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Textbook of Tuberculosis & Nontuberculous Mycobacterial Diseases

THIRD EDITION



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JAYPEE

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2

Epidemiology of Tuberculosis: Global Perspective

Dennis Falzon, Knut Lönnroth, Mario C Raviglione

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INTRODUCTION

No country in the world today, rich or poor, can claim to be free of tuberculosis [TB]. In some high income countries, the rates of TB have been brought down to very low levels, but the demographic realities of aging and migration, shifts in host vulnerability, as well as the evolution of the organism itself, constantly threaten a comeback. The burden of TB morbidity and mortality in the world as a whole impinges most heavily on the people of developing countries, and disproportionately on the poor and other disadvantaged subpopulations of better resourced countries. In 2014, 9.6 million new TB cases were estimated by the World Health Organization [WHO] to have occurred globally, with 4 million in the South-East Asian Region [SEAR] of WHO and 2.2 million in India alone (1). Apart from posing a formidable burden of disease worldwide, TB ranks as the 10th leading cause of global deaths and 13th in terms of years of healthy life lost worldwide (2). It competes with human immunodeficiency virus [HIV] as the leading cause of death from an infectious disease. These staggering statistics jar with the fact that the large majority of TB patients could be cured and many TB deaths avoided with 6 months of treatment, which is generally well-tolerated, accessible and affordable in most settings. This chapter traces the historical imprint of TB upon humankind and looks at the major determinants of TB in the world today and the evolution of the epidemic in recent decades in different geographical regions. In conclusion, we outline the actions that need to be taken in future to consign TB to history, as the perspective for global health and development policy shifts beyond the 2015 horizon of the United Nations Millennium Development Goals [MDG] (3).

This Chapter uses findings from several published sources. In addition to those referenced throughout the text we use estimates derived by WHO based on notification and surveillance data reported by the national authorities responsible for TB control in their respective countries. The burden of disease is expressed as the TB incidence and prevalence; the burden of death as TB mortality. The background data are collected online in aggregated format by the Global TB Programme of WHO on an annual basis and are also supplemented periodically with data from special surveys [e.g., drug-resistance and disease prevalence]. Following collection, data undergo checks for internal consistency and are then consolidated into a central database. Modelled estimates are used when data are missing; the methodology employed to derive these estimates has been described elsewhere (1,4). The updated information is published each year in the annual Global Tuberculosis Reports that WHO has issued uninterruptedly since 1997 (5,6). The information is updated each year and the raw data can be downloaded free-of-charge or via interactive query tools [e.g., country profiles]. Mortality data are also collected by WHO through a separate mechanism from the one described above and estimates are also used to replace missing data in the countries where vital registration is not functional (7). The definitions and indicators in use in this Chapter have been revised and standardised over a number of years, and their latest update was released in 2013 (8). The countries included in the regional groupings in this Chapter are as defined by WHO (1).

HISTORICAL PERSPECTIVE

Deoxyribonucleic acid [DNA] studies of archaeological material show that TB has afflicted mankind since the Neolithic period (9). However, it is also likely that this host-pathogen relationship dates back much further than nine millennia (10). Hippocrates [c.460-c.377 BCE], the Father of Western Medicine, described the public health importance of what was referred to as phthisis at his time. Over the years,

the disease acquired evocative names such as "galloping consumption", "the white plague" and "captain of all these men of death", all attesting to its tragic legacy (11,12). At the height of the epidemic in western Europe around the end of the 18th and start of the 19th centuries, TB was likely to be killing an astounding 1% of the population each year (13). Around this time, TB was the cause of one-fourth of deaths in London and of between one-third and one-sixth elsewhere in England and Wales (14). TB mortality declined during the 19th century in western Europe, albeit it remained a major killer even at the end of the century (15). This decrease is commonly ascribed to improvements in socioeconomic conditions (16), although it has been argued that the isolation of cases in sanatoria and possibly the evolution of natural immunity may have contributed to this trend (17). The decline in TB was disturbed during the period of the two World Wars in the 20th century but resumed immediately after their end. In countries like France, Great Britain, the Netherlands, and Norway, the annual risk of TB infection fell at the fastest rates ever documented in the decades after 1950 (18,19). Continued improvements in the economic situation, nutrition, and living conditions, effective preventive measures, and expanded curative services equipped with the newly introduced anti-TB medicines brought the burden of disease in European countries to very low levels. Even if this decline was temporarily halted or even reversed in a number of industrialised countries from the late 1980s (20,21), rates have since continued to fall bringing the TB incidence lower than 10/100,000 in many of them today [Figure 2.1]. In western countries, the TB burden has now become largely concentrated in two broad age-bands in the population: [i] the elderly native patient with reactivation of TB infection contracted at a time when TB was rife and [ii] younger adults who have a higher risk of recent infection [e.g., homeless persons, migrants from high prevalence settings] or of progression [e.g., people living with HIV].

However, the TB caseload in the world today concentrates to a large extent in poorer countries where the disease remains an important public health threat. There is much less documentation about trends of TB in the developing world. In many low and lower-middle income countries the impact of control efforts on annual risk of TB infection has been less dramatic than in the richer ones (22).

NATURAL HISTORY, RISK AND DETERMINANTS OF TUBERCULOSIS

In humans, the natural course of TB from infection to disease shares some characteristics with other infectious conditions

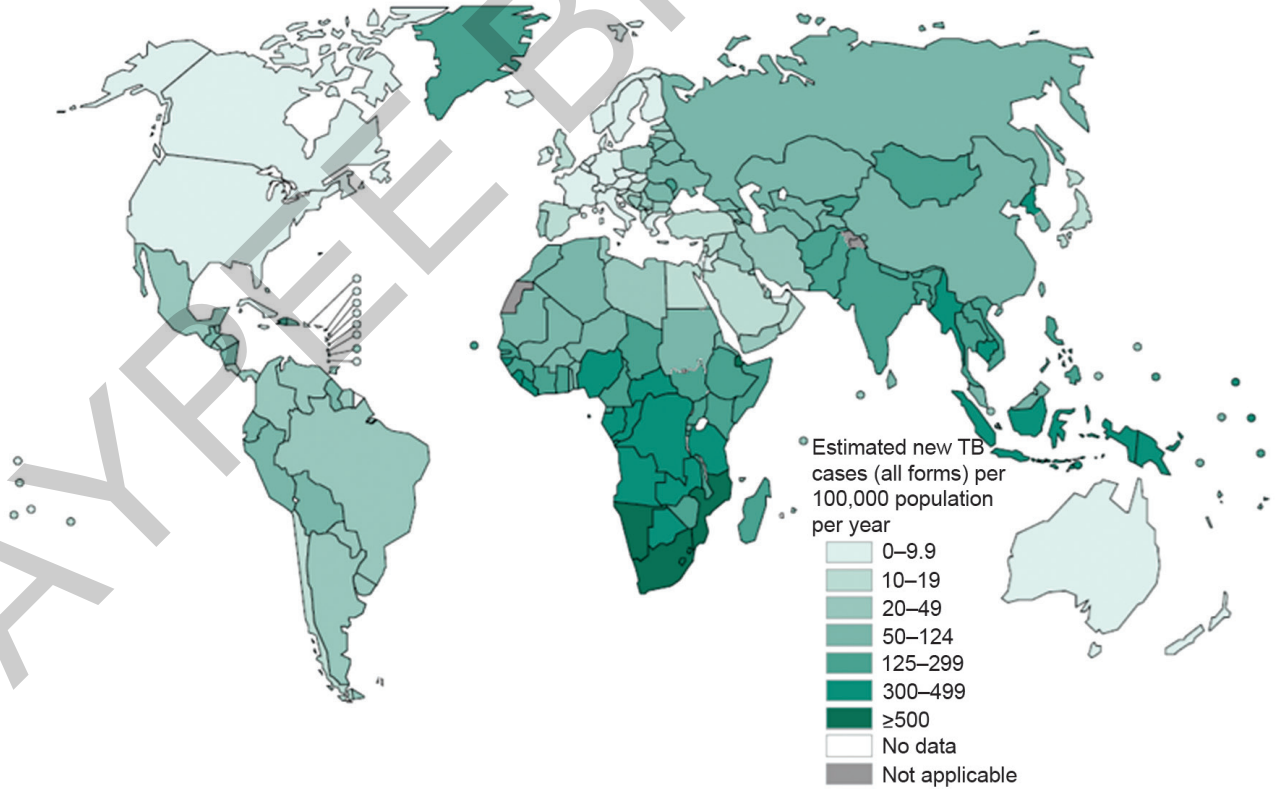

Figure 2.1: Estimated TB incidence rates by country, 2014
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The World Health Organization updates these data annually. The reader can access the updated information from the WHO report of the current year available at the URL: http://www.who.int/topics/tuberculosis/en/

