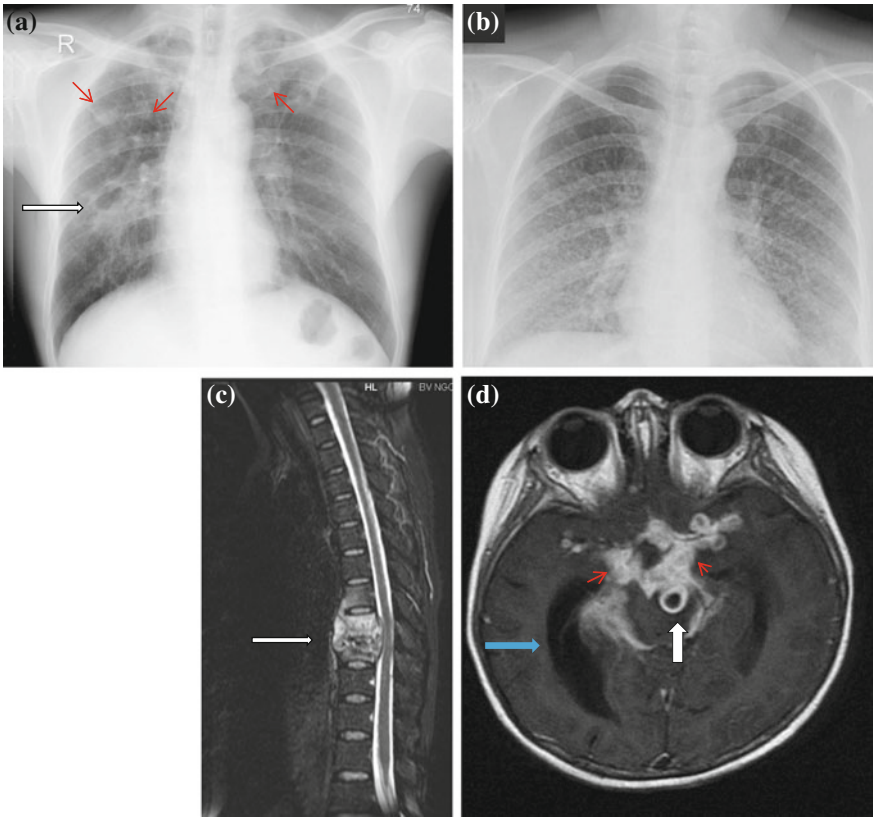


Fig. 3.1 **a** Chest X-ray showing cavitary lung lesions (*white arrow*) and upper lobe opacities (*smaller red arrows*) in 46 year old male. **b** Chest X-ray with the classic 'scattered millet seed' appearance of milliaryTB 49 year old female. **c** Magnetic resonance image (MRI) of a 35 year old female with spinal TB, showing destruction of thoracic vertebral bodies (T8 and T9) and compression of the spinal cord. **d** MRI scan showing tuberculoma (*large white arrow*), basal meningeal enhancement (*small red arrows*) and hydrocephalus (*blue arrow*) in a 2 year old child with tuberculous meningitis

immune-suppressed patients and young children are less likely to present with cavitation on chest X-ray, and more frequently have miliary (disseminated) disease.

3.2.2 Endobronchial Tuberculosis

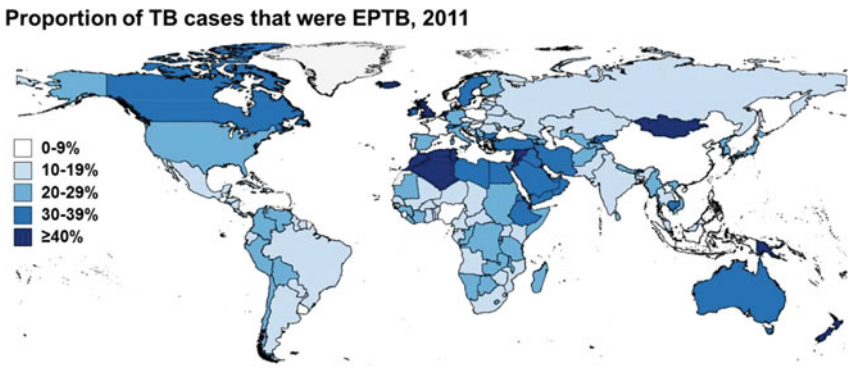
Endobronchial TB is a specific form of pulmonary TB affecting the trachea and major bronchi. It is often misdiagnosed as bronchial asthma or bronchial malignancy. If unrecognized, the endobronchial lesions progress and cause stenosis. Symptoms are as those of pulmonary TB, however examination may include wheezing and dyspnoea may be more prominent. There may be a female predominance, with a male:

female ratio of 1:2 (Qingliang and Jianxin 2010; Xue et al. 2011). Bronchoscopy and biopsy is the most useful diagnostic tool and to establish a prognosis depending on which histological subtype is found. Sputum smear and culture should be performed, but varying test sensitivities are reported. Early therapy is needed in order to prevent strictures, treatment with standard first-line short-course regimen (see Treatment section), but treatment prolongation may be considered on a case by case basis, for those patients with intractable disease (Xue et al. 2011).

3.2.3 Intra-Thoracic Lymphnode Disease

Following first-time infection the regional lymph nodes form part of the primary (Ghon) complex. Progressive disease may occur within these affected regional lymph nodes and is typically seen in young children. Symptoms are similar to those described for other forms of pulmonary TB, although the cough is rarely productive or the sputum blood-stained. Young children are unable to expectorate and the organism load is greatly reduced compared to adults with lung cavities, which complicates diagnosis (Perez-Velez and Marais 2012). Enlarged peri-hilar and/or paratracheal lymph nodes may obstruct large airways with resultant collapse or hyperinflation of distal lung segments, form cold abscesses with persistent high fever, or erode into surrounding anatomical structures such as the pericardium leading to TB pericarditis. Peri-hilar and/or paratracheal lymph node enlargement with/without airway compression is the cardinal sign of intra-thoracic lymph node disease. Lymph nodes may also erupt into the airways with aspiration of infectious caseum leading to lobar consolidation and an expansile caseating pneumonia if the airway is completely obstructed.

3.3 Extra-Pulmonary Tuberculosis



3.3.1 Pleural Tuberculosis

Between 3 and 25 % of TB patients will have tuberculouspleuritis or pleural TB. As with all forms of extrapulmonary TB, incidence is higher in HIV-infected patients. In some high burden countries, TB is the leading cause of pleural effusions. Typical presentation is acute with fever, cough and localized pleuritic chest pain. It may follow recent primary infection or result from reactivation. If part of primary infection, the effusion may be self-limiting. However, if it occurs in pregnancy it signals a potential risk to foetus, since recent primary infection is frequently associated with the occult dissemination. TB pleural effusions are usually unilateral and of variable size. Approximately 20 % of patients have concurrent parenchymal involvement on chest X-ray, however CT-scans have higher sensitivity and may detect parenchymal lesions in up to 80 % of patients (Light 2010). HIV infected patients may present with atypical symptoms, often with less pain and longer duration of illness and more generalized signs.

Pleural fluid is mostly lymphocytic with high protein content. Bacillary load is generally low and smear is typically negative, although this may be higher in HIV positive patients, in whom diagnostic yield from smear may be as high as 50 %. Elevated levels of adenosine deaminase (ADA) may be indicative; sensitivity and specificity estimates from a meta-analysis of published studies were 92 and 90 % respectively, with a cut-off value of 40U/l (Liang et al. 2008). However ADA levels can be increased in other diseases, such as empyema, lymphomas, brucellosis, and Q fever, and the test cannot differentiate between these diseases. A negative result suggests that TB is unlikely, but should always be interpreted in the clinical context. Pleural biopsy may show granuloma in the parietal pleura and are highly suggestive of TB, even in the absence of caseation or AFB. Stain and culture of the pleural biopsy is reported to have a higher yield than pleural fluid (positive results in approximately 25 and 56 % of biopsies respectively) (Light 2010).

3.3.2 Miliary Tuberculosis

Miliary TB can occur during primary infection and in post-primary disease. It indicates dissemination of disease and arises from the haematogenous spread of bacilli, which may occur shortly after primary infection or from any active disease site. Miliary granulomas are 1–3 mm in diameter (the size of a millet seed (Latin: milia)), are widespread and may be found in any visceral organ (Davies et al. 2014). In immunocompetent patients, miliary TB accounts for approximately 3 % of TB cases and is more commonly found in immunocompromised patients (>10 % of HIV-infected patients) and in young children (Sharma et al. 2005).

Clinical symptoms are mostly constitutional, including malaise, fever, weight-loss, sweats, anorexia. Pulmonary signs may be similar but often less pronounced than in uncomplicated pulmonary TB. If the brain is involved, neurological

symptoms may include headache, reduced consciousness and cranial nerve palsies. Involvement of other organs usually does not elicit localized symptoms. In immunocompromised patients physical signs may be less apparent and include dyspnoea, wasting, lymphnode enlargement, hepatosplenomegaly, cutaneous lesions. These patients are more at risk of meningeal involvement. Cutaneous involvement is rare (tuberculosis miliaria cutis), but if present may provide a valuable clue to the diagnosis. Rare complications including adult respiratory distress syndrome (ARDS), pneumothorax, cardiac and multi-organ dysfunction have been described. Due to the non-specific symptomatology, miliary TB is often only be discovered at post-mortem. A chest radiograph is pivotal in diagnosis, but is notoriously treacherous (Fig. 3.1b). A high index of suspicion is needed to be able to perceive the fine nodular lesions in more obscure cases. In uncertain cases, (high resolution) CT-scan is more sensitive in detecting the miliary lung nodularity (Sharma et al. 2005). Miliary TB may be accompanied by consolidation (30 %), parenchymal lung cavities (3–12 %), or mediastinal and/or hilar lymphadenopathy (15 %) on chest X-ray (Sharma et al. 2005). A missed diagnosis is grave, as untreated miliary TB often leads to TB meningitis and can be rapidly fatal.

