1
Global Epidemiology and Control of Tuberculosis

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1.1
Introduction

The recent discoveries that *Mycobacterium tuberculosis* has probably been a human pathogen for millions of years [1], and that cattle and other animals are likely to have acquired mycobacteria from humans rather than the reverse [2,3], have profound implications for the epidemiology and control of human tuberculosis (TB). Epidemiological theory and data have shown that, for directly-transmitted pathogens to persist, host population size (or density) must exceed a threshold, because the size of the host population determines the rate of production of susceptible hosts [4]. If *M. tuberculosis* once survived and reproduced only in small human populations, it must have evolved mechanisms for doing so. Partial immunity and latent infection are both devices that increase the chance of persistence, the former by ensuring that the number of hosts available for infection does not become too small, and the latter by spreading the risk (to the pathogen) of infection over decades.

Whether or not these biological characteristics of *M. tuberculosis* actually did evolve to aid persistence, they are at the heart of two major, contemporary problems in TB control – the difficulty of developing an effective vaccine, and the removal of the huge reservoir of latent infection. Without an efficacious vaccine, or an effective way of removing latent infection, the dominant method of TB control at present is through the treatment of active disease, standardized as the DOTS component (based on Directly Observed Treatment and Short-course chemotherapy) of the World Health Organization's (WHO) Stop TB Strategy [5,6]. The treatment of active disease reduces the burden of illness and death, and curtails transmission. However, while curative treatment for TB is comparatively cost-effective among health interventions [7], the ultimate goal must be the prevention of this life-threatening disease.

The targets for global TB control are set within the framework of the United Nations Millennium Development Goals (MDGs), and are reinforced by the additional goals of the Stop TB Partnership (Table 1.1). The overarching MDG Goal 6,

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Table 1.1 The Stop TB Strategy [5,6].

Vision: A world free of TB
Goal: To dramatically reduce the global burden of TB by 2015 in line with the Millennium Development Goals and the Stop TB Partnership targets

Objectives:
- Achieve universal access to high-quality diagnosis and patient-centered treatment
- Reduce the human suffering and socioeconomic burden associated with TB
- Protect poor and vulnerable populations from TB, TB/HIV and MDR-TB
- Support development of new tools and enable their timely and effective use

Targets:
MDG 6, Target 8: Halt and begin to reverse the incidence of TB by 2015
Targets linked to the MDGs and endorsed by the Stop TB Partnership:
By 2005: detect at least 70 % of infectious TB cases and cure at least 85 % of these cases
By 2015: reduce TB prevalence and deaths rates by 50 % relative to 1990
By 2050: eliminate TB as a public health problem (<1 case per million population)

Components of the strategy and implementation approaches
1. Pursuing high-quality DOTS expansion and enhancement
   a. Political commitment with increased and sustained financing
   b. Case detection through quality-assured bacteriology
   c. Standardized treatment with supervision and patient support
   d. An effective drug supply and management system
   e. Monitoring and evaluation system, and impact measurement
2. Addressing TB/HIV, MDR-TB and other challenges
   - Implement collaborative TB/HIV activities
   - Prevent and control MDR-TB
   - Address prisoners, refugees, other high-risk groups and special situations
3. Contributing to the strengthening of health systems
   - Actively participate in efforts to improve system-wide policy, human resources, financing, management, service delivery and information systems
   - Share innovations that strengthen health systems, including the Practical Approach to Lung Health (PAL)
   - Adapt innovations from other fields
4. Engaging all care providers
   - Public–Public and Public–Private Mix (PPM) approaches
   - Implement International Standards for Tuberculosis Care
5. Empowering people with TB, and communities
   - Advocacy, communication and social mobilization
   - Community participation in TB care
   - Patients' Charter for Tuberculosis Care
6. Enabling and promoting research
   - Program-based operational research
   - Research to develop new diagnostics, drugs and vaccines

Target 8 is 'to have halted and begun to reverse incidence by 2015', that is the incidence rate of all forms of TB should be falling by 2015 [8]. The Stop TB Partnership targets are to halve TB prevalence and death rates by 2015, in comparison with the rates estimated for 1990 [9]. These reductions in incidence, prevalence and deaths are to be accomplished mainly by detecting (target $\geq$70%) and curing (target $\geq$85%) sputum smear-positive cases [10]. These levels of case detection and cure should have been achieved by 2005, and maintained thereafter. Going beyond MDG target year 2015, the Stop TB Partnership is also committed to eliminating TB as a public health problem (i.e. reducing incidence to $<$1 per million population) by 2050, which would require new combinations of drugs, diagnostics and vaccines.