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caused by directly transmissible organisms. Exposure to the viable organisms, usually through respiratory droplets expelled during coughing, but also possible through infected milk can lead to implantation in the lung or other tissues. This normally results in asymptomatic [latent or persistent] infection. Progression to disease with the clinical manifestations may then ensue rapidly in the first 12-18 months post-exposure or after many decades. In up to half of cases, pulmonary forms of the disease develop which are infectious to their contacts; other individuals contract less infectious pulmonary or non-infectious extrapulmonary forms. The disease, if left untreated, results in death in over two-thirds of pulmonary sputum-smear positive cases within 10 years [without HIV infection], as was documented in the pre-antibiotic era (23). Alternatively, it may resolve spontaneously in a minority of cases or evolve towards a chronic form of disease that may last for years. Successful resolution of the disease does not confer a lasting immunity and the disease may later reactivate. Patients with chronic disease may survive for several years and be infectious until death or, rarely, spontaneous resolution. The propensity of TB to chronicity and to recurrence makes it different from many other infectious conditions.

Spontaneous mutations create strains of *Mycobacterium tuberculosis* [*Mtb*] which are resistant to different drugs used in their treatment (24). These events are rare, and have been estimated to occur at average rates of 2.56×10^{8} and 2.25×10^{10} per bacterium per generation for isoniazid and rifampicin respectively (25). However, exposure to individual anti-TB medicines favours the selection and replication of drug-resistant strains within an affected individual. TB patients who acquire drug-resistance from treatment may transmit these strains to their contacts [primary drug-resistant infection].

A number of factors influence the natural history of TB at its different stages in an individual. Exposure to infection is more likely when the number of infectious cases is high in a particular setting, when the period of transmissibility is long, and when opportunities for effective contact between infectious and susceptible persons are high. In situations where population density is high such as during rapid urbanization and the expansion of slum settlements, the risk of exposure may also increase, as crowded and poorly ventilated settings are conducive to an intense exposure to the infectious agent. Once exposed, not all individuals have the same risk of infection and other factors come into play: these determinants are largely external to the host and include those related to the infecting inoculum [critical size of droplets, concentration of bacilli in sputum], environmental conditions which promote the persistence of infectious nuclei in the air, and virulence of the strain. Certain genotypes of the Beijing lineage of *Mtb* have been associated with rapid worldwide spread and an association with disease clustering, suggesting increased virulence even when drug-resistance is acquired by these strains, an added concern (26-28). It has been estimated in the past that, if left untreated, each person with active TB may infect on average between 10 and 15 people every year. TB patients infected with HIV are on average less infectious, albeit the overall transmission of TB is increased within a community where HIV prevalence is elevated.

In contrast to infection, the risk of progression to disease is largely determined by predisposing factors in the host. Many conditions which modulate the immune response can thus increase the likelihood of disease in a person infected with *Mtb*. HIV stands out as the most potent risk factor, increasing the relative risk for TB by more than 20, but others such as under-nutrition, silicosis, tobacco smoking, diabetes, harmful alcohol use, and immunomodulatory drugs such as anti-tumour necrosis factor agents also play a role. Age is also an important factor and risk appears higher in late adolescence and young adulthood. Finally, besides these risks, the likelihood that a person is cured or dies of TB is influenced also by an array of other factors, including the form of disease, for e.g., higher mortality in miliary TB and TB meningitis (29-31) and whether effective chemotherapy for TB is provided (32,33). If treated with combined, first-line anti-TB chemotherapy, the chances of cure may exceed 90% among patients with drug-susceptible bacilli. Patients treated for multidrug-resistant TB [MDR-TB], defined as isolates of *Mtb* resistant to rifampicin and isoniazid, with or without resistance to other anti-TB drugs, however, are less likely to have a successful outcome than those without, and success is less likely if additional resistance is present (34,35). The provision of anti-retroviral treatment [ART] to TB/HIV patients has been shown to significantly decrease the chances of unsuccessful outcomes (36-38).

The impact that different risks factors for TB infection, disease progression and unfavourable outcome have on TB epidemiology varies substantially across the world. The sum effect of the interplay of these risks on a population is a function of the potency of these factors at the individual patient level and their prevalence in the population. For instance, the overall population level effect of HIV is very pronounced in southern African countries, where infection is highly prevalent in contrast to countries of the Indian subcontinent, where less potent risk factors which occur more frequently are more important. The use of population attributable fractions [PAF] is useful to analyse this interaction in individual countries (39,40). There are sharp differences among the 22 highest TB burden countries which concentrate about 80% of TB incidence in the world in the relative contribution of each of these determinants to their TB incidence. For instance, in all countries except Thailand and those in Africa, the PAF for adult TB associated with smoking was higher than for HIV while in 14 of the 22 countries the total PAF related to under-nutrition was the highest. Problems of alcohol use and diabetes are important in certain countries but if their prevalence increases in the world, they may become more prominent in future. These risk factors for TB are eminently modifiable and, therefore, amenable to public health interventions; in contrast, other risk factors like age and genetic predisposition could serve to profile individuals and risk groups where action could be more meaningfully targeted.

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THE GLOBAL BURDEN OF TUBERCULOSIS

Incidence

In 2014, there were an estimated 9.6 million [range 9.1-10 million] incident cases of TB in the world, equivalent overall to 133 cases per 100,000 population but with very extreme geographical variations [Figure 2.1] (1). One million incident cases were children and 3.2 million [range, 3.0-3.4 million] occurred among women. Fifty-eight percent of incident TB cases occurred in Asia and 28% in the African Region. India [23%], Indonesia and China [10% each] accounted for two-fifths of global cases in 2014. Over one third of the world's caseload was concentrated in the 11 countries of the South-East Asia Region, where the rate, at 211/100,000 population, was much higher than the global value [Table 2.1] (1).

In South Africa and Swaziland, about 1% of the population is estimated to develop TB each year, while many countries in western Europe, the US, Australia and New Zealand have rates about a 100 times lower than this. In 2014, 1.2 million [13%] of the 9.6 million new TB cases were HIV-seropositive globally, and 74% of TB cases among people living with HIV worldwide were in the African Region [Figure 2.2] (1). In parts of southern Africa, more than 50% of TB cases were co-infected with HIV. Globally, the estimated TB incidence rate was relatively stable from 1990 until around 2000, since when it has been slowly declining [Figure 2.3] achieving this MDG target far ahead of the 2015 deadline. The MDG target has also been met in all six WHO regions and in 16 of the 22 HBCs (1).