Rapid diagnostic confirmation is not easily achieved, since cough is often non-productive, the sensitivity of conventional sputum smear is low. Smear may be performed on other bodily fluids such as gastric fluid, urine, cerebrospinal fluid, bronchial lavage and pleural fluid. Sputum culture may be positive in 30–60 % of patients. Tissue biopsy or fine needle aspiration may be indicated and should be sent for smear and biopsies examined for granulomatous disease. In tissue biopsies (liver, bonemarrow, transbronchial, pleura or lymphnode) confirmation rate is high and a diagnosis may be found in up to 83 % of cases.

3.3.3 Extra-Thoracic Lymphnode Disease

Cervical lymphadenitis (scrofula) is the most common form of extra-pulmonary TB. In the middle-ages it was known as 'the King's evil' because it was believed the touch of royalty could cure the disease. Before the pasteurization of milk, the more likely causative agent was *Mycobacterium bovis*, which is non-distinguishable from *M. tuberculosis* on ZN stain. Some non-tuberculous mycobacteria (NTM) are known to cause lymphadenitis: *Mycobacterium scrofulaceum, Mycobacterium avium-intracellular complex, Mycobacterium malmoense, Mycobacterium fortuitum, Mycobacterium chelonei* and *Mycobacterium kansassi,* of which Mycobacterium avium-intracellular complex is the most common causative agent (Handa et al. 2012). The route of entry is thought to be through ingestion, via the oropharyngeal mucosa or tonsils, or through skin abrasions.

In the US, lymphadenitis accounts for 40 % of extra-pulmonary TB cases. The most common site is the cervical region, followed by mediastinal, axillary, mesenteric, hepatic portal, peripancreatic, and inguinal lymphnodes (Rieder et al. 1990). Lymph node involvement may follow first-time infection as part of the

primary (Ghon) focus, with subsequent haematogenous or lymphatic spread, with reactivation of a dormant focus or with direct extension of a contiguous focus.

The patient usually presents with a palpable (lymph node) mass greater than 2 × 2 cm and mostly in the cervical area (60 %), either in the jugular, posterior triangle or supraclavicular region, with or without fistula or sinus formation (Handa et al. 2012). Other complications are overlying violaceous skin inflammation and cold abscess formation. Tenderness or pain is not typically described, unless there is secondary bacterial infection. Generalised constitutional symptoms and pulmonary symptoms or signs may be absent, but are more often reported in HIV-infected patients. The differential diagnosis includes bacterial adenitis, fungal infection, viral infection, toxoplasmosis, cat-scratch disease, neoplasms (lymphoma, metastatic carcinoma, Hodgkin's disease, sarcoma), sarcoidosis, drug reactions and non-specific hyperplasia.

The history is important and chest X-ray should be obtained but may be normal in the majority. TST may be helpful in non-endemic countries, reported positive in over 85 % of patients, however it may be negative in patients with HIV infection and non-tuberculous lymphadenitis (Razack et al. 2014).

Diagnosis is classically confirmed by excisional biopsy and histological and microbiological examination. Incisional biopsy has been associated with increased risk of sinus tract formation and is not recommended. Caseating granulomatous inflammation with Langhans and giant cells is highly suggestive of TB. Positive culture from biopsies are reported in between 60 and 80 %, with even higher rates reported fine needle aspiration biopsy (FNAB), which has replaced more invasive biopsies as the diagnostic procedure of choice (Handa et al. 2012). The diagnosis of lymph node TB can be achieved with a combination of FNAB cytology (detection of epithelioid cells), AFB smear, PCR and culture in over 80 % of cases (Razack et al. 2014).

3.3.4 Central Nervous System Tuberculosis

The most common clinical manifestation of central nervous system (CNS) TB is tuberculous meningitis (TBM). Other entities are CNS tuberculoma, which may be present without symptoms or rarely with seizures, tuberculous encephalopathy (rare, only described in children) and tuberculous radiculomyelitis. Pathogenesis is thought to be through a two-step process, in which heamotogenous spread leads to a tuberculous focus (Rich focus) in the brain, which then invades and release bacilli in the subarachnoid space (Donald et al. 2005). In HIV-infected patients and young children it is more often associated with miliary disease, which may indicate more direct haematogenous spread in these patients. TBM is the most lethal form of TB. Almost a third of HIV uninfected patients, and more than half of patients that are co-infected with HIV die from TBM, despite treatment. Half of the survivors suffer from permanent neurological impairment (Thwaites et al. 2004).

Early recognition and appropriate treatment are key to improved outcome. Early symptoms are non-specific, including the suggestive triad of fever, nightsweats and weightloss and headache of increasing intensity. A duration of symptoms (headache and fever) of more than 5 days should prompt clinicians to include TBM in the differential diagnosis. In the more advanced stages patients become more confused, present with reduced consciousness, hemiplegia, paraplegia and urinary retention (seen with spinal involvement) and cerebral nerve palsies, most frequently involved is nerve VI (up to 40 % of cases), but also III and VII. Seizures are not frequently a presenting symptom in adults (seen in less than 5 % of cases), however often reported in children (50 % of TBM cases). Movement disorders may be seen and are associated with typical basal ganglia involvement. Upon examination, nuchal rigidity is typically less pronounced than in acute bacterial meningitis. Sixth nerve palsy is pathognomonic (Thwaites and Tran 2005).

Diagnosis is often based on a clinical algorithm rather than mycobacterial isolation. Typical features on cerebral imaging on presentation are basal meningeal enhancement, hydrocephalus, and tuberculoma solitary or multiple (MRI shown in Fig. 3.1d). Cerebral infarction may occur during treatment, mostly in the basal ganglia, or paradoxical tuberculoma may form. The cerebrospinal fluid (CSF) is paucibacillary, thus diagnosis confirmed by AFB smear of the CSF is relatively rare (less than 20 % in most laboratories). CSF cellularity is typically lymphocytic (although neutrophils may predominate in the early stages), has raised protein content and moderately raised lactate (typically between 3 and 8 mmol/l), in contrast with bacterial meningitis in which lactate is generally higher. Raised ADA may aid diagnosis, however is not specific, particularly for the differentiation of bacterial meningitis (Tuon et al. 2010). If TBM is suspected, large volumes (>6 ml) of CSF should be drawn and concentrated by centrifugation in order to facilitate microbiological confirmation. Meticulous examination of the smear for up to 30 min can significantly increase detection to over 60 % of those clinically diagnosed (Thwaites et al. 2004).

In contrast to pulmonary TB where sputum smear is less often positive in HIV-infected individuals, CSF is more often positive in HIV-infected individuals with TBM. Liquid culture still provides the ‘gold standard’ (positive cultures found in approximately 65 % of clinical TBM cases), however results take 2–4 weeks and should not be awaited for treatment initiation. Xpert MTB/RIF is more sensitive than conventional smear and WHO currently recommends this PCR based test for the diagnosis of TBM (Nhu et al. 2013; World Health Organization 2013). The current treatment guidelines are extrapolated from pulmonary regimens, with durations varying from 9 to 12 months of at least 4 first-line agents and including adjunctive corticosteroids (Prasad and Singh 2008; Chiang et al. 2014). However a recent study suggests that the addition of fluoroquinolones and higher doses of rifampicin may improve treatment outcome, since CSF penetration of most of the first-line TB drugs (particularly rifampicin, streptomycin and ethambutol) is poor (Ruslami et al. 2012). Surgical intervention may be indicated in cases with severe non-communicating hydrocephalus and large tuberculousabcesses.

3.3.5 Tuberculous Pericarditis

Cardiac TB most frequently involves the pericardium. TB endocarditis or involvement of the myocardium is extremely rare. Clinical progression is characterized by insidious onset, classically with a presentation with fever of unknown origin. Upon examination a pericardial friction rub may be auscultated. ECG changes consist of diffuse ST elevations, without reciprocal changes, T wave inversion, PR segment deviations. Typical changes as found in acute pericarditis (The PR-segment deviation and ST-segment elevation) are only found in roughly 10 % of cases (Mayosi et al. 2005). Usually the rise in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are less marked compared to the same parameters measured in viral or bacterial pericarditis. A chest X-ray may reveal left pleural effusion, however this is a non-specific finding. Echocardiogram is central in diagnosis, revealing effusion and if present, tamponade. Confirmation of diagnosis is by demonstration of AFB in the pericardial aspirate by smear. In pericardial TB the sensitivity of smear is 15–20 % and of mycobacterial culture 30–75 % (Gooi and Smith 1978). The presence of cardiac tamponade is the most predictive sign of later development of constrictive pericarditis.

The optimal treatment duration remains uncertain, but suggested treatment regimens range from 6 to 12 months. The addition of corticosteroids as an adjuvant to prevent further accumulation of fluid and the development of constrictive pericarditis is recommended (Fowler 1991; Mayosi et al. 2005). Open surgical drainage may be indicated to prevent tamponade, however little data exists on the benefit of closed percutaneous drainage (Reuter et al. 2007).

3.3.6 Spinal Tuberculosis

Spinal TB can cause deformities, typically kyphosis, in extreme forming a gibbus, which can result in paraplegia. Depictions of sufferers are found originating from Ancient Egypt 5000 years ago. Since the late 18th century it became known as Pott's disease. After haematogenous spread, tuberculous spondylitis develops, initially affecting a single vertebra, but with progressing of infection, softening may result in wedging or collapse of the vertebral body and subligamentous spread may involve adjacent vertebrae (Jung et al. 2004). Cold abscesses formation or severe spinal angulation may cause compression of the spinal cord with neurological sequelae. In rare instances bacilli may be released into the subarachnoid space, leading to meningitis, or an abscess may drain externally with sinus formation (Cheung and Luk 2013).

MRI is the imaging modality of choice (Fig. 3.1c) (Jung et al. 2004). Evidence of pulmonary TB or other organ involvement, should heighten suspicion and provides an opportunity for the collection of samples for microbiological examination. Confirmation of diagnosis relies on the detection of AFB on CT-guided

tissue biopsies or abscess aspirates. Treatment regimens are as for pulmonary TB, however some advocate longer duration of treatment. Based on the results of a series of randomized clinical trials conducted by the MRC Working party on TB of the spine, spanning a period of 15 year follow up, it is currently accepted that early and mild disease, without significant neurological deficits, may be treated conservatively with anti-tuberculous chemotherapy without operative intervention. Patients treated with debridement alone or combined with spinal fixation (with anterior strut graft) had the tendency to earlier resolution of abscesses, earlier bony fusion and less kyphotic deformity (Mak and Cheung 2013). It is important to identify the poor prognostic factors that are associated with severe kyphosis development, such as the degree of vertebral body loss before treatment, and the separation of facet joints, to identify patients that would benefit for operative intervention by reducing kyphotic deformity.