Against that backdrop, Section 1.2 of this chapter describes the status of the TB epidemic, globally and in different regions and countries of the world. Section 1.3 reviews the progress made in large-scale efforts to treat active TB, via the WHO DOTS Strategy, as implemented up to the end of 2005. In Section 1.4 we examine whether the MDGs can be achieved via the Global Plan to Stop TB, the blueprint for implementing the extended Stop TB Strategy (of which DOTS is a part) over the decade 2006–2015 [11]. The biggest challenge of all is to eliminate TB during the 21st century. In this context, Section 1.5 assesses the potential impact of new technology on TB control, especially drugs and vaccines that could shift the emphasis from cure to prevention. We draw together our conclusions in Section 1.6.

1.2 Global and Regional Dynamics

Based on surveys of the prevalence of infection and disease, assessments of the performance of surveillance systems, and death registrations, there were an estimated 8.8 million new cases of TB in 2005 [5,12–14]. An estimated 3.9 million new cases were sputum-smear positive, the form of pulmonary TB that is most infectious, and which carries the highest case fatality rate if not treated. The WHO African region had the highest estimated incidence rate (343 per 100 000 population), but the majority of TB patients live in the most populous countries of Asia. Five countries – Bangladesh, China, India, Indonesia and Pakistan – had about half the world's population (46 %) and produced about half (49 %) of all new TB cases arising worldwide in 2005. The 22 highest-burden countries account for about 80 % of all new cases each year.

TB is mainly a disease of adults, and affects more men than women. It is an important cause of death among young adults who are raising families and in their most productive working years. In regions where the transmission of *M. tuberculosis* has been stable or increasing for many years, the incidence rate is relatively high among infants and young adults, and most cases are due to recent infection or reinfection [15]. As transmission falls, the burden of illness shifts to older adults, and a higher proportion of cases arises from the reactivation of latent infection. Therefore, in the countries of Western Europe and North America that now have low incidence rates, indigenous TB patients tend to be elderly, whereas patients who are immigrants from high-incidence countries tend to be young adults.

Although there are difficulties in diagnosing childhood TB [16], estimation exercises indicate that there are fewer cases among 0–14-year-olds than among adults, even in areas of high transmission (18 % of all new cases in Africa in 2005, and 4 % in the established market economies). In 2005, countries reported 1.4 million TB cases among men, but only 775 000 among women. In some instances, women have poorer access to diagnostic facilities, but the broader pattern also reflects real epidemiological differences between the sexes. Although there is some evidence that young adult women (15–44 years) are more likely than men to develop active TB following infection, this effect is typically outweighed by the higher exposure and infection rates among adult men.

TB incidence rates have been steady or falling for at least two decades in the Southeast Asia and Western Pacific Regions, Western and Central Europe, North and Latin America and the Middle East (as judged from trends in case notifications). They have been increasing until recently in Eastern Europe (mainly the former Soviet Union) and in sub-Saharan Africa (Figure 1.1). The resurgence of TB in Eastern European countries, which took place mainly during the 1990s, can be explained indirectly by political changes and economic decline, and more directly by the failure of TB control and other health services [17]. Based on periodic surveys, more than 10 % of new TB cases in Estonia, Latvia, and some parts of the Russia are multidrug-resistant (MDR) TB, that is resistant to at least isoniazid and rifampicin, the two most potent anti-TB drugs [18,19]. Drug resistance is likely to be a by-product of the events that led to TB resurgence in these countries, not the primary cause of it.

Most of the recent increase in TB incidence in Africa is likely to be due to the spread of Human Immunodeficiency Virus (HIV). In places where HIV infection rates are high in the general population, they are much higher among TB patients. The ratio of HIV-positive TB incidence to HIV-negative TB incidence was typically in the range of 6–8 up to 2005 [13,20], and estimates of the prevalence of HIV infection among TB patients in 2005 exceeded 50 % in Botswana, Malawi, South Africa, Zambia and Zimbabwe, among other countries [5]. Across sub-Saharan Africa, 28 % of new adult TB cases were infected with HIV in 2005, far higher than in any other region of the world. HIV infection rates in TB patients have so far remained below 1 % in Bangladesh, China, Indonesia and Pakistan. In African populations with higher rates of HIV infection, a higher proportion of TB patients are women aged 15 to 24 years [21].