Table 2.1: TB incidence and case detection, South-East Asia Region of WHO, by country, 2014

Country	*Incidence [in thousands; including HIV]*	*Case detection (%)*
Bangladesh	360 [320-410]	53 [47-60]
Bhutan	1.3 [1.1-1.4]	85 [77-94])
DPR Korea	110 [100-120])	93 [87-100]
India	2200 [2000-2300]	74 [70-80]
Indonesia	1000 [700-1400]	32 [23-46]
Maldives	0.15 [0.130-0.170]	89 [78-100]
Myanmar	200 [180-220]	70 [64-78]
Nepal	44 [39-50]	79 [71-90]
Sri Lanka	13 [12-15]	69 [62-79]
Thailand	120 [61-190]	59 [36-110]
Timor-Leste	5.8 [4.8-6.9]	63 [53-77]
All S-E Asia Region	4000 [3700-4400]	62 [56-68]

TB = tuberculosis; WHO = World Health Organization; HIV = human immunodeficiency virus; S-E = South-East

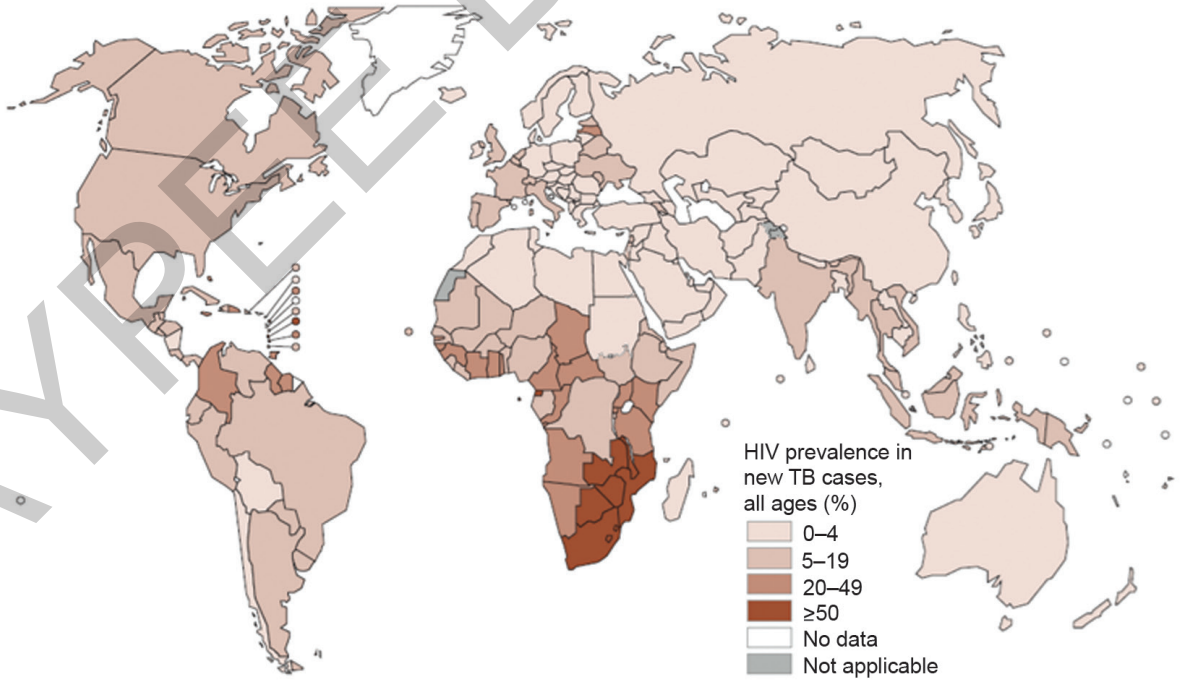

Figure 2.2: Estimated HIV prevalence in new and relapse TB cases, 2014
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The World Health Organization updates these data annually. The reader can access the updated information from the WHO report of the current year available at the URL: http://www.who.int/topics/tuberculosis/en/

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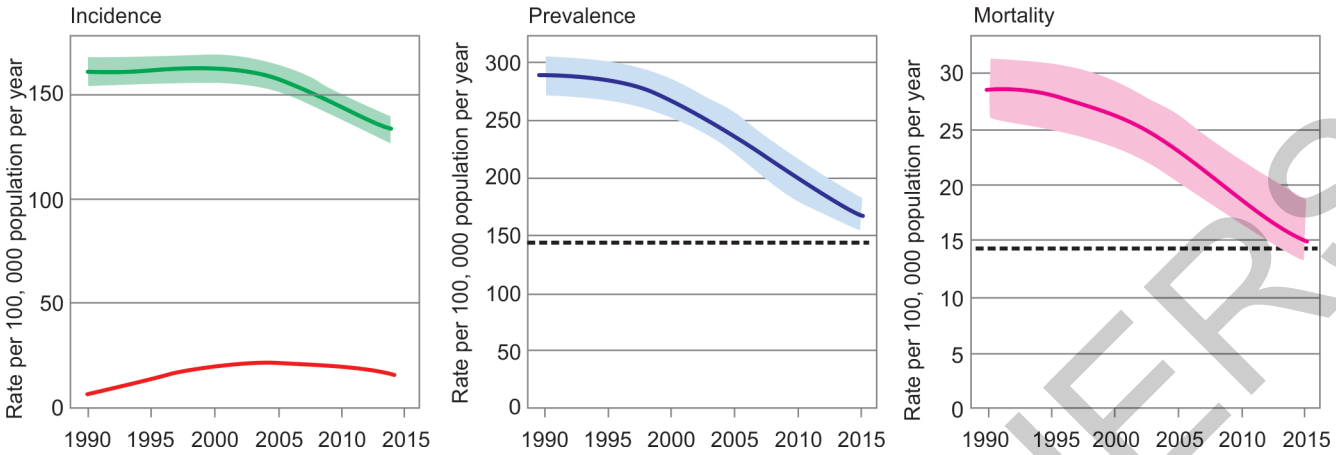

Figure 2.3: Global trends in estimated rates of TB incidence [1990-2014], and prevalence and mortality rates [1990-2015]. Left: estimated incidence rate including HIV-positive TB [green] and estimated incidence rate of HIV-positive TB [red]. Centre and right: The horizontal dashed lines represent the Stop TB Partnership targets of a 50% reduction in prevalence and mortality rates by 2015 compared with 1990. Shaded areas represent uncertainty bands. Mortality excludes TB deaths among HIV-positive people.
HIV = human immunodeficiency virus
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Prevalence

There were an estimated 13 million prevalent cases [range, 11-14 million] of TB in 2014, equivalent to a rate of 174 cases per 100,000 population. TB prevalence rates are declining in all six WHO regions and by the end of 2015 and are estimated to have fallen by 42% globally since 1990 missing the international target of halving TB prevalence by 2015, compared with the baseline in 1990. However, the target has already been met by the Region of the Americas and the Western Pacific Region and SEAR (1).

Deaths

There were an estimated 1.5 million total TB deaths in 2014 or about 16 deaths per 100,000 population in the world. About 390,000 of these deaths were among people living with HIV. Approximately 90% of total TB deaths occurred in the African Region and SEAR, with India and Nigeria accounting for about one-third of the global TB deaths in 2014. TB mortality rate [excluding deaths among HIV-positive people] has fallen by 47% between 1990 and 2015 narrowly missing the target of a 50% reduction [Figure 2.4]. Mortality rates are declining in all six WHO regions but at a different pace (1).

Drug-resistant TB

The prospect of an increase in the number of drug-resistant cases among the TB burden remains a matter of concern, even if the overall number of TB patients is on the decline. Cases with drug-resistant TB need more resources and support to treat appropriately with regimens that are longer, more toxic and costly than those in general use for drug-susceptible disease (34,41,42). Representative data from surveys performed at least once or on routine surveillance of diagnostic drug susceptibility testing of TB patients is now available from 144 countries worldwide.