3.3.7 Other Forms of Extra-Pulmonary Tuberculosis

Tuberculous arthritis, almost always affects only a single joint, usually the hip and knee. It can be diagnosed by examination of synovial fluid or synovial tissue biopsies. Gastrointestinal TB may mimic Crohn's disease, both clinically and radiographically. Preferred sites are the ileocecum, ileum and jejunum and is usually associated with peritonitis. Barium contrast studies can reveal ulceration, strictures, bowel wall thickening, skip lesions and fistulae. In endemic countries, diagnosis is usually made on clinical suspicion. Biopsies may be useful in establishing the diagnosis (Nagi et al. 2002, 2003).

Urogenital TB is notoriously asymptomatic. TB of the urinary tract, occasionally causes flank pain or present with a renal or pelvic mass. Persistent "sterile" pyuria on urine analysis, especially early morning samples, require further investigation with urine AFB smear, PCR and culture. Further investigations include intravenous urography (Merchant et al. 2013a, b).

Laryngeal TB is one of the most infectious forms of TB. Sputum smear is reported positive in up to 70 % of cases. It can result from primary infection with infected droplet nuclei or secondary to pulmonary disease. Hoarseness and dysphagia can be among the presenting signs. Laryngeal TB can be primary, when bacilli directly invade the larynx or secondary from bronchial spread of advanced pulmonary TB (Benwill and Sarria 2014). It presents with hoarseness and dysphagia, or chronic cough if associated with pulmonary TB (Michael and Michael 2011). It should be differentiated from laryngeal malignancy. TB can potentially affect any organ in the human body, further discussion of all rare forms fall beyond the scope of this chapter.

Chapter 4
Diagnosis

Abstract At the turn of the century, it was widely recognized that an accurate point-of care test for TB was required to make significant reductions in the pandemic. At this time, many novel tests had been developed by research groups or small biotech companies, but had never been standardized or evaluated for scale-up and application in low-resource, high-burden settings where the need is greatest. This motivated a major drive to systematically evaluate existing tests such as commercial liquid culture and nucleic acid amplification tests (NAAT), and to develop new approaches, principally led by the Foundation for Innovative New Diagnostics (FIND www.finddiagnostics.org) in collaboration with industry, government and clinical partners. The evidence generated by this renewed focus on novel TB diagnostic tests, processes and algorithms has led to a substantial number of policy revisions and new WHO recommendations (Table 4.1, see also www.tbevidence.org).

Keywords Smear microscopy · Ziehl neelsen stain · Mycobacterial culture · Nucleic acid amplification tests (NAAT) · Xpert MTB/RIF · GeneXpert · Line probe assay · Drug-resistant tuberculosis · Interferon gamma release assays (IGRA)

4.1 Smear Microscopy

The confirmation of TB disease still rests upon identification or isolation of *M. tuberculosis* bacilli from a clinical sample. This can be achieved by smear microscopy for acid-fast bacilli (AFB), mycobacterial culture or nucleic acid amplification (NAAT) tests. The appropriate sample will depend upon the suspected site of disease. The quality of the sample may greatly affect the chances of a positive result therefore care should be taken to instruct the patient in producing a sputum sample. Children are often unable to produce sputum and in young children gastric aspirate is usually necessary.

D. Heemskerk et al., *Tuberculosis in Adults and Children*,
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Table 4.1 Laboratory tests for diagnosis of active tuberculosis and drug resistance

Diagnostic tests for active TB

Test type	Principal commercial tests	WHO policy recommendation	Advantages	Limitations
Smear microscopy	Non-commercial	Recommended	Inexpensive, simple, rapid, specific	Cannot differentiate NTM[a] and *M. tuberculosis*
LED microscopy		Recommended	Inexpensive, simple, rapid	Cannot differentiate NTM[a] and *M. tuberculosis*
Automated real-time nucleic acid amplification	GeneXpert MTB/RIF	Recommended	Rapid (2 h to result). Detects smear-negative TB. Also detects RIF resistance	Higher cost than smear
Loop-mediated isothermal amplification test kit for TB	LAMP assay	Not recommended. Under further development	Rapid, simple	Subjective interpretation and poor specificity
Rapid speciation strip technology		Recommended	For rapid differentiation of NTM[a] and *M. tuberculosis*	Expensive
Serodiagnostic tests	Over 20 commercial variants	Not recommended		Poor sensitivity and specificity
Interferon-Gamma release assays	QuantiFERON-TB Gold In-Tube test, T-Spot test	Not recommended for diagnosis of active TB		Complex to perform and indeterminate results relatively common

Drug susceptibility tests

Test type	Principal Commercial tests	WHO policy recommendation	Drugs tested	Advantages	Limitations
Phenotypic DST on solid or liquid media	Non-commercial	**Recommended for USE**	All drugs[b]	Gold-standard	Extremely long time to result (6–12 weeks)
Commercial liquid culture and DST systems	Bactec MGIT	**Recommended for USE**	STR, INH, RIF, EMB, PZA	Faster than solid culture media. Ten days if direct testing	Expensive

(continued)

Table 4.1 (continued)

Drug susceptibility tests					
Test type	Principal Commercial tests	WHO policy recommendation	Drugs tested	Advantages	Limitations
Line probe assay first-line	MTBDR-Plus; INNO LiPA-RIF TB	**Recommended for USE on smear-positive samples**	RIF, INH	Result in 2 days	Expensive
Line probe assay second-line	MTBDRsl	**Not yet recommended due to insufficient evidence**	Fluoroquinolones, aminoglycosides and EMB	Result in 2 days	Low sensitivity for ethambutol
Automated real-time nucleic acid amplification	GeneXpert MTBRIF	**Recommended for USE**	RIF	Result in 2 h	Cartridge price reductions only available in low middle income countries
Microscopic observation drug susceptibility (MODS)	Non-commercial	**Recommended for USE**	RIF, INH	Low-tech. 10–14 days for result	Subjective interpretation. Laborious manual plate reading[c]
Colometric redox indicator (CRI)	Non-commercial	**Not yet recommended due to insufficient evidence**	RIF, INH	Low-tech. 10–14 days for result	Subjective interpretation
Nitrate reductase assays (NRA)	Non-commercial	**Not yet recommended due to insufficient evidence**	RIF, INH	Low-tech 10–14 days for result	Subjective interpretation

(continued)

Table 4.1 (continued)

Drug susceptibility tests					
Test type	Principal Commercial tests	WHO policy recommendation	Drugs tested	Advantages	Limitations
Phage assays	FASTplaque, lucerferase reporter phage assay	Not recommended	RIF, INH	N/a	Poor specificity
Sequencing	Non-commercial	No policy	Depends on gene regions sequenced	Can provide information on multiple drugs simultaneously	Requires specialist interpretation. Not generally available outside research centres

Details of policy guidance at: http://www.who.int/tb/laboratory/en/

[a]NTM: non-tuberculous mycobacteria

[b]Reliable for first-line drugs (except pyrazinamide), fluoroquinoloes and aminoglycosides. Second-line DST should be interpreted in context of treatment history and local prevalence of resistance (if known)

[c]Indicator well must be incorporated to differentiate NTM from *M. tuberculosis*

Diagnosis for the majority of patients worldwide suspected of TB is still made by sputum smear microscopy for acid-fast bacilli. The test, which was developed 100 years ago by Franz Ziehl and Frederick Neelsen, is inexpensive, simple, rapid and specific but is only positive in around half of patients with active TB. The Ziehl-Neelsen smear exploits the acid-fast property of mycobacteria by staining bacilli with carbol-fuschin, using gentle heat to facilitate penetration of the dye, and then using a decolorising acid solution, which fails to penetrate the mycobacteria, leaving them stained red while other bacilli are decolorised. The slide is usually then counterstained with methylene blue to improve visualization of the mycobacteria (World Health Organisation 1998). The Kinyoun stain is an alternative cold-stain method. The sensitivity of the test is substantially lower in children and patients with HIV. In addition the test is not specific for *M. tuberculosis*, but detects all acid-fast bacilli including NTMs. Sensitivity may be increased by concentration of samples prior to microscopy, usually by centrifugation or filtration (Van Deun et al. 2000) but direct (unconcentrated) ZN stain is the most widely applied methodology due to resource limitations.

Traditional TB control focused on the identification and treatment of sputum smear-positive TB patients, considered to be most infectious cases, in the mistaken belief that systematic identification and treatment of smear-positive cases would be sufficient to reach eventual TB elimination. Recent efforts to improve the sensitivity of basic smear microscopy have developed improved fluorescent microscopes to decrease the reading time and increase the sensitivity of smear microscopy without significantly affecting specificity if training and quality control are maintained. WHO now recommends the replacement of conventional microscopy with fluorescent microscopy wherever possible, using rugged and energy efficient LED fluorescent microscopes that can be battery operated. In a further policy change, WHO recommended in 2010 that two sputum samples are sufficient, rather than the standard three samples (spot-morning-spot) which had been recommended for several decades (World Health Organisation 2010). This is due to the low diagnostic yield of a third sputum sample and the resource limitations of TB programmes. If clinical suspicion is high repeated testing may still be warranted. A single positive smear is now also considered sufficient for a TB diagnosis (Bonnet et al. 2007; Mase et al. 2007).

4.2 Mycobacterial Culture

Culture of *M. tuberculosis* is a more sensitive technique for diagnosis but due to the slow growth of the organism (replication time of 24–30 h) sputum cultures take 4–6 weeks to become positive on solid media and 10–21 days in liquid media. Solid culture is usually performed on Lowenstein Jensen (LJ), Ogawa or Middlebrook 7H10/11 agar media. Liquid culture of *M. tuberculosis* is more sensitive and rapid than solid culture but can be prone to contamination in some laboratories. Early commercial automated liquid culture systems for mycobacteria used radiometric

assay but have now been replaced with fluorescence based quenching systems which has improved safety. The most widely used system is the Bactec Mycobacterial Growth Indicator Tube (MGIT) (Becton Dickinson, Sparks, Massachusetts) system which can also be used for susceptibility testing to first line drugs using a commercially available kit. A culture is necessary to confirm drug susceptibility, particularly for second-line drugs in cases of multi-drug resistance (MDR TB). *M. tuberculosis* culture and phenotypic DST requires significant training, infrastructure, strict infection control and on-going quality assurance, which is only available in regional reference laboratories in most countries.