Trends in case reports suggest that the rate of increase of TB in both Eastern Europe and Africa has been slowing since the mid-1990s, and the incidence rate in both regions may now be stable or in decline. The downturn in case notifications in Eastern Europe is clear in several former Soviet states including Russia, Belarus, Kazakhstan, Turkmenistan and the Baltic States of Estonia, Latvia and Lithuania. In Africa, case notification rates are stable or beginning to fall in Malawi, Tanzania, Zambia and Zimbabwe, among other countries where HIV infection rates have been relatively high. Because these slow declines in case notifications are visible in several countries, and because they follow a drop in estimated HIV incidence and prevalence rates, they may reflect real trends in TB incidence. The direction of the epidemic in

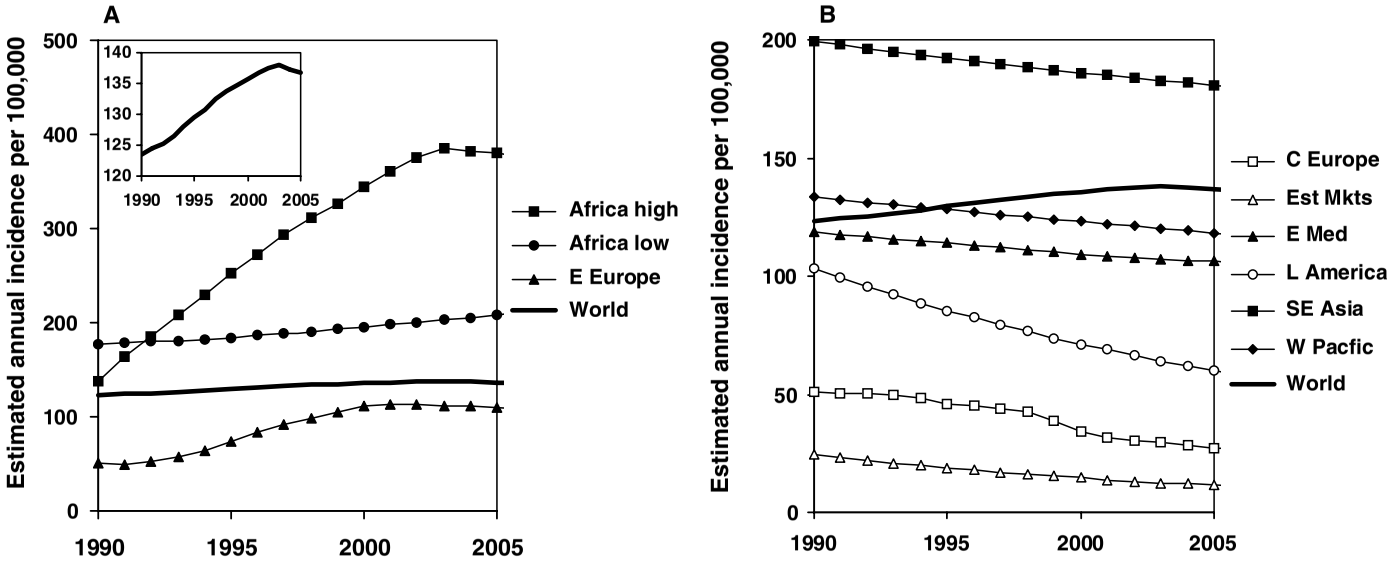

Figure 1.1 Trajectories of the TB epidemic for nine epidemiologically different regions of the world. Lines trace the trends in incidence rates, derived from case notifications for 1990–2005. The graphs distinguish regions where incidence was mostly increasing during the 1990s (A) from those where incidence was mostly falling (B). The insert in (A) shows the global trend in incidence on an expanded *y*-axis. Groupings of countries are based on the World Health Organization (WHO) regions of Africa (subdivided into two regions comprising those countries with high HIV infection rates, ≥4% in adults aged 15–49 years in 2005, and those with low rates of HIV infection, <4%), Central Europe, Eastern Europe (former Soviet countries plus Bulgaria and Romania), Eastern Mediterranean, Established Market Economies (all 30 OECD countries, except Mexico, Slovakia and Turkey, plus Singapore), Latin America, Southeast Asia, and the Western Pacific. The countries in each region are listed in full elsewhere [5]. Adapted and updated from [14].