Based on these data, it is estimated that in 2014 there were 480,000 [360,000-600,000] newly emerging MDR-TB cases in the world, and 190,000 [120,000-260,000] MDR-TB deaths. Globally, 3.3% {95% confidence intervals [CI] 2.2% to 4.4%} of new [previously untreated] TB cases and 20% [95% CI 14% to 27%] of previously treated cases are estimated to have MDR-TB. These proportions, however, differ markedly between countries, showing low levels in the SEAR 2.2% [95% CI 1.9% to 2.6%] in new and 16% [14% to 18%] in previously treated patients and very high levels in eastern Europe and central Asia compared with the rest of the world [Figure 2.5]. Among new cases in Belarus MDR-TB is present in 34%, and in 23%-26% in Kazakhstan, Kyrgyzstan, the Republic of Moldova, and Uzbekistan; between 55% and 62% of previously treated patients in these countries had MDR-TB. Levels vary across the vast expanse of the Russian Federation but some regions have the highest proportions ever reported worldwide. The time trends in drug resistance levels vary substantially between countries (43), although comparable data from serial measurements over time are not available for many countries. Extensively drug-resistant TB [XDR-TB] or MDR-TB with additional resistance to both the fluoroquinolones and the second-line injectable drugs, the two most important classes of medicines in the treatment of MDR-TB, has now been reported by 105 countries globally, including all countries of the WHO SEAR except Sri Lanka and Timor-Leste. In countries with representative data, globally 9.7% [95% CI 7.4% to 12%] of MDR-TB cases have XDR-TB.

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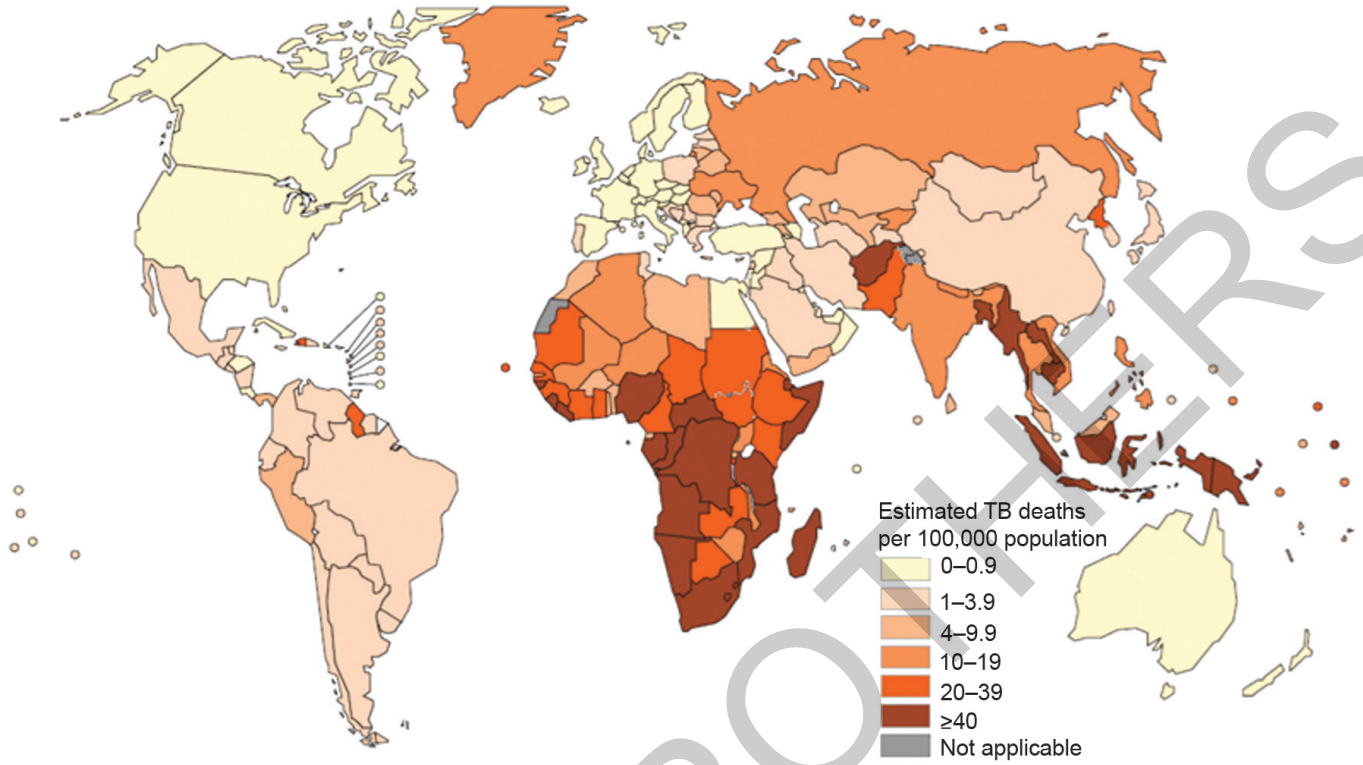

Figure 2.4: Estimated TB mortality rates [excluding TB deaths among HIV-positive people], 2014
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The World Health Organization updates these data annually. The reader can access the updated information from the WHO report of the current year available at the URL: http://www.who.int/topics/tuberculosis/en/

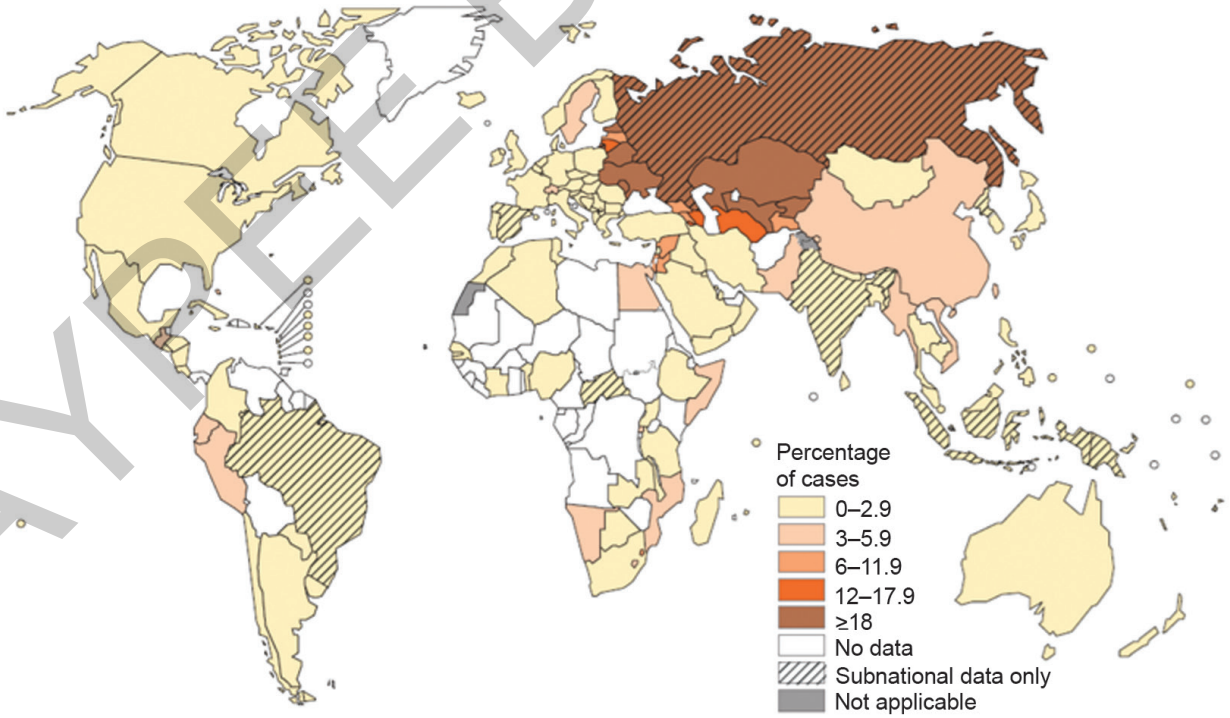

Figure 2.5: Percentage of MDR among new [previously untreated] TB cases. Figures are based on the most recent year for which data have been reported, which vary among countries. Data reported before the year 2000 are not shown.
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A GLOBAL RESPONSE

In the early 1990s, after more than a decade of neglect, WHO published new estimates showing that millions of people were affected with TB and died from it (44). As a result, in 1993, WHO declared TB to be a global health emergency (45). It was realised back then that many countries were ill-prepared to counter the challenge that TB posed for the future. Political commitment was lacking, surveillance was neglected, and treatment regimens and diagnostic services varied greatly in effectiveness. In 1994, WHO proposed a basic package of interventions to address the emergency, which eventually acquired the term DOTS [originally an acronym for "directly-observed treatment, short course"] (46). In 2006, DOTS evolved into a more comprehensive framework—the Stop TB Strategy—with activities covering a larger set of dimensions important for TB care and prevention (47,48).