4.3 Nucleic Acid Amplification Tests

Various commercial and in-house nucleic acid amplification tests (NAAT) have been available since the 1990s. Detection of *M. tuberculosis* in clinical samples is generally less sensitive than NAAT for other pathogens due to the relatively low numbers of bacilli present and the difficulty of efficiently extracting DNA from the tough mycobacteria. The development of Line Probe assays (LPA) allowed the simultaneous detection of *M. tuberculosis* and determination of resistance to rifampicin and later isoniazid. However these tests are only endorsed for use on smear positive sputum and therefore do not aid greatly in the diagnosis of TB itself. The MTBDR-Plus assay (HainLifesciences, Nehren, Germany) has recently been adapted to enhance detection for use on smear negative sputum samples but large-scale evaluation data is not yet available. The use of LPA for detection of drug resistance is discussed in more detail in the section on diagnosis of drug resistance below.

The most significant advance in the diagnosis of TB in the last decade has been the advent of the GeneXpert MTB/RIF test (Cepheid, California, USA). This test system was originally developed for testing for the presence of anthrax spores in the United States bioterrorism-scares. A specific cartridge was later developed to detect *M. tuberculosis* and simultaneously determine resistance to rifampicin. In 2010 results of a multi-country demonstration study sponsored by FIND demonstrated that the Xpert MTB/RIF test detected TB and rifampicin resistance with high sensitivity and specificity compared to liquid culture; confirmed by a Cochrane review in 2013. The test was officially endorsed by WHO, followed by an unprecedented rapid scale up of the new technology [http://who.int/tb/laboratory/mtbrifrollout/en/]. A key factor in wide-scale implementation was a negotiated price reduction facilitated by a large guaranteed buy-down from UNITAID, USAID, PEPFAR and the Bill and Melinda Gates Foundation which reduced the price per cartridge from more than 40 USD to less than 10 USD for public health facilities in 141 low and middle income countries. A major advantage of the Xpert MTB/RIF test is the ability to detect smear negative TB in HIV-infected individuals (World Health Organization 2013).

In 2013 WHO issued updated policy guidance on the use of Xpert MTB/RIF additionally endorsing its application for extrapulmonary and pediatric samples. This policy update expanded the recommended application of Xpert MTB/RIF to include pediatric and extrapulmonary samples, including gastric aspirate, lymph aspirate, pleural fluid and cerebrospinal fluid. There was insufficient evidence to estimate sensitivity with urine, pericardial fluid and ascitic fluid, although specificity is generally high with these sample types. Optimal sample processing for blood and stool samples has not been determined and therefore the Xpert MTB/RIF test is not recommended pending further research. Full recommendations can be found at http://tbevidence.org/wp-content/uploads/2013/11/WHOstat.pdf.

By facilitating early detection of TB, prior to smear positivity, the application of Xpert MTB/RIF should have a significant impact on transmission chains and push back the epidemic. However, many of the patients diagnosed by Xpert MTB/RIF would have been initiated on treatment due to chest X-ray findings or clinical findings consistent with TB and the extent to which the use of Xpert MTB/RIF will increase case finding is not yet clear. Theoretical modelling studies suggest that the application of the test will improve targeting of treatment, with less patients who do not have TB incorrectly started on treatment and a greater number of smear negative 'true TB' cases detected. South Africa has implemented the Xpert MTB/RIF test nationwide and data on the cost-effectiveness and impact on the epidemic are

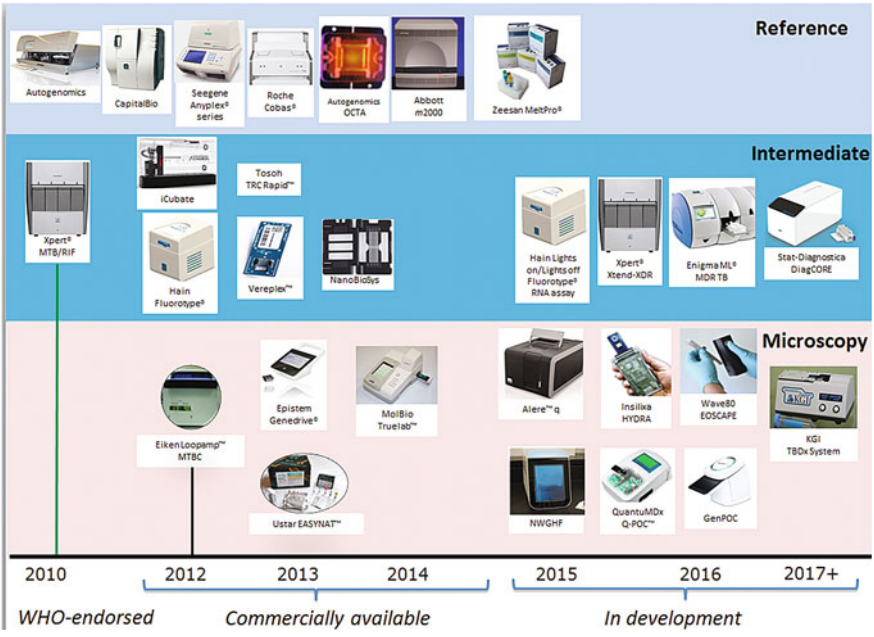

Fig. 4.1 Current development in TB diagnostics. Only the Xpert® MTB/RIF has received WHO endorsement. *From* UNITAID, Diagnostic technology and market landscape, 3rd edition, 2014. Reprinted with permission

eagerly awaited. Although relatively simple to perform and rapid, the Xpert MTB/RIF is not a true point-of-care test and many challenges have been encountered during scale-up. The need for a reliable electricity supply is a major barrier in some settings, problems with module calibration and maintenance, the need for the bulky cartridges to be stored below 30 °C, determining optimal testing algorithms and logistics of kit supply have been some of the challenges encountered (Abdurrahman et al. 2014) (Fig. 4.1).

4.4 Diagnosing Drug-Resistant Tuberculosis

A major impact of the scale-up of Xpert MTB/RIF is increased detection of RIF resistance, which is a surrogate marker for MDR TB. Classical diagnosis of drug resistance in *M. tuberculosis* involves culture of the bacilli on solid or liquid media and comparison of growth between drug-free and drug containing media. Even with the advent of direct liquid culture methodology, detection of drug resistance takes over two weeks, and with indirect methods, two months or more. Standardisation of drug susceptibility testing for the antituberculous drugs is difficult and should be performed in a biosafety level 3 laboratory by trained personnel participating in an external quality assurance scheme. Isoniazid, rifampicin and streptomycin are the most reliable drug susceptibility tests.

Molecular detection of drug resistance mutations provides a rapid alternative, but the accuracy of these tests varies according to the drug. Rifampicin resistance detection is the most accurate, as 95 % of phenotypically rifampicin resistant strains carry a mutation in the 81 base pair rifampicin—resistance-determining-region (RRDR) of the rpoB gene. For isoniazid, molecular methods can detect approximately 75 % of phenotypically resistant strains by detecting mutations in the katG gene or InhA promoter region. Development of commercial NAAT for the other antituberculous drugs has been hampered by incomplete understanding of the molecular mechanisms of resistance. The principal commercial NAAT for drug resistance are the Xpert MTB/RIF test and the line probe assays. The most recent pooled estimates for *M. tuberculosis* detection by Xpert MTB/RIF were sensitivity of 88 % (95 %CI; 83–92%) and specificity of 98 % (95 %CI; 97–99 %); for rifampicin resistance sensitivity 94 % (95 %CI; 87–97 %) and specificity 98 % (95 %CI; 97–99 %) (Steingart et al. 2014). Line Probe assays detect both rifampicin and isoniazid resistance simultaneously and the MTBDR-sl assay detects resistance to fluoroquinolones, ethambutol and aminoglycosides. The MTBDR-sl test has high sensitivity for fluoroquinolones, but low sensitivity for aminoglycoside and ethambutol resistance (Feng et al. 2013). However, specificity is high for all drugs and therefore the test can be used to detect resistance but should not be used to rule-out resistance. Unfortunately, the need remains to confirm susceptibility by laborious phenotypic DST. Rapid sequencing techniques provide more comprehensive drug susceptibility data but are not yet widely available beyond research settings.

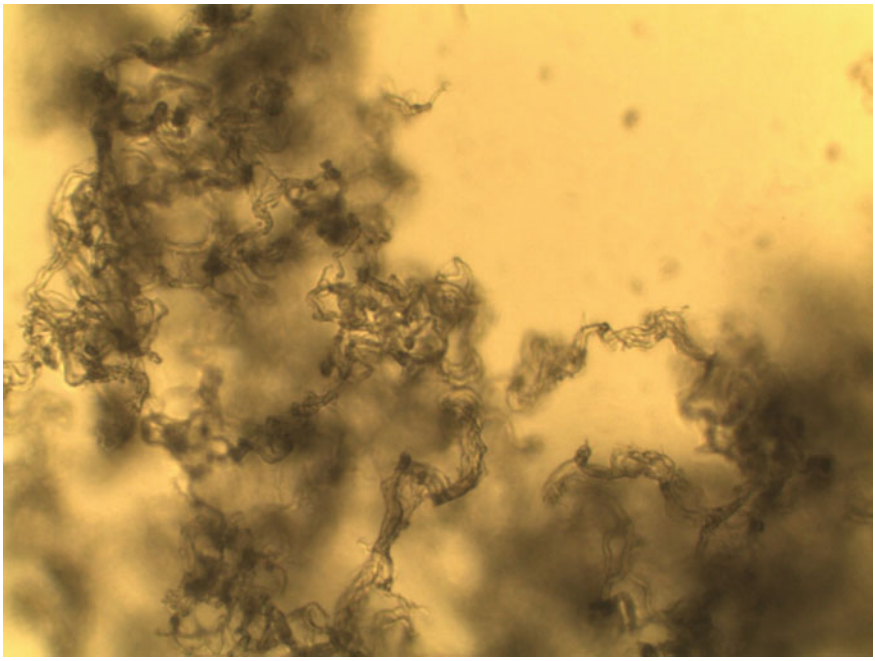

Image 4.1 Mycobacterial cording in MODS. *Image* courtesy of Dr. Dang Thi Minh Ha

Several non-commercial phenotypic DST approaches have been developed including microscopic observation drug susceptibility testing (MODS), nitrate reductase assay (NRA) and colorimetric redox indicator (CRI) tests. A MODS test kit is now available to improve standardization (Hardy diagnostics). In 2010 WHO issued a recommendation that MODS could be used as an 'interim' approach for increased DST in high-burden countries but concluded that there was insufficient data to recommend NRA or CRI. Reservations particularly around biosafety and quality control have limited scale-up of the techniques (Image 4.1).