South Africa is unclear because the trend in case notifications (upwards) is dominated by recent improvements in case detection and reporting.

Summing incident cases across the nine regions depicted in Figure 1.1 gives the global trend. The incidence rate per capita was increasing most quickly at 1.5 % per year in 1995 but, because of the recent dynamics in Africa and Eastern Europe, has since stabilized, and was probably falling by 2005 [5]. If the global TB incidence rate is now in decline, then Goal 6, Target 8 of the MDGs has been achieved. However, because population growth was faster in 2005 (1.2 % per year) than the decline in incidence, the total number of new TB cases arising each year was still increasing.

Approximately 1.6 million people died of TB in 2005, including 195 000 patients who were co-infected with HIV. Although these are usually reported as AIDS deaths under the International Classification of Diseases-10 and by WHO [22], TB control programs need to know, for the purposes of case management, the total number of TB deaths, whatever the underlying cause. Because few countries with high burdens of TB compile reliable statistics on the cause of death, the global and regional trends in TB deaths are uncertain. However, recent assessments based on modeling have suggested that the global TB mortality rate began to fall before 2000, that is, after prevalence but before incidence [5].

1.3 Progress in the Implementation and Impact of TB Control

TB can be controlled, in principle, by three methods: preventing transmission and infection (e.g. vaccination, isolation), stopping the progression from latent infection to active TB (e.g. vaccination, drug treatment), and treating active disease (presently, with a combination of drugs).

1.3.1 Vaccination

The current TB vaccine is used mainly to prevent severe disease (meningitis and miliary TB) in children under 5 years of age. Roughly 100 million infants (more than 80 % of the annual cohort) are vaccinated each year with BCG (Bacille Calmette-Guérin). The most complete analysis of effectiveness to date suggests that BCG given to children worldwide in 2002 will have prevented approximately 30 000 cases of childhood meningitis and about 11 500 cases of miliary TB during their first 5 years, or one case for every 3400 and 9300 vaccinations, respectively [23]. The protective efficacy against pulmonary TB in adults is highly variable, and often very low, and BCG is unlikely to have a major effect on the incidence of adult TB and transmission anywhere in the world [24].

1.3.2 Preventive Therapy (Treatment of Latent TB Infection)

Individuals at high risk of TB who have a positive tuberculin skin test but not active disease (e.g. anyone likely to have been infected within the past 2 years; associates of active cases, especially children; immigrants to low-incidence countries) can be offered preventive therapy (also called treatment of latent TB infection), most commonly with the relatively safe and inexpensive drug, isoniazid (isoniazid preventive therapy, IPT) [25]. Randomized, controlled, clinical trials have shown that 12 months of daily isoniazid gives 25–92 % protection (range of point estimates from trials) against developing active TB (range of point estimates), but towards the upper end of this range when patients adhere fully to the treatment regimen [26]. However, IPT has not been widely used, mainly because compliance with long-term daily treatment tends to be poor among healthy people – a relatively high risk of TB among people carrying latent infections is usually still a low risk in absolute terms. It is also imperative to exclude patients with active TB, who have a low chance of cure with isoniazid treatment alone, and who risk developing isoniazid resistance. IPT is efficacious among people who are co-infected with *M. tuberculosis* and HIV [27], and the exceptionally high risk of TB among HIV-positive individuals is one reason for encouraging its wider use, especially in Africa.

1.3.3 Treatment of Active TB

Up to 2005, progress in TB control has been measured principally in terms of the implementation of DOTS, the central component of the Stop TB Strategy. Data collected by the end of 2006 have allowed WHO to assess whether the targets for 70 % case detection and 85 % treatment success were met by the end of 2005.

1.3.3.1 Case Detection

Over the 11 years between 1994 and 2005, a total of 26.5 million TB patients were diagnosed and reported under DOTS. In 2005, DOTS programs worldwide reported 4.8 million new and relapsed cases, among which 2.3 million were smear-positive. The smear-positive case detection rate by DOTS programs was 60 % (90% uncertainty limits, 52–69 %) of the 3.9 million new cases estimated (Figure 1.2A). The point estimate of case detection was therefore below the 70 % target. The estimated case detection rate by DOTS programs increased almost linearly from 11 % globally in 1995 to 28 % in 2000. Case detection has since accelerated, though the increment from 2004 to 2005 was not as great as that from 2003 to 2004 (Figure 1.2A).