In 2000, an ambitious Global Plan to Stop TB was launched by WHO and the Stop TB Partnership with the long-term vision of eliminating TB as a public health problem (49). The planning became more elaborate over the following years and in its latest update, in 2010, it was estimated that US$ 47 billion would be required to be spent between 2011 and 2015 in order to achieve the targets set for 2015 (50).

More than two decades after the WHO emergency announcement, TB remains one of the principal public health concerns due to an infectious condition in all countries in the world. But despite the plight of the millions of patients who have fallen ill with TB and died since 1993, much important progress has been registered. National programmes have been strengthened and learnt to adapt to the changes in the epidemic such as the challenges of HIV-associated TB and of drug-resistant strains as well as the environment around them, including the impact of migration, health sector reforms, financial crises and perennial pressure to integrate TB services in primary health care. As a result, about 43 million lives have been saved between 2000 and 2014 through effective diagnosis and treatment (1). The efforts of treatment programmes have thus had a profound impact on sustaining the substantial decline in TB incidence and mortality over the last decade in all regions of the world. TB/HIV interventions have progressed and by 2014, 51% of TB patients worldwide knew their HIV status [79% in the African Region where the TB/HIV burden is the highest]. Among known TB/HIV patients coverage of therapy with anti-retroviral drugs reached 77% in 2014, up from 49% in 2011. However, only 23% of countries globally reported provision of isoniazid preventive therapy [IPT] to people living with HIV in 2014.

In 2014, countries notified a total of 6.3 million TB cases, just over 6 million newly diagnosed and 261,000 on treatment [Table 2.2]. About 15% of newly emerging cases reported globally were extrapulmonary; the proportion of these cases varied substantially from 7% in the Western Pacific Region to 23% in the Eastern Mediterranean Region. These differences may reflect geographical variations in TB epidemiology as well as diagnostic and reporting practices. The 5.7 million new and relapse cases notified in 2013 represent about 64% [range: 61-66%] of the estimated incidence that year. Case detection ratio [CDR] was highest in 2014 in the Region of the Americas [77%; range 75%-81%], the Western Pacific Region [85%; range 81%-90%] and the European Region [79%; range 75-83%]. All regions have improved their estimated CDRs since 1995, when the global estimate was 39% [range 38%-41%] and when DOTS started to be expanded in the world. However, in 2014, there still remained a gap of approximately 3.6 million people with TB who were "missed" [Table 2.1]. The gap between estimated TB incidence and notified cases is a result of either under-reporting of TB cases to the national surveillance systems of under-detection or both. Under-reporting of diagnosed TB cases may occur when the private sector providers fail to notify cases to the national TB programme or else when reporting from diagnostic facilities and laboratories within the national TB programmes is dysfunctional. Under-diagnosis of patients with TB may occur because of lack of awareness of TB among communities, poor access to the health care services to appropriate diagnostics for people who do present to health facilities seeking care or a low index of suspicion of TB among health professionals.

The detection and treatment of patients with rifampicin-resistant disease and MDR-TB, conditions requiring longer, more toxic and expensive treatment regimens, has also increased; in 2014, the number of new enrollments on MDR-TB treatment reached about one third of estimated cases that could potentially be detected among the pulmonary TB cases notified by the countries.

The World Health Assembly [WHA] in a resolution in 2009 urged countries to work towards providing universal access to care for drug-resistant TB patients (51). Drug-resistant strains have been detected in an increasing number of countries over the last two decades, and the widespread introduction and use of new, rapid molecular assays are destined to snowball this trend. The response of countries has varied but some of the countries with the highest burden are on track to achieve universal access to treatment for their population if they sustain the efforts put in place in the last few years (52).

As a result of the worldwide expansion of effective care, treatment success in new TB cases has reached 86% among patients placed on treatment in 2013 globally, a substantial increase from 2000 when it was 69%. The target of 85% success has thus been reached and sustained. Success rates are lower among retreatment patients [65%] and among MDR-TB patients [48%] attesting to the worse prognosis when the effectiveness of first line drugs is diminished [Figure 2.6]. Treatment of XDR-TB and forms of TB with additional resistance is fraught with difficulties and outcomes are generally poorer than in MDR-TB (35,53,54); patients with infectious forms of TB bearing such advanced patterns of resistance present a challenge to infection control.

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Table 2.2: TB case notifications in the 22 high TB burden countries, WHO Regions and globally, 2014

				New or previous treatment history unknown			*Relapse*			*Percentage of pulmonary cases bacteriologically confirmed*
	Total notified	*New and relapse*	*Retreatment excluding relapse*	*Pulmonary bacteriologically confirmed*	*Pulmonary clinically diagnosed*	*Extrapulmonary*	*Pulmonary bacteriologically confirmed*	*Pulmonary clinically diagnosed*	*Extrapulmonary*	
Afghanistan	32,712	31,746	966	14,737	8,573	7,227	1,209			65
Bangladesh	196,797	191,166	5,631	106,767	42,832	37,406	2,989	863	309	72
Brazil	81,512	73,970	7,542	41,120	17,801	9,479	3,602	1,488	480	70
Cambodia	43,738	43,059	679	12,168	11,286	18,310	445	709	141	51
China	826,155	819,283	6.872	235,704	526,106	32,348	25,125			33
DR Congo	116,894	115,795	1,099	75,631	13,494	19,566	4,298	1,892	914	84
Ethiopia	119,592	119,592		40,087	41,575	37,930				49
India	1,683,915	1,609,547	74,368	754,268	343,032	275,502	124,679	112,066		66
Indonesia	324,539	322,806	1,733	193,321	101,991	19,653	6,449	1,391	1	66
Kenya	89,294	88,025	1,269	34,997	30,872	14,640	3,569	2,947	1,000	53
Mozambique	58,270	57,773	497	24,430	23,455	6,276	1,542	2,070		50
Myanmar	141,957	138,352	3,605	42,608	70,305	16,108	5,276	3,650	405	39
Nigeria	91,354	86,464	4,890	49,825	29,460	4,764	2,415		0	64
Pakistan	316,577	308,417	8,160	122,537	120,350	57,463	7,420	426	221	52
Philippines	267,436	243,379	24,057	92,991	139,950	4,161	6,277			41
Russian Federation	136,168	102,340	33,828	37,296	40,894	8,763	7,982	6,753	652	49
South Africa	318,193	306,166	12,027	155,473	106,482	33,522	7,430	2,693	566	60
Thailand	71,618	67,722	3,896	34,394	21,115	10,244	1,969	0	0	63
Uganda	46,171	44,187	1,984	26,079	11,854	4,180	1,499	468	107	69
UR Tanzania	63,151	61,571	1,580	23,583	23,380	13,600	1,008			51
Viet Nam	102,087	100,349	1,738	49,938	25,179	18 118	7,114			69
Zimbabwe	32,016	29,653	2,363	11,224	13,151	3,909	1,369			49
High-burden countries	5,160,146	4,961,362	198,784	2,179,178	1,763,137	653,169	223,666	137,416	4,796	56
AFR	1,342,400	1,300,852	41,548	635,560	399,155	212,057	39,782	11,217	3,081	62
AMR	228,476	215,243	13,233	127,864	40,746	32,501	10,193	2,918	1,021	76
EMR	465,677	453,393	12,284	183,630	151,696	103,959	12,368	866	874	56
EUR	321,421	266,058	55,363	112,416	76,759	39,175	23,935	11,483	2,290	61
SEAR	2,580,605	2,482,074	98,531	1,188,654	632,418	389,819	152,498	117,970	715	64
WPR	1,375,572	1,335,816	39,756	449,845	734,179	103,085	44,354	3,037	1,316	40
Global	6,314,151	6,053,436	260,715	2,697,969	2,034,953	880,596	283,130	147,491	9,297	58

TB = tuberculosis; WHO = World Health Organization; AFR = African; AMR = American region; EMR = Eastern Mediterranean region; EUR = European region; SEAR = South-East Asia region; WPR = Western Pacific region

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THE FUTURE OF TB: A LONG-TERM PERSPECTIVE

The last 150 years have seen significant improvement in the social conditions of large swathes of the world's population. They have also been characterised by significant scientific discoveries and the broad scale application of interventions based on this knowledge. These two phenomena have contributed hugely to the gradual decline in global burden of TB in the world. However, these gains have not benefited the whole of humanity in an equitable manner and huge disparities have emerged within the globalised economies of today's world. TB remains a barometer of poverty, insecurity, malnutrition and low basic health coverage, risk factors that abound in poor and rich countries alike. The HIV-epidemic has influenced the TB dynamic in many countries in Africa and elsewhere over the last three decades.