4.5 Other Diagnostic Methods

In 2011 WHO issued an unprecedented negative advisory on the use of serodiagnostic tests for TB (Steingart et al. 2011). These tests are appealing because of they are simple, rapid, inexpensive and non-invasive and are marketed with claims of high sensitivity and specificity. However, systematic evaluation of 19 commercially available tests using a well-characterised serum bank, and systematic review of all published studies concluded that none was accurate for use in clinical practice (Steingart et al. 2011). The search for accurate biomarkers for use in serodiagnostic tests continue, but has so far yielded little promise. Tests under evaluation by the

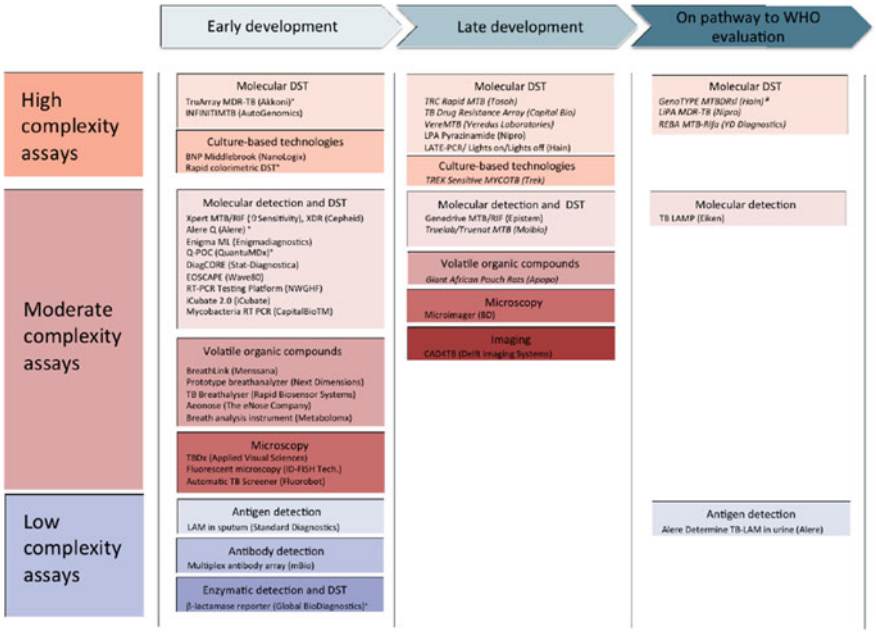

Fig. 4.2 Current FIND TB diagnostics pipeline listing the development phases and the types of technologies in development or evaluation, from UNITAID diagnostic technology and market landscape, 2014, reprinted with permission

Foundation for Innovative New Diagnostics (FIND; www.finddiagnostics.org) include the loop-mediated isothermal amplification test (LAMP) assay, mobile NAAT devices, volatile organic compound (VOC) or 'electronic nose' tests, an adapted interferon-gamma release assay, and enzymatic detection systems. It is unlikely that a true point-of-care test for TB will be available in the next 2–3 years given the current pipeline of diagnostic tests under evaluation (Thwaites et al. 2003; UNITAID 2014) (Fig. 4.2).

4.6 Diagnosing Latent Tuberculosis Infection

The interferon gamma release assays (IGRA) were developed as an alternative to the tuberculin skin test which is confounded by BCG vaccination. Two commercial IGRAs are currently FDA approved for the diagnosis of *M. tuberculosis* infection: The QuantiFERON-TB Gold In-Tube test (QFT-GIT) (Cellestis Limited, Carnegie, Victoria, Australia, approved 2007); T-Spot test (Oxford Immunotec Limited, Abingdon, United Kingdom, approved 2008). Whole blood or Peripheral blood mononuclear cells (PBMC) are stimulated with antigens from *M. tuberculosis* and the interferon gamma release stimulated is measured. IGRA which use ESAT-6 and

CFP-10 antigens for stimulation are not confounded by prior BCG vaccination because these antigens are found in a region (RD1) of the *M. tuberculosis* genome which is deleted from BCG and thought to be partially responsible for the loss of virulence.

In the United States, IGRA are widely used for the diagnosis of latent TB infection and are recommended by CDC guidelines (available at: http://www.cdc.gov/mmwr/pdf/rr/rr5905.pdf). WHO do not recommend the use of IGRA in endemic settings or for the diagnosis of active TB. It should be noted that 95 % of IGRA positive individuals do not go on to develop active TB and therefore the predictive value of a positive IGRA is extremely low; no statistically significant difference in the incidence of active TB between IGRA positive and IGRA negative individuals has been demonstrated in the small number of studies which have addressed this question.

Chapter 5
Treatment

Abstract In this chapter the treatment of drug sensitive and drug resistant TB and timing of antiretroviral treatment for HIV infected patients will be reviewed. Emphasis is placed on results of recent trials of fluoroquinolones for treatment shortening of drug sensitive TB. The use of two relatively novel agents in MDR-TB treatment, bedaquiline and delamanid, will be discussed.

Keywords First-line antituberculous treatment · Rifampicin · Isoniazid · Pyrazinamide · Streptomycin · Ethambutol · HIV associated tuberculosis · Antiretroviral therapy (ARV, ART) · Treatment of drug-resistant tuberculosis · Fluoroquinolones · Bedaquiline · Delamanid

5.1 First-Line Antituberculous Treatment

The introduction of rifampicin to the first-line combination regimen in the late 1970s allowed the shortening of treatment for TB from 18–24 months to 6 months. This "short-course" regimen, consists of an 'intensive phase' of 4 first line drugs; ethambutol (EMB) [or streptomycin (SM)], isoniazid (INH), pyrazinamide (PZA) and rifampicin (RIF) for 2 months followed by a 'continuation phase' of 2 months of RIF and INH (Table 5.1). The continuation phase may be extended in more complex cases and some countries still use an 8-month standard regimen which is no longer recommended by WHO. Ethambutol should be used in place of the injectable streptomycin where possible for HIV-infected individuals. Since the development of the short-course regimen, standard TB-treatment has remained largely unchanged for the past 40 years. Daily, directly observed therapy (DOT) is preferable to intermittent regimens and fixed dose combination (FDC) drugs may be used to ensure multi-drug therapy (Nunn et al. 2014). Pyridoxine should be administered with isoniazid to prevent peripheral neuropathy. The historic events that have led to the current treatment schedule are comprehensively reviewed by Diacon and colleagues (Diacon et al. 2012).

D. Heemskerk et al., *Tuberculosis in Adults and Children*,
SpringerBriefs in Public Health, DOI 10.1007/978-3-319-19132-4_5

Table 5.1 Drugs used in the treatment of tuberculosis

	Drug	Adult dose mg/kg (range); [maximum dose]	Pediatric dose mg/kg (range); [maximum dose]	Common side effects[a]
Group 1: first-line oral drugs				
	Isoniazid[b]	5 (4–6) [300 mg]	10 (7–15) [300 mg]	Hepatitis; peripheral neuropathy
	Rifampicin (rifapentine/rifabutin alternative rifamycins)	10 (8–12) [600 mg]	15 (10–20) [600 mg]	Hepatitis; orange discoloration of secretions; drug-drug interactions
	Pyrazinamide	25 (20–30)	35 (30–40) [2000 mg]	Hepatitis; arthralgia
	Ethambutol	15 (15–20 mg/kg)	20 (15–25) [1200 mg]	Visual disturbance (acuity, colour vision)
Second-line drugs (group 2, injectables)				
	Streptomycin (S)	15 (12–18) [1000 mg]	Not recommended as first-line. 15 (12–18) [1000 mg]	Auditory nerve damage
	Kanamycin (Km)	15–20 mg/kg [1000 mg]	15–30 [1000]	Renal failure (usually reversible)
	Amikacin (Am)	15–20 mg/kg [1000 mg]	15–22.5 [1000]	Proteinuria, serum electrolyte disturbances including hypokalaemia and hypomagnesaemia
	Capreomycin (Cm)	15–20 mg/kg [1000 mg]	15–30 [1000]	Nephrotoxicity (20–25 %), tubular dysfunction, azotaemia, proteinuria, urticaria or maculopapular rash
Group 3: fluoroquinolones				
	Levofloxacin (Lfx)	750 mg [1000 mg]	7.5–10	Generally well tolerated
	Moxifloxacin (Mfx)	400 mg daily dose	7.5–10	
	Ofloxacin (Ofx)	800 mg [1000 mg]	15–20 [800]	

(continued)

Table 5.1 (continued)

	Drug	Adult dose mg/kg (range); [maximum dose]	Pediatric dose mg/kg (range); [maximum dose]	Common side effects[a]
Group 4: oral bacteriostatic second-line				
	Ethionamide (Eto)	15–20 mg/kg [1000 mg]	15–20 mg/kg [1000 mg]	Severe gastrointestinal intolerance (nausea, vomiting, diarrhoea, abdominal pain, excessive salivation, metallic taste, stomatitis, anorexia and weight loss. Unable to tolerate 1 g as a single dose
	Prothionamide (Pto)	15–20 mg/kg [1000 mg]	15–20 mg/kg [1000 mg]	
	Terizidone (Trd)	15–20 mg/kg [900 mg]	10–20 [1000]	Neurological and psychiatric disturbances, including suicidal and psychotic episodes
	Cycloserine (Cs)	15–20 mg/kg [1000 mg]	10–20 [1000]	Neurological and psychiatric disturbances, including headaches, irritability, sleep disturbances, aggression, and tremors, gum inflammation, pale skin, depression, confusion, dizziness, restlessness, anxiety, nightmares, severe headache, drowsiness
	Para-aminosalicylic acid (PAS)	150 mg/kg [8 g]	150 mg/kg [8 g]	Gastrointestinal intolerance (anorexia and diarrhoea); hypo-thyroidism (increased risk with concomitant use of ethionamide)