The global acceleration in case detection has been driven principally by South-East Asia (mostly India) since 2000, supported by the Western Pacific Region (mostly China) since 2002. However, only six of the 22 high-burden countries (including China), 66 countries in total, and one WHO region (Western Pacific), reached the 70 % target by 2005 (Figure 1.2B) [28,29].

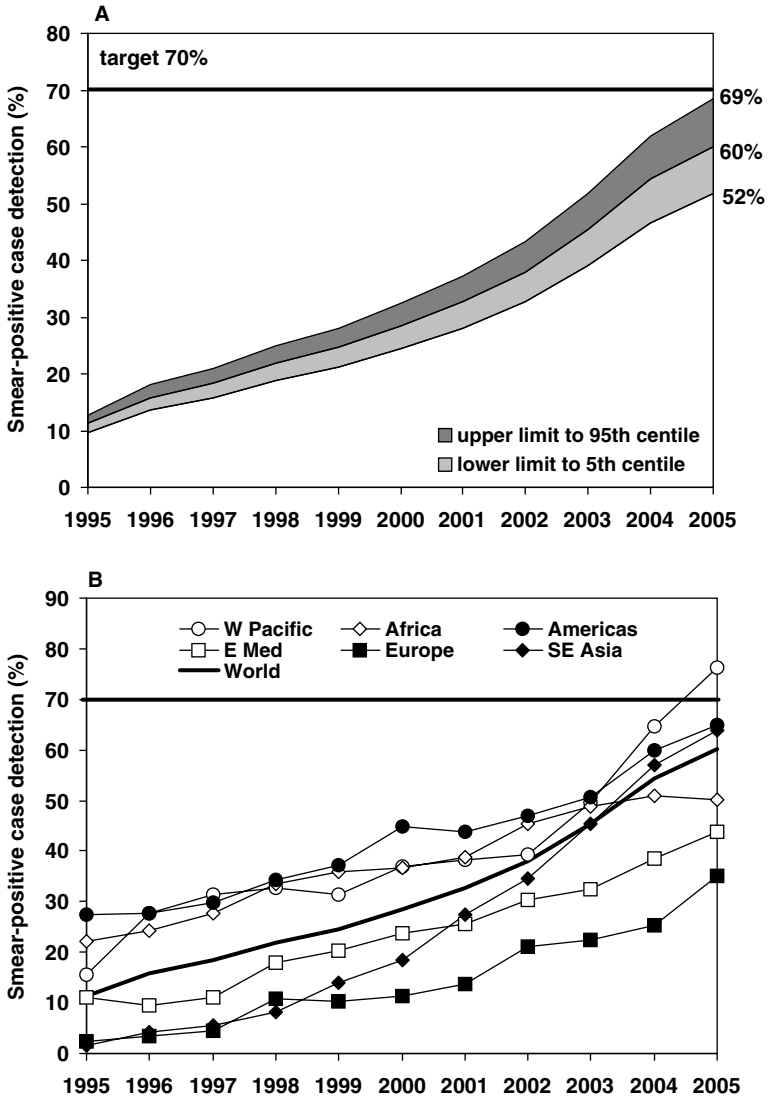

Figure 1.2 (A) Case detection and (B) treatment success for sputum smear-positive patients under DOTS in 22 high-burden countries. Treatment success is for the cohort of patients registered in 2004; case detection is for cases reported during 2005. The horizontal lines show the 70 % (A) and 85 % (B) targets [5,29].

1.3.3.2 **Treatment Success**

Of 2.1 million smear-positive patients registered for treatment under DOTS in 2004, 1.8 million (84 %) were successfully treated by the end of 2005 (i.e. cured, as judged by sputum smear conversion or completion of treatment), just short of the 85 % target.