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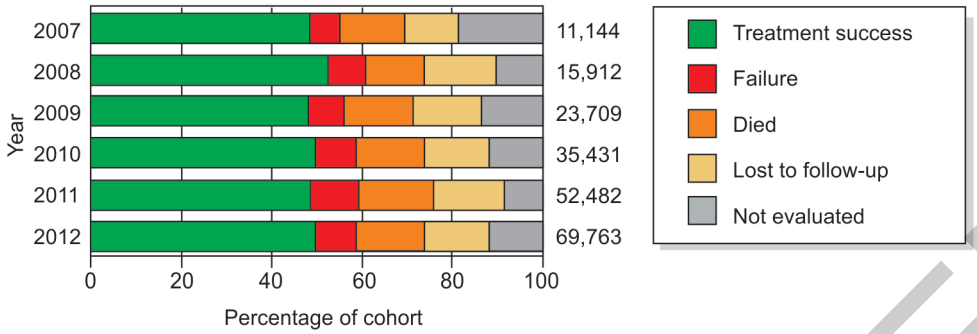

Figure 2.6: Treatment outcomes for patients diagnosed with MDR-TB by WHO Region, 2007-2012 cohorts. The total number of cases with outcome data is shown beside each bar

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MDR-TB = multidrug-resistant tuberculosis; WHO = World Health Organization

The World Health Organization updates these data annually. The reader can access the updated information from the WHO report of the current year available at the URL: http://www.who.int/topics/tuberculosis/en/

For a disease that is largely curable, the fact that millions of people still develop it each year and that about 4,000 TB patients die each day is a sordid reminder of the sad inequities of today's world and the ability of the TB bacillus to elude modern medicine and public health measures. Nonetheless, recent advances in diagnostics, vaccine science and therapeutics bring fresh optimism to the future perspective of the TB pandemic. For the first time in four decades, new TB drugs are starting to become available with an express indication for TB (55,56). In addition, new compounds are being tested in clinical trials and other medicines are being repurposed for use in TB. About 10 vaccine candidates have now entered clinical trials (57), albeit the prospect of having an effective vaccine for the prevention of TB in adults in the near future remains uncertain.

For new technologies to make a difference to TB care and control they need to be effectively implemented in the target settings using, where possible, innovative methods. One illustrative example was the broad scale adoption of Xpert® MTB/RIF, a rapid, reliable molecular diagnostic method that the WHO endorsed in December 2010 (58,59). By September 2014, more than 3,500 machines and 8.8 million test cartridges had been procured by 110 low- or middle-income countries [http://www.who.int/tb/areas-of-work/laboratory/mtbrifrollout/en/]. This rapid, unprecedented transfer of technology and expanded adoption of a new test was made possible in these countries through a lowering of the price for the equipment and the consumables following negotiations with the manufacturers by its co-developer, Foundation for Innovative and New Diagnostics [FIND] [www.finddiagnostics.org], and the financial support of the US Government, the Bill and Melinda Gates Foundation [www.gatesfoundation.org] and UNITAID [www.unitaid.eu].

A new vision beyond 2015 has now been endorsed by the WHA (60). This strategy [End TB Strategy] envisages a reduction in the importance of TB as a public health priority worldwide, bringing down its burden to levels which have only been achieved by industrialized countries to date. Three key targets are aimed for by 2035, namely: [i] a 95% reduction of TB mortality [in comparison with 2015 levels]; [ii] a 90% reduction of TB incidence [down to <10 cases per 100,000 population]; and [iii] the elimination of catastrophic costs due to TB for all families affected by the disease. The reader is referred to the chapter *"WHO'S New end TB strategy [Chapter 52]"* for further details.

The activities encompassed by the new strategy will build upon the successes achieved up until now but will also embark upon new ones within territories that lie beyond the traditional confines of TB care programs. The activities are grouped under three pillars: [i] integrated, patient-centred care and prevention; [ii] bold policies and supportive systems; and [iii] intensified research and innovation. Components within all of the three pillars concern the practice of surveillance and epidemiology in one way or another. For instance, the drive to rapidly find and treat the 3.6 million TB patients who escape detection or reporting will involve a number of articulated actions to improve the coverage of reliable diagnostics, implement early diagnostic strategies, increase the awareness about TB of the public and health care workers, mandate the obligatory notification of TB, and ensure that this is matched by means to facilitate the reporting of cases and the capture of data from laboratories and diagnostic centers [e.g., wider use of information and communication technology], provide universal health coverage and build links with the private health care sector. Broad-scale interventions aimed at active and earlier case finding, increasing contact tracing and treatment of latently-infected persons (61), will require close measurement of the response. Health workers who are monitoring patients on treatment would likewise need to exploit better the communication technologies which are available even in

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low resource settings, particularly mobile phones and data services; more evidence is required on the interventions which are most effective in this promising field and how they can be best adopted by programmes (62). Drug-safety monitoring in the context of the early introduction of new medicines will be important to fully understand the potential toxicity of these agents (63). Many countries will need to invest on more effective vital registration systems to monitor deaths from TB and M-/XDR-TB. The increased use of surveys of TB prevalence and drug-resistance would be needed where appropriate to assess the size of the burden and to monitor response (64,65). Local knowledge of TB epidemiology, including social studies, will be important to adjust interventions accordingly; thus, for instance, the relevance of a focus on migration, vulnerable groups, cities and large settlements in the high- and in some middle income countries in particular (66,67). Research will be required to optimize the implementation of interventions and inform upon the direction of new interventions. Linkages and alliances with other global initiatives, such as the drive to address antimicrobial drug resistance, may represent added opportunities to increase the span of public health efforts (68).

In conclusion, while TB has been a formidable threat to the wellbeing of mankind for many millennia, the population-scale interventions which have truly made an impact on its progression- improvements in living conditions and in health care have only occurred in the last two centuries. The latter six decades have seen acceleration in technological advances never before experienced in the history of man. Some of these have benefited TB control and made it possible to start thinking seriously about the prospect of TB elimination. The WHA Resolution 67.1 of 2014 now reflects the reinvigorated will of the world's political establishment to take bold action (60). This is thus an opportunity for national and international actors to help secure more resources and focus towards the global control of TB and to change the common perception surrounding this disease from that of a shameful icon of global neglect into the biggest public health success story.