(continued)

Table 5.1 (continued)

	Drug	Adult dose mg/kg (range); [maximum dose]	Pediatric dose mg/kg (range); [maximum dose]	Common side effects[a]
Group 5: Agents with unclear role in treatment of drug resistant-TB[c]				
	Clofazimine (Cfz)	100 mg daily		Ichthyosis, and dry skin; pink to brownish-black discoloration of skin, cornea, retina and urine; anorexia and abdominal pain
	linezolid (Lzd)	600 mg daily		Gastrointestinal disturbance, vision disturbances, anaemia
	Amoxicillin/clavulanate (Amx/Clv)	875 twice daily		Gastrointestinal disturbance, psychiatric disturbance, sleep disturbance
	Thioacetazone (Thz)[d]	2.5 mg/kg [150]		Gastrointestinal disturbance, arthralgia, seizures, hepatitis
	High-dose isoniazid (high-dose H)	16–20 mg/kg/day		Hepatitis; peripheral neuropathy
	Clarithromycin (Clr)	500 mg daily		Gastrointestinal disturbance
Novel Agents	Bedaquiline	400 mg once daily		Nausea, arthralgia, headache, vomiting, gastrointestinal disturbance, QT prolongation
	Delaminid	200 mg twice daily		QT prolongation

[a]Hypersensitivity reactions and drug rashes may occur with any anti-tuberculous drug
[b]Pyridoxine should be given with isoniazid to prevent peripheral neuropathy. Guidelines variously recommend 10 or 25 mg/kg daily
[c]Optimal dose and long-term safety not well established for group 5 drugs
[d]Do not use thioazetone for HIV-infected individuals (significant risk of Stevens-Johnson syndrome)

WHO treatment guidelines can be found at http://www.who.int/tb/publications/tb_treatmentguidelines/en/index.html. Treatment recommendations for pediatric TB were revised in 2010, with an increased dose of all first-line drugs (http://whqlibdoc.who.int/publications/2010/9789241500449_eng.pdf) and a request not to use streptomycin as a first-line drug in children (World Health Organisation

2014). This followed systematic review of evidence showing that children achieve inadequate serum exposure when receiving the same dose/kg as adults and there was no evidence of adverse toxicity from the higher doses. Pharmacokinetic data from South Africa showed substantially improved serum levels with the novel regimen but it remains to be demonstrated if these doses are sufficient to achieve improved outcomes (Thee et al. 2011).

5.2 HIV Associated Tuberculosis

The advent of HIV has severely impacted the burden of TB. All HIV patients should be screened for TB and all TB patients should be offered HIV testing. Dual treatment of HIV and TB is complex, as patients are faced with a higher pill-burden, increased risk of toxicity, drug-interactions and IRIS (Lawn et al. 2013; Lai et al. 2013). Routine administration of co-trimoxazole (960 mg/day) is recommended in all patients with HIV-associated TB, since it has been shown to substantially reduce mortality in patients in Sub Saharan Africa. Rifampicin is an inducer of the cytochrome P450 2B6 enzyme, which is the main pathway for the non-nucleaside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) either of which are the basis of ARV treatment (Bonnet et al. 2013). The most commonly used NNRTI is efavirenz. Although the US FDA recommends that the dose of efavirenz should be increased when co-administered with rifampicin, this is not substantiated in the most recent clinical trials, which show excellent virological response in those patients receiving standard dose (600 mg) of efavirenz (Kwara et al. 2010). Nevarapine is an alternative NNRTI used for those patients who cannot tolerate efavirenz, but plasma levels are very low in patients receiving rifampicin during the lead-in phase of nevarapine. This may predispose to resistance formation and virological failure. Dose increase is not recommended because concerns of toxicity, however it is plausible to omit the 14 day lead-in phase of nevirapine dosing after the CARENIMO trial showed that nevirapine was well tolerated at full dose when introduced in patients with CD4 cell counts <250/mm^3 while receiving rifampicin (Bonnet et al. 2013). The co-administration of second-line ARV regimens containing PIs remains a challenge and there is an urgent need for clinical trials evaluating safety and efficacy. ‘Superboosting’ of ritonavir or doubling dose of lopinavir/ritanovir combination formulation are suggested, as is substituting rifabutin for rifampicin (Lawn et al. 2013).

Timing of initiation of ARV treatment in ARV-naïve TB/HIV patients has been evaluated in a recent series of clinical trials published in 2011 (SAPIT [NCT00398996], CAMELIA[NCT01300481] and the AIDS clinical trial group study A5221). Results showed that there is a reduction in mortality in patients with CD4 cell counts lower that 200/mm^3 (CAMELIA trial) or 50/mm^3 (other two trials) when ARV treatment was initiated within 2 weeks of TB treatment (GRADE A^3), (Abdool Karim et al. 2010, 2013; Blanc et al. 2011). However this carries an increased risk of IRIS and treatment toxicity. The management in patients with

higher CD4 cell counts is less clear and it may be acceptable to defer ARV treatment until the continuation phase of TB treatment. The majority of patients in these trials had pulmonary TB. For patients with TB meningitis, a recent large Vietnamese randomised controlled trial showed no benefit of early initiation of ARVs and deferred treatment at 2 months was associated with less toxicity and less occurrence of IRIS (Torok et al. 2011). Patients in this cohort had extremely low median CD4 count and the results may not be generalizable to other populations.

5.3 Treatment of Drug-Resistant Tuberculosis

The use of multi-drug therapy for TB treatment from the early days of discovery of antituberculous drugs has actually preserved the efficacy of the five first line agents for TB remarkably well for over 50 years. However, drug resistance in *M. tuberculosis* is increasing and has now reached alarming levels, particularly in the former Soviet states, India, South Africa and part of Asia. Approximately 8 % of *M. tuberculosis* cases globally are now resistant to isoniazid. Multi-drug resistant TB (MDR TB) is defined as TB resistant to at least isoniazid and rifampicin, the two key first line drugs in the treatment regimen. MDR TB is much harder to treat, requiring a minimum of 18 months treatment with expensive, toxic and weak second line drugs. Worldwide, 3.6 % of newly diagnosed and 20 % of patients previously treated for TB have MDR TB but there are dramatic regional variations with the highest proportion in Eastern Europe and Central Asia (WHO 2014).

In 2012 there were an estimated 450,000 new cases of MDR TB worldwide and 170,000 deaths but only 17 % were diagnosed and enrolled into high quality treatment programmes. This figure does however represent a 42 % increase on 2011, reflecting scale-up efforts for MDR detection and treatment. In 2006 WHO defined a new category of drug resistant TB as extensively drug resistant TB (XDR TB). XDR TB is MDR TB additionally resistant to a fluoroquinolone and a second line injectable drug (amikacin, capreomycin or kanmycin). This followed a documented outbreak in Kwa-Zulu Natal province of South Africa in which 53 cases of XDR TB were identified among HIV patients, all but one of whom died with a median survival time of 16 days from diagnosis. Following acceptance of the definition of XDR TB, 92 countries have reported cases by 2013 (Fig. 5.1). It is estimated 10 % of MDR cases are in fact XDR and it is now clear that XDR TB is present in almost every country although the extent of transmission within communities is not established due to the limited availability of second-line drug susceptibility testing for *M. tuberculosis*. The term totally drug resistant TB has been used in the literature to describe *M. tuberculosis* strains resistant to all first and second line drugs but the use of this term is not recognised by WHO due to the difficulty of standardising drug susceptibility testing for second line drugs and the introduction of treatment options (Cegielski et al. 2012).

Drug resistant TB should be treated with at least four drugs to which the organism is susceptible, prioritising any first-line agents and then including a

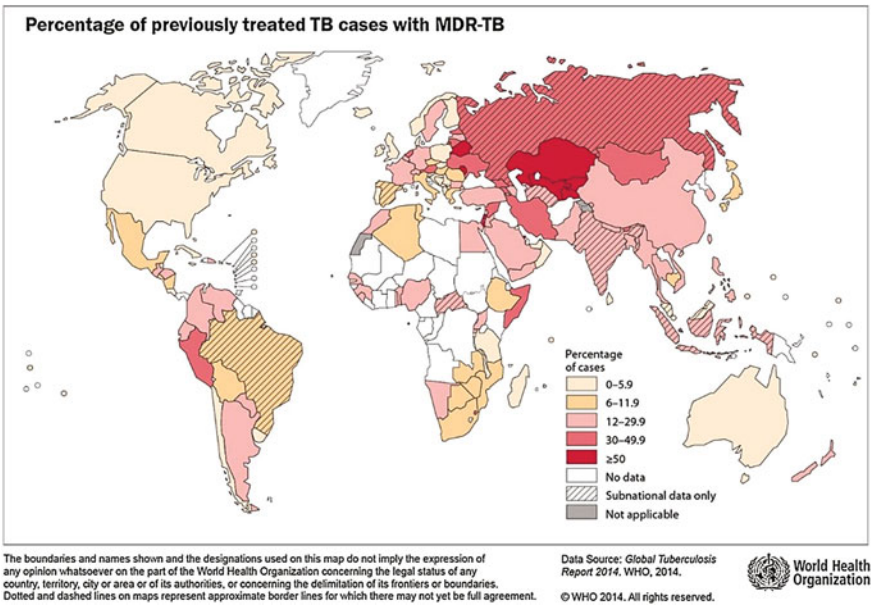

Fig. 5.1 Percentage of previously treated TB cases with multidrug-resistant TB. *Source* WHO, reprinted with permission

fluoroquinolone and an injectable agent. In order to protect against drug resistance amplification, a single drug should never be added to a failing regimen (Daley and Caminero 2013). Key principles of MDR treatment are summarised in Table 5.2 (Kaufmann et al. 2014; Ulrich et al. 2006).