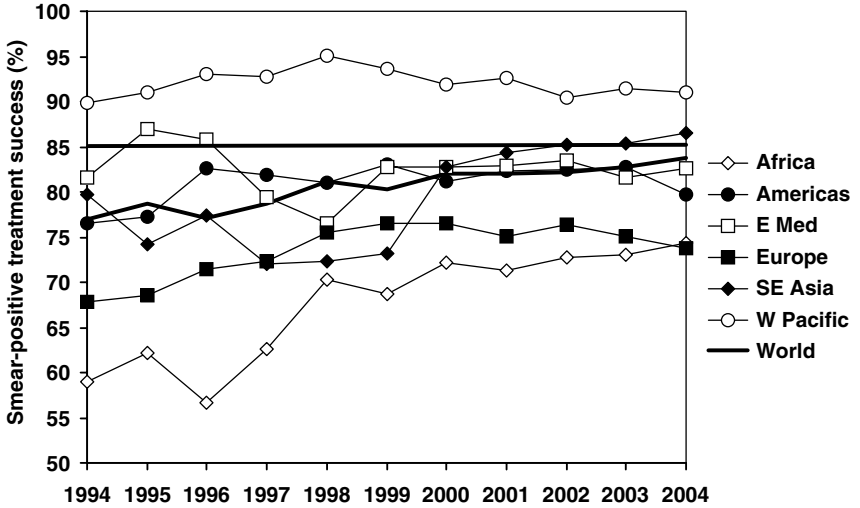

Figure 1.3 Treatment success under DOTS for smear-positive patients registered between 1994 and 2004, in the six WHO regions. The horizontal line shows the 85 % target [5].

The global treatment success rate under DOTS has been high since the first cohort was observed in 1994 (77 % of 245 000 patients), and has remained above 80 % since 1998 (Figure 1.3) [5,29].

In 2004, the 85 % target was reached by seven of the 22 high-burden countries, and by two WHO regions (South-East Asia, Western Pacific; Figure 1.3). In the four regions that did not meet the target, the reasons for poor results were, variously, high rates of death (Africa, Europe), treatment failure (Europe) and unknown outcomes through default, transfer or no evaluation (Africa, Americas, Eastern Mediterranean, Europe).

1.3.3.3 Impact of DOTS on Incidence, Prevalence and Mortality

Although the decline in TB has almost certainly been accelerated by good chemotherapy programs, which have been implemented for decades in countries such as Chile, Cuba and Uruguay, there have been few recent, unequivocal demonstrations of their impact in high-burden countries. This is because large-scale public health programs are not carried out as controlled experiments, and because there are other factors that influence transmission or susceptibility to disease (housing, nutrition, co-infection, and others). However, Morocco and Peru provide two persuasive examples. Between 1994 and 2005, the incidence of all forms of TB in children aged 0–4 years fell at 8–10 % per year, suggesting that the risk of infection was falling at least as quickly [29a]. The average age of TB cases has been rising for over 20 years in Morocco, and yet the overall reduction in pulmonary TB was only 4 % per year, in part because of the large reservoir of infection in adults. In Peru, DOTS was launched in 1991, and high rates of case detection and cure pushed down the incidence rate of pulmonary TB by 6 % per year [30]. Indirect assessments of the effect of DOTS suggest that 70 % of the

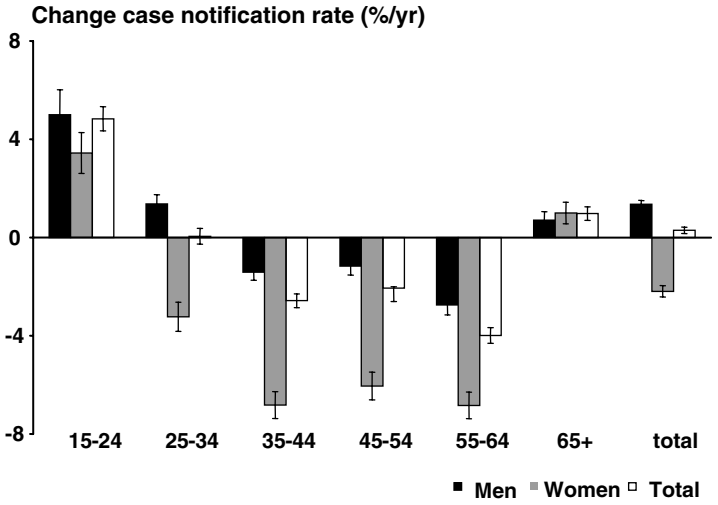

Figure 1.4 Average annual change in TB case notification rates for men (black), women (gray) and both together (white) in different age classes in Vietnam, 1997–2004. Error bars are 95 % confidence limits. Data from [5, 29b] and the KNCV Tuberculosis Foundation.

TB deaths expected in the absence of DOTS were averted in Peru between 1991 and 2000.