DISCLAIMER

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REFERENCES

1. World Health Organization. Global tuberculosis report 2015. WHO/HTM/TB/2015.22. Geneva: World Health Organization; 2015.
2. Institute for Health Metrics and Evaluation. The Global Burden of Disease: Generating Evidence, Guiding Policy. Seattle: Institute for Health Metrics and Evaluation; 2013.
3. United Nations Millennium Development Goals. Available from URL: http://www.un.org/millenniumgoals/. Accessed on December 29, 2017.
4. Glaziou P, Sismanidis C, Pretorius C, Timimi H, Floyd K. Global TB Report 2015: Technical appendix on methods used to estimate the global burden of disease caused by TB [available online only] Available from URL: http://www.who.int/tb/publications/global_report/gtbr15_online_technical_appendix.pdf. Accessed on January 5, 2017.
5. Raviglione MC, Dye C, Schmidt S, Kochi A. Assessment of worldwide tuberculosis control. WHO Global Surveillance and Monitoring Project. Lancet 1997;350:624-9.
6. World Health Organization. TB data. Available from URL: http://www.who.int/tb/country/en/. Accessed on December 28, 2017.
7. World Health Organization. WHO Mortality Database. Available from URL: http://www.who.int/healthinfo/mortality_data/en/. Accessed on January 5, 2017.
8. World Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision. WHO/HTM/TB/2013.2. Geneva; World Health Organization; 2013. Available from URL: http://www.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf. Accessed on December 28, 2017.
9. Hershkovitz I, Donoghue HD, Minnikin DE, Besra GS, Lee OY-C, Gernaey AM, et al. detection and molecular characterization of 9000-Year-Old Mycobacterium tuberculosis from a Neolithic settlement in the Eastern Mediterranean. PLoS ONE 2008;3: e3426.
10. Comas I, Coscolla M, Luo T, Borrell S, Holt KE, Kato-Maeda M, et al. Out-of-Africa migration and Neolithic coexpansion of Mycobacterium tuberculosis with modern humans. Nat Genet 2013;45: 1176-82.
11. Dunglison R. Medical lexicon: a dictionary of medical science. Philadelphia: Lea and Blanchard; 1868.p.1031.
12. Bunyan J. The Life and Death of Mr. Badman. 1680. Available from URL: http://acacia.pair.com/Acacia.John.Bunyan/Sermons.Allegories/Life.Death.Badman/. Accessed on January 5, 2017.
13. Rieder H. Epidemiologic basis of tuberculosis control. 1st edition. Paris: UNION; 1999.
14. Chalke HD. The impact of tuberculosis on history, literature and art. Med Hist 1962;6:301-18.
15. Koch R. Die Aetiologie der Tuberculose. Berl Klin Wochenschr. 1882;15:221-30.
16. McKeown T. The role of medicine: dream, mirage or nemesis? The Nuffield Provincial Hospitals Trust; London: 1976. Available from URL: www.nuffieldtrust.org.uk/sites/files/nuffield/publication/The_Role_of_Medicine.pdf. Accessed on December 26, 2017.

JAYPEE BROTHERS

17. Davies RP, Tocque K, Bellis MA, Rimmington T, Davies PD. Historical declines in tuberculosis in England and Wales: improving social conditions or natural selection? Int J Tuberc Lung Dis 1999;3:1051-4.
18. Styblo K, Meijer J. Recent advances in tuberculosis epidemiology with regard to formulation or adaptation of tuberculosis control programs. Bull Int Union Tuberc 1978;53:301-12.
19. Sutherland I, Stýblo K, Sampalík M, Bleiker MA. Annual risks of tuberculosis infection in 14 countries according to the results of tuberculosis surveys from 1948 to 1952. Bull Int Union Tuberc 1971;45:80-122.
20. Raviglione MC, Sudre P, Rieder HL, Spinaci S, Kochi A. Secular trends of tuberculosis in western Europe. Bull World Health Organ 1993;71:297-306.
21. Centers for Disease Control and Prevention. Tuberculosis morbidity–United States, 1992. MMWR Morb Mortal Wkly Rep 1993 Sep 17;42:696-7, 703-4.
22. Cauthen G, Pio A, ten Dam H. Annual risk of tuberculosis infection. Bull World Health Organ. 2002;80:503-11.
23. Tiemersma EW, van der Werf MJ, Borgdorff MW, Williams BG, Nagelkerke NJD. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV negative patients: a systematic review. PLoS ONE 2011;6:e17601.
24. Silva PEAD, Palomino JC. Molecular basis and mechanisms of drug resistance in Mycobacterium tuberculosis: classical and new drugs. J Antimicrob Chemother 2011;66:1417-30.
25. David HL. Probability distribution of drug-resistant mutants in unselected populations of Mycobacterium tuberculosis. Appl Microbiol 1970;20:810-4.
26. European Concerted Action on New Generation Genetic Markers and Techniques for the Epidemiology and Control of Tuberculosis. Beijing/W Genotype Mycobacterium tuberculosis and Drug Resistance. Emerg Infect Dis 2006;12:736-43.
27. López B, Aguilar D, Orozco H, Burger M, Espitia C, Ritacco V, et al. A marked difference in pathogenesis and immune response induced by different Mycobacterium tuberculosis genotypes. Clin Exp Immunol 2003;133:30-7.
28. Toungoussova OS, Caugant DA, Sandven P, Mariandyshev AO, Bjune G. Impact of drug resistance on fitness of Mycobacterium tuberculosis strains of the W-Beijing genotype. FEMS Immunol Med Microbiol 2004;42:281-90.
29. Sharma SK, Mohan A, Sharma A, Mitra DK. Miliary tuberculosis: new insights into an old disease. The Lancet Infectious Diseases 2005;5:415-30.
30. Marx GE, Chan ED. Tuberculous meningitis: diagnosis and treatment overview. Tuberc Res Treat 2011:e798764.
31. Christensen A-SH, Roed C, Omland LH, Andersen PH, Obel N, Andersen ÅB. Long-Term Mortality in Patients with Tuberculous Meningitis: A Danish Nationwide Cohort Study. PLoS One 2011;6:e27900.
32. Pablos-Méndez A, Sterling TR, Frieden TR. The relationship between delayed or incomplete treatment and all-cause mortality in patients with tuberculosis. JAMA 1996;276:1223-8.
33. Velásquez GE, Becerra MC, Gelmanova IY, Pasechnikov AD, Yedilbayev A, Shin SS, et al. Improving outcomes for multidrug-resistant tuberculosis: aggressive regimens prevent treatment failure and death. Clin Infect Dis 2014;59:9-15.
34. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med 2012;9:e1001300.
35. Falzon D, Gandhi N, Migliori GB, Sotgiu G, Cox H, Holtz TH, et al. Resistance to fluoroquinolones and second-line injectable drugs: impact on MDR-TB outcomes. Eur Respir J 2013;42:156-68.
36. Abdool Karim SS, Naidoo K, Grobler A, Padayatchi N, Baxter C, Gray A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. N Engl J Med 2010;362:697-706.
37. Blanc F-X, Sok T, Laureillard D, Borand L, Rekacewicz C, Nerrienet E, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. N Engl J Med 2011;365:1471-81.
38. Padayatchi N, Abdool Karim SS, Naidoo K, Grobler A, Friedland G. Improved survival in multidrug-resistant tuberculosis patients receiving integrated tuberculosis and antiretroviral treatment in the SAPiT Trial. Int J Tuberc Lung Dis 2014;18:147-54.
39. Rockhill B, Newman B, Weinberg C. Use and misuse of population attributable fractions. Am J Public Health 1998;88:15-9.
40. Lönnroth K, Castro KG, Chakaya JM, Chauhan LS, Floyd K, Glaziou P, et al. Tuberculosis control and elimination 2010-50: cure, care, and social development. Lancet 2010;375:1814-29.
41. Falzon D, Jaramillo E, Schünemann HJ, Arentz M, Bauer M, Bayona J, et al. WHO guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. Eur Respir J 2011;38:516-28.
42. World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2014.11. Geneva: World Health Organization. 2014. Available from URL: apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf. Accessed on December 28, 2017.
43. Zignol M, van Gemert W, Falzon D, Sismanidis C, Glaziou P, Floyd K, et al. Surveillance of antituberculosis drug resistance in the world: an updated analysis, 2007-2010. Bull World Health Organ 2012;90:111-9D.
44. Sudre P, ten Dam G, Kochi A. Tuberculosis: a global overview of the situation today. Bull World Health Organ 1992;70:149-59.
45. World Health Organization. TB - a global emergency. WHO/TB/94.177. Geneva: World Health Organization; 1994. Available from URL: http://whqlibdoc.who.int/hq/1994/WHO_TB_94.177.pdf. Accessed on December 27, 2017.
46. World Health Organization. WHO Tuberculosis Programme: framework for effective tuberculosis control. WHO/TB/94.179. Geneva: World Health Organization; 1994.
47. World Health Organization. An expanded DOTS framework for effective tuberculosis control. WHO/CDS/TB/2002.297. Geneva, World Health Organization; 2002. Available from URL: http://whqlibdoc.who.int/hq/2002/WHO_CDS_TB_2002.297.pdf?ua=1. Accessed on December 29, 2017.
48. Raviglione MC, Uplekar MW. WHO's new Stop TB Strategy. Lancet 2006;367:952-5.
49. Global Plan to Stop TB. Phase 1: 2001-2005. Geneva, Stop TB Partnership and World Health Organization; 2001. Available from URL: http://www.stoptb.org/assets/documents/global/plan/GLOBAL_PLAN_TO_STOP_TB_2001_2005.pdf. Accessed on December 24, 2017.
50. World Health Organization. The Global Plan to Stop TB 2011-2015: transforming the fight towards elimination of tuberculosis. WHO/HTM/STB/2010.2. Geneva: World Health Organization; 2010. Available from URL: http://www.stoptb.org/assets/documents/global/plan/TB_GlobalPlanToStopTB2011-2015.pdf. Accessed on December 30, 2017.
51. World Health Organization. Resolution WHA62.15. Prevention and control of multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis. In: Sixty-second World Health Assembly, Geneva, 18-22 May 2009, Resolutions and decisions; annexes. Geneva, World Health Organization, 2009 [WHA62/2009/REC/1]:25-9. Available from URL: apps.who.int/gb/ebwha/pdf_files/WHA62-REC1/WHA62_REC1-en.pdf. Accessed on December 30, 2107.