Comprehensive CDC guidelines on both susceptible and drug resistant TB can be found on http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm.

The painstakingly sluggish decline in incidence of TB and the rise of MDR- and XDR-TB underlines the inadequacies of current treatment and prevention measures. Priority questions for research, in addition to the search for novel agents include shortened regimens, optimal regimens for all forms of drug resistant TB, optimal dose of drugs (especially rifampicin), and treatment of HIV-associated TB.

Several existing and newly developed compounds are under evaluation for drug-sensitive and drug-resistant TB (Fig. 5.2). In light of the growing epidemic of MDR-TB and lack of new drug development there has been renewed interest in obsolete compounds for TB (Chang et al. 2013). In 2010, the Damien Foundation published the results of an observational study, comparing six regimens for MDR-TB, derived by sequential modification. The addition of gatifloxacin and use of clofozimine throughout the regimen apparently allowed a reduced duration of treatment, to between 9–12 months, depending on time to smear conversion. All 427 patients received clofazimine in the intensive phase and 206 patients received a shortened regimen of 9–12 months, using clofazimine throughout treatment [4(+) KCGEHZP, 5 GCEZ]. Treatment success-rate was highest in the short regimen

Table 5.2 Guidelines for the management of tuberculosis caused by drug-resistant organisms

Do not add a single drug to a failing regimen
When starting or modifying therapy, add three previously unused drugs (one an injectable) to which there is likely to be susceptibility
Use any of the first-line oral agents (Group 1) that are likely to be effective
In multidrug-resistant tuberculosis (MDR TB), when there is resistance to additional first-line drugs, treat with 4–7 drugs (dependent on degree of confidence in susceptibility and strength of derived regimen)
Patients with MDR TB have the highest priority for directly observed therapy because treatment failure may be associated with extensively drug-resistant TB
Intermittent therapy should not be used (except for injectables after 2–3 months)
Do not use drugs to which the *M. tuberculosis* isolate is resistant. Low-level resistance to isoniazid may be an exception
There is cross-resistance among rifamycins but not between streptomycin and other aminoglycosides. Amikacin or kanamycin are preferred aminoglycosides for MDR as most MDR strains are resistant to streptomycin
Drug susceptibility testing for pyrazinamide is complex technically and not performed in most laboratories. Monoresistance to pyrazinamide suggests *M. bovis*
Drug susceptibility results for second line agents (except fluoroquinolones and aminoglycosides) may be unreliable and should be interpreted within context of treatment history
Levofloxacin, or moxifloxacin are preferred flouroquinolones. Ciprofloxacin should not be used to treat TB

treatment group with a relapse-free cure of 87.9 % (95 %CI 82.7–91.6), with relatively good tolerability (Van Deun et al. 2010). This shortened 'Bangladesh' regimen is now being subjected to a large multicentre (including sites in Ethiopia, India, South Africa, Vietnam) randomised controlled trial, known as the STREAM trial (ISRCTN78372190). The STREAM trial is being conducted by the British Medical Research Council and will compare the standard MDR regimen (according to local National TB program guidelines, duration ranging from 18–24 months) with a modified form of the Bangladesh regimen. Moxifloxacin, clofazimine, ethambutol and pyrazinamide will be given for nine months, supplemented by kanamycin, isoniazid and prothionamide in the four months of the intensive phase. All drugs are given daily except for kanamycin which is administered thrice weekly after 12 weeks. The target is to include at least 400 participants. The results of this major trial are expected in October 2016.

5.4 The Role of Fluoroquinolones

The fluoroquinolones levofloxacin, gatifloxacin and moxifloxacin have strong antimycobarterial activity with an early bactericidal activity (EBA) similar to that of isoniazid and are the strongest of the second-line agents. Fluoroquinolones are the keystone of MDR treatment regimens and should also be considered in cases of non-MDR drug resistant TB requiring additional agents or if a first-line agent in the standard regimen is not tolerated, particularly in case of hepatotoxicity. Fluoroquinolones are excreted via the kidneys and thus have a lower potential to disturb liver function. They inhibit bacterial replication via the DNA gyrase, a mechanism distinct from those of the first-line agents. They have broad-spectrum antibacterial activity, particularly against gram-negative bacteria, favourable pharmacokinetic profile, are relatively safe, have good tissue penetration and high in vitro activity against *M. tuberculosis*. Fluoroquinolones may therefore work synergistically to the other TB agents and penetrate well in the tuberculoma. A recent Cochrane review, evaluating RCTs on ofloxacin, levofloxacin, moxifloxacin and gatifloxacin, reported that there is insufficient evidence to be clear whether fluoroquinolones, either added to the first-line regimen or as a substitution for ethambutol or isoniazid, may prevent relapse or death, or increase sputum culture conversion at 8 weeks (Ziganshina et al. 2013). Three large multicountry trials have been established to determine if the use of fluoroquinolones can shorten treatment regimens to four months rather than six: OFLOTUB (NCT00216385), REMOX TB (NCT00864383) and RIFAQUIN (ISRCTN44153044) studies (Merle et al. 2014; Gillespie et al. 2014; Jindani et al. 2013). The RIFAQUIN trial reported in April 2013 and showed inferiority of the four month regimen; Two months of daily ethambutol, moxifloxacin, rifampicin and pyrazinamide followed by two months of twice weekly moxifloxacin (500 mg) and rifapentine (900 mg) compared to the standard 6-month WHO regimen (2HRZE/4HR).

The OFLOTUB trial which tested a 4 month regimen of 2 months gatifloxacin (400 mg/day), isoniazid, rifampicin and pyrazinamide followed by two months gatifloxacin, isoniazid and rifampicin reported in September 2013 and (2GHRZ/2GHR) failed to show non-inferiority of the Gatifloxacin regimen at the pre-specified 6 % margin (Merle et al. 2014). Although Gatifloxacin has been banned by the FDA due to toxicity concerns, there was no increased risk of disgylcemia or QTc prolongation with the gatifloxacin regimen. The REMOX trial which tested two moxifloxacin containing regimens lasting 17 weeks, reported in 2014. The moxifloxacin-containing regimens produced a more rapid initial decline in bacterial load, as compared with the control group. However, noninferiority for these regimens was not shown, which indicates that shortening treatment to 4 months was not effective in this setting (Gillespie et al. 2014). Several existing and newly developed compounds are under evaluation for drug- sensitive and drug-resistant TB (Fig. 5.2) (Ma et al. 2010; Chang et al. 2013; Gopal et al. 2013).

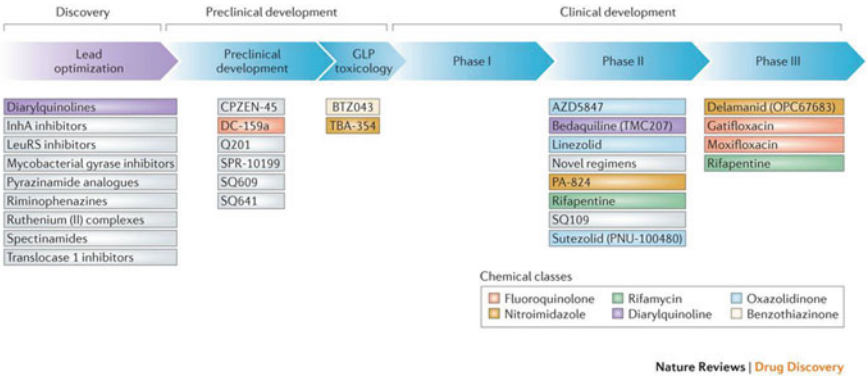

Fig. 5.2 TB drug discovery pipeline

5.5 Bedaquiline

Bedaquiline (trade name Sirtuto) is a diarylquinoline drug, formerly known under its code name TMC207, which was discovered in 2005 by Koen Andries and colleagues in Belgium. It has a novel mode of action, acting by inhibiting ATP synthase, and is active against replicating and non-replicating bacilli. The first phase II trial on 47 patients was published in 2009 in the New England Journal of Medicine and showed that addition of TMC207 to a standard second line regimen led to a higher proportion of patients with sputum conversion at 8 weeks of treatment (48 % vs. 9 %), (Diacon et al. 2012). The long-term 2 year follow up results for this pilot trial were published in 2012 and showed a significant reduction in time to sputum conversion in the TMC207 patients compared to placebo and less acquisition of resistance to companion drugs in the TMC207 group, however this did not reach statistical significance. With the exception of nausea, which was more frequently reported in the TMC207 patients, the occurrence of adverse events was not different between the two groups (Diacon et al. 2014). These results combined with two other phase II trials have led to accelerated approval of the drug by the FDA in 2012. This was the first new TB drug added to the arsenal of agents in decades. FDA approval was conditional upon prioritisation of phase three trials, but these have not yet started. The WHO and CDC have published provisional guidelines on the use of bedaquiline: http://www.who.int/tb/challenges/mdr/bedaquiline/en/index.html and http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6209a1.htm?s_cid=rr6209a1_e (Provisional CDC guidelines for the use and safety monitoring of bedaquiline fumarate (Sirturo) for the treatment of multidrug-resistant tuberculosis 2013).

5.6 Delamanid

Delamanid, (OPC 67683) is a nitro-dihydro-imidazooxazole derivative which acts by blocking the synthesis of myolic acids, thus interfering with cell-wall integrity of the mycobacteria. It was first proposed to be a potential new candidate for treatment of TB in 2006 by Japanese scientists working for Otsuka Pharmaceutical. Subsequently it has shown promising results in phase IIa and b trials. In a seminal RCT including 481 patients recruited in 17 centers in 9 countries, the proportion of sputum positive MDR-TB patients that converted to sputum negative after 2 months of treatment with delamanid (100 mg BID) added to an optimised background regimen (n = 161) was 45.4 % opposed 29.6 % in those patients receiving a background regimen and placebo (n = 160) (p = 0.008). The patients receiving delamanid had significantly shorter time to sputum negativity and, additionally, a mortality benefit was observed for those in the active arms of this trial (Gler et al. 2012). Phase III trials are underway.

The European Medicines Agency (EMA) approved the drug for use in MDR-TB in November 2013, making Delamanid the second drug to be approved for use in (MDR-)TB in 50 years. It will be manufactured under the name of Deltyba.