JAYPEE BROTHERS

52. Falzon D, Mirzayev F, Wares F, Garcia Baena I, Zignol M, Linh N, et al. Multidrug-resistant tuberculosis around the world: what progress has been made? Eur Respir J 2015;45: 150-60.
53. Jacobson KR, Tierney DB, Jeon CY, Mitnick CD, Murray MB. Treatment outcomes among patients with extensively drug-resistant tuberculosis: systematic review and meta-analysis. Clin Infect Dis 2010;51:6-14.
54. Migliori GB, Sotgiu G, Gandhi NR, Falzon D, DeRiemer K, Centis R, et al. Drug resistance beyond extensively drug-resistant tuberculosis: individual patient data meta-analysis. Eur Respir J 2013;42:169-79.
55. World Health Organization. The use of bedaquiline in the treatment of multidrug-resistant tuberculosis. Interim policy guidance. WHO/HTM/TB/2013.6. Geneva: World Health Organization. 2013. Available from URL: http://apps.who.int/iris/bitstream/10665/84879/1/9789241505482_eng.pdf. Accessed on April 22, 2017.
56. European Medicines Agency. Human medicines - Deltyba. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-Summary_for_the_public/human/002552/WC500166235.pdf. Accessed on April 22, 2017.
57. Kaufmann SHE, Hussey G, Lambert P-H. New vaccines for tuberculosis. Lancet. 2010;375:2110-9.
58. Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F, et al. Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med 2010;363:1005-15.
59. World Health Organization. WHO endorses new rapid tuberculosis test. Available from URL: http://www.who.int/mediacentre/news/releases/2010/tb_test_20101208/en/. Accessed on December 24, 2017.
60. World Health Organization. Resolution WHA67.1. Global strategy and targets for tuberculosis prevention, care and control after 2015. Geneva: World Health Organization; 2014. Available from URL: http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_R1-en.pdf. Accessed on December 25, 2017.
61. World Health Organization. Guidelines on the management of latent tuberculosis infection. WHO/HTM/TB/2015.01. Geneva: World Health Organization. 2014. Available from URL: http://apps.who.int/iris/bitstream/10665/136471/1/9789241548908_eng.pdf. Accessed on December 21, 2017.
62. Nglazi MD, Bekker L-G, Wood R, Hussey GD, Wiysonge CS. Mobile phone text messaging for promoting adherence to anti-tuberculosis treatment: a systematic review. BMC Infect Dis 2013;13:566.
63. Active tuberculosis drug-safety monitoring and management [aDSM]. Framework for implementation. WHO/HTM/TB/2015.28. Geneva, World Health Organization; 2015. Available from URL: http://apps.who.int/iris/. Accessed on December 27, 2017.
64. World Health Organization. Tuberculosis prevalence surveys: a handbook. The lime book. WHO/HTM/TB/2010.17. Geneva: World Health Organization. 2011. Available from URL: http://whqlibdoc.who.int/publications/2011/9789241548168_eng.pdf. Accessed on December 26, 2017.
65. Guidelines for surveillance of drug resistance in tuberculosis. 5th ed. WHO/TB/2015.13. Geneva, World Health Organization. 2015. Available from: http://apps.who.int/iris/bitstream/10665/174897/1/9789241549134_eng.pdf. Accessed on December 28, 2017.
66. Van Hest NA, Aldridge RW, de Vries G, Sandgren A, Hauer B, Hayward A, et al. Tuberculosis control in big cities and urban risk groups in the European Union: a consensus statement. Euro Surveill 2014;19[9]. pii:20728.
67. Dara M, de Colombani P, Petrova-Benedict R, Centis R, Zellweger J, Sandgren A, et al. Minimum package for cross-border TB control and care in the WHO European region: a Wolfheze consensus statement. Eur Respir J 2012;40:1081-90.
68. World Health Organization. Antimicrobial drug resistance. Report by the Secretariat. A67/39. Geneva: World Health Organization; 2014. Available from URL: http://apps.who.int/gb/ebwha/pdf_files/WHA67/A67_39-en.pdf. Accessed on December 27, 2017.

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Textbook of Tuberculosis & Nontuberculous Mycobacterial Diseases

The third edition of this multi-authored, popular *Textbook of Tuberculosis and Nontuberculous Mycobacterial Diseases* has been thoroughly revised, updated and rewritten to present a comprehensive account of tuberculosis [TB] and nontuberculous mycobacterial diseases. It has contributions of experts from several parts of the world with a vast experience. Beginning with insights into the history and epidemiology of tuberculosis, the book deals extensively with the current understanding of the immunology, and immunopathogenetic mechanisms of this disease. The chapters on biology of mycobacterium tuberculosis, nontuberculous mycobacterial infections, susceptibility factors of tuberculosis with special emphasis on HLA and molecular mechanisms underlying the clinical manifestation of TB provide an excellent account of these topics. The clinical presentation, laboratory diagnosis, the treatment of TB of various organ systems, prevention and control of TB are exhaustively covered. Chapters have also been devoted to HIV-TB co-infection, drug-resistant TB [including M/XDR-TB], ethical and legal issues in TB, Revised National Tuberculosis Control Programme, global TB control programme, and the role of medical schools in TB control programmes. This edition carries a comprehensively revised chapter on nontuberculous mycobacterial diseases. This edition will be an asset to both undergraduate and postgraduate medical students, a source of reference to the researchers and will help practicing doctors to update their knowledge and aid in rationale, scientific and efficient management of patients with TB. It is hoped that the reader who has gone through 'Tuberculosis [3rd edition]' from cover to cover will get a comprehensive bird's eye view of this subject.



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Under his leadership, Indian Obstructive Sleep Apnea [INOSA] guidelines and also Indian Extrapulmonary TB [INDEX-TB] guidelines were formulated. He was an expert Member of the WHO [Geneva] guidelines on latent TB infection for high and middle-income countries. He conceived, lead and implemented the unique involvement of all Indian Medical Colleges in the Revised National TB Control Programme.

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