Chapter 6
Prevention

Abstract Prevention is the key to stop transmission of TB. It consists of early diagnosis and treatment of active TB to stop infectiousness, the prevention of active disease in exposed or known latently infected individuals and vaccination. Vaccination with the Bacillus Calmette-Guerin (BCG) vaccine is unfortunately largely ineffective in interrupting transmission. However a more powerful vaccine will have the potential to cause a major shift in the management of TB. In this chapter prophylactic treatment in latently infected and HIV infected patients is reviewed. Additionally the prevention of active disease in MDR-exposed persons and vaccine development will be discussed.

Keywords Prophylactic treatment · Prophylactic treatment in multi-drug resistant tuberculosis · Vaccine · Latent tuberculosis · Prevention

6.1 Prophylactic Treatment

TB transmission to susceptible contacts primarily occurs in enclosed, poorly ventilated locations. High risk locations for transmission are high density congregate living environments such as hospitals, care homes, prisons or student/migrant worker hostels. Transmission within institutional environments such as hospitals can be reduced by implementing effective infection control policies covering administrative, environmental and respiratory protection (refer to CDC guidelines for detailed recommendations: http://www.cdc.gov/tb/publications/guidelines/infectioncontrol.htm).

The standard regimen for treatment of latent TB infection is nine months isoniazid, also known as isoniazid prophylaxis therapy (IPT). Pyrodoxine should be given with isoniazid (Udani et al. 1971). In 2011 a trial of a novel 12 dose regimen of isoniazid and rifapentine showed higher completion rates and no loss of efficacy

D. Heemskerk et al., *Tuberculosis in Adults and Children*,
SpringerBriefs in Public Health, DOI 10.1007/978-3-319-19132-4_6

compared to the standard 9-month isoniazid treatment (Sterling et al. 2011). The 12-dose regimen has since been incorporated into US recommendations but is not recommended for children younger than 2 years of age, people with HIV/AIDS who are taking antiretroviral therapy (ART), people presumed to be infected with INH or rifampin-resistant *M. tuberculosis* or pregnant women, or women expecting to become pregnant while taking this regimen: http://www.cdc.gov/tb/publications/ltbi/treatment.htm.

A recent mass isoniazid prevention trial in South African mine workers showed no reduction in TB incidence and prevalence beyond the 9 months of IPT, suggesting that in high TB burden areas, transmission is not interrupted and the unchanged incidence is due to reinfection (Churchyard et al. 2014).

HIV is the strongest risk factor for developing TB in those with latent or recent *M. tuberculosis* infection, between 20 and 37 times the risk for those without HIV. To avoid treating an active TB case with monotherapy, HIV-infected individuals should be screened for active TB before the administration of IPT (Rangaka et al. 2014).

There is considerable debate around the duration of IPT in HIV-infected individuals since the trial data from South African miners who are heavily exposed showed that the protective effect of IPT quickly wanes, with the protective effect disappearing after one year. This is likely to be due to IPT clearing any latent infection, and therefore preventing reactivation disease, but not preventing re-infection after completion of therapy. WHO recommends extended IPT (36 months) for individuals living in areas with a high background prevalence of HIV and TB. There is concern that the widescale application of long-term IPT will lead to increases in isoniazid resistance and decrease in efficacy over time, but there is no evidence that this is occurring. Trials of long-term IPT are now underway in South Africa.

The reservoir of latently infected individuals is clearly a major barrier to eventual TB elimination, and shorter, less toxic regimens for latent TB will be a major boost to elimination efforts.

For more information on TB prevention: http://www.tbfacts.org/tb-prevention.html.

6.2 Prophylactic Treatment in Multi-drug Resistant Tuberculosis

Evidence to guide the choice of regimen for prophylatic treatment of the contacts of MDR and XDR TB patients is extremely limited. Derivation and testing of standardised regimens is complicated by the diverse spectrum of possible susceptibility patterns of an index case.

The American Thoracic Society (ATS) and the US Centers for Disease Control and Prevention (CDC) recommend prophylactic therapy for MDR TB contacts with the regimen to be used determined by the drug susceptibility profile of the potential source case. WHO and European guidelines [The International Standards for TB Care (ISTC) and European Union Standards for TB Care (ESTC)] favour careful clinical follow-up for a period of at least two years.

The European Centre for Disease prevention and control issued guidance on management of contacts of MDR and XDR patients in 2012 based upon systematic review of the available evidence: http://www.ecdc.europa.eu/en/publications/publications/201203-guidance-mdr-tb-contacts.pdf. The guidance recommends that each case must be considered individually with a comprehensive assessment of the likely risks and benefits of preventative therapy of unknown efficacy versus intensive clinical monitoring for signs of disease. The risk assessment should include consideration of any known individual risk factors for progression to active disease, the drug susceptibility pattern of the index case and any known risk factors for adverse events with the prophylactic regimen. A recent prospective observational study on an island in Micronesia, followed MDR-TB contacts who were offered 12-month preventive treatment with a fluoroquinolone. Among the 119 infected contacts, 15 refused, while 104 began treatment for MDR latent TB infection. None of the 104 contacts who undertook treatment with fluoroquinolones developed MDR-TB disease; however, 3 of 15 contacts who refused and 15 unidentified contacts developed MDR-TB disease (Bamrah et al. 2014). These data are compelling and warrant randomized studies, as the ability to prevent MDR-TB transmission would be the paradigm shift in MDR-TB management.

6.3 Vaccines

The only vaccine currently available for TB is the bacillus Calmette-Guerin (BCG) vaccine developed by serial passage of *Mycobacterium bovis* and introduced in 1921. BCG is the most widely used vaccine in the world but measures of effectiveness have varied widely, between 0 and 80 %. Studies have however, consistently shown a protective effect against the most severe forms of childhood TB, including TB meningitis. Meta-analysis of all published studies produced an estimate of 50 % for overall efficacy and 80 % efficacy in preventing TB meningitis (Colditz et al. 1994). BCG should not be administered to HIV-infected individuals (Nuttall and Eley 2011). Several theories have been proposed for the differences in observed effectiveness, including the use of different strains of BCG, variation in early exposure to non-tuberculous mycobacteria prior to vaccination, host genetic

variation and pathogen genetic variation but none of these theories has strong supporting evidence to date.

Clearly, given the huge burden of global TB and the major barrier to elimination that the 'silent' reservoir of latently infected individuals represents, an effective TB vaccine would be a major advance in the battle to eradicate TB. However, the correlates of protective immunity in TB are not understood which represents a major hurdle to developing an effective vaccine. The most advanced vaccine candidate for a primary TB vaccine, MVA85A, failed to show any efficacy in a phase IIb trial in HIV-uninfected infants published in 2013 (Tameris et al. 2013). This trial should however provide valuable data to guide further development of novel vaccine candidates.

The current pipeline includes three distinct approaches to the development of a TB vaccine, known as Prime, boost or immunotherapy. An alternative strategy also being explored is post-infection vaccination. Vaccine types currently under-development include (1) modification of the BCG vaccine (recombinant BCG), (2) Boosting of BCG with adjuvants, (3) incorporation of TB antigen expression into vaccine vectors or (4) killed whole cell or extracts (Kaufmann et al. 2014).

6.4 Concluding Remarks

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 factor in a favourable outcome for all forms is early recognition and appropriate treatment. TB is the most common cause of death among HIV patients, estimated to cause a quarter of AIDS related deaths.

Drug resistant TB is a growing problem and threatens to reverse the recent gains in global TB control. In regions of the former soviet states MDR TB is found in over half of all new TB cases and threatens a return to untreatable strains of TB disseminating globally without immediate and sustained action. 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.

Table of useful online TB resources

Topic	Source	Website
Non-tuberculous mycobacterial disease	American Thoracic Society (ATS)	http://www.thoracic.org/statements/resources/mtpi/nontuberculous-mycobacterial-diseases.pdf
United States TB statistics	Center for Disease Control (CDC)	http://www.cdc.gov/tb/statistics/reports/2012/default.htm
Tuberculin skin test (TST) interpretation	CDC	http://www.cdc.gov/tb/publications/factsheets/testing/skintesting.htm
Novel tuberculosis diagnostics	Foundation for Innovative New Diagnostics (FIND)	http://www.finddiagnostics.org
Evidence-based TB diagnosis	McGill University	http://www.tbevidence.org
TB diagnostics; XpertMTB/RIF Roll-out	World Health Organisation (WHO)	http://who.int/tb/laboratory/mtbrifrollout/en/
Xpert MTB/RIF for diagnosis of pulmonary and extrapulmonary TB in adults and children Policy Update	WHO	http://tbevidence.org/wp-content/uploads/2013/11/WHOstat.pdf
IGRA for detecting infection with Mtb	CDC	http://www.cdc.gov/mmwr/pdf/rr/rr5905.pdf
TB diagnostics and laboratory strengthening	WHO	http://www.who.int/tb/laboratory/en/
TB treatment guidelines	WHO	http://www.who.int/tb/publications/tb_treatmentguidelines/en/index.html
TB treatment in children	WHO	http://whqlibdoc.who.int/publications/2010/9789241500449_eng.pdf
Comprehensive treatment susceptible and drug resistant TB	CDC	http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5211a1.htm
Use of bedaquiline in MDR TB	WHO	http://www.who.int/tb/challenges/mdr/bedaquiline/en/index.html
Use of bedaquiline in MDR TB	CDC	http://www.cdc.gov/mmwr/preview/mmwrhtml/rr6209a1.htm?s_cid=rr6209a1_e
TB infection control and prevention guidelines	CDC	http://www.cdc.gov/tb/publications/guidelines/infectioncontrol.htm
Management of contacts of MDR TB and XDR TB patients	European Centre for Disease prevention and Control (ECDC)	http://www.ecdc.europa.eu/en/publications/publications/201203-guidance-mdr-tb-contacts.pdf
TB vaccine resources	StopTB partnership	http://www.stoptb.org/wg/new_vaccines/documents.asp
Global Plan to stop TB 2006–2015	WHO	http://www.who.int/tb/features_archive/global_plan_to_stop_tb/en/
Tuberculosis treatment success rate	WHO	http://www.who.int/gho/tb/epidemic/treatment/en/

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Index

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