There have been few direct measures of the reduction in TB prevalence over time. The Republic of Korea carried out seven surveys at 5-year intervals between 1965 and 1995, during which time the prevalence of bacteriologically positive cases (smear- and/or culture-positive) of the disease fell from 940 per 100 000 to 219 per 100 000 [31]. Two prevalence surveys carried out in China in 1990 and 2000 showed a 32 % (95 % confidence limits (CL) 5–68 %) reduction in the prevalence per capita of smear-positive TB in DOTS areas, as compared with the negligible change in prevalence in other parts of the country [32]. A national survey in Indonesia in 2004 found that the prevalence of smear-positive TB had fallen by a factor of 3 since a set of regional surveys were carried out between 1979 and 1982 [33,34]. But most of this reduction is not attributable to the DOTS program, which has expanded case detection only since the beginning of this century [5].

Some investigations into the impact of DOTS programs have shown that, after several years of implementation, incidence is not falling as expected. Vietnam has apparently exceeded the targets for case detection and treatment success since 1997, and yet the case notification rate has remained approximately stable over that period [5,29b,35]. Closer inspection of surveillance data shows that, while case notification rates are falling among adults aged 35–64 years (especially women), they are increasing among 15–24-year-olds (especially men) (Figure 1.4). These increases and decreases in different age groups, and for men and women, are almost equal in magnitude. This pattern of change in case notifications by age and sex is also observed in routine surveillance data from Sri Lanka. In Indonesia and Myanmar, TB patients in the age

group 15–54 years are becoming younger on average, and yet the average age should be increasing if transmission and incidence are falling. The reasons for the rejuvenation of these epidemics are not fully understood, though HIV infection is bound to be a contributing factor.

Some states of India have been implementing DOTS since 1998, and yet there was no detectable decline in case notification rates at state level by 2006 (Revised National Tuberculosis Control Program, personal communication). The case notification rates in different states and in different years are closely correlated with the number of suspected TB patients examined. This suggests that the number of cases diagnosed and reported is determined by the performance of the public health service, as well as by the true incidence of TB. The southern states of Kerala and Tamil Nadu show an increase in the average age of TB cases, which may reflect falling transmission. This has yet to be translated into a clear demonstration of falling incidence across a whole state, though transmission and prevalence have been reduced on a smaller scale in the Tiruvallur District of Tamil Nadu [36,37].

Calculations carried out for the WHO 2007 report on Global Tuberculosis Control suggest that, although prevalence and death rates are falling globally, the rate of decline is not fast enough to meet the MDGs by 2015 [5]. While the surveillance data from certain Asian countries show worryingly slow rates of decline, the biggest regional challenges in reducing TB burden are in sub-Saharan Africa and Eastern Europe.

1.4 Achieving the Millennium Development Goals by 2015

Since the launch of the DOTS strategy during the 1990s, a series of specific, emerging problems in TB epidemiology and control have demanded specific solutions. These include *M. tuberculosis* and HIV co-infection, drug resistance, the quality of treatment in the private sector, and the need to evaluate the epidemiological impact of TB control (not simply the implementation of DOTS). For this reason, DOTS has been extended as the Stop TB Strategy, with the additional elements listed in Table 1.1 [5,6]. The blueprint for implementing the Stop TB Strategy over the next decade is the Global Plan to Stop TB (2006–2015) [11]. The plan imagines and compares three scenarios:

Scenario 1: No DOTS. This assumes that the strategy was never introduced in any region, so chemotherapy would continue as it was pre-DOTS, with variable rates of case detection and typically lower rates of cure. This gives a baseline against which to compare gains that have already been made, and which might be made in future.

Scenario 2: Sustained DOTS. Case detection and treatment success increase until 2005, and then remain steady until 2015. Approximately 50 million patients would be treated under DOTS between 2006 and 2015, as compared with around 25 million in the previous decade, 1996–2005.

Scenario 3: Enhanced DOTS. Case detection and treatment success continue to increase beyond 2005, up to 2015. As in

scenario 2, roughly 50 million patients would be treated between 2006 and 2015 (a higher proportion of patients treated sooner means that as a result of reduced transmission, there are fewer patients later). To reach high rates of case detection and cure requires various additions to the basic DOTS strategy, including community-based care, a syndromic approach to diagnosing and treating TB among other respiratory conditions, and improved collaboration between public and private health sectors. To improve the management of drug-resistant disease, more patients will be given drug sensitivity tests, and around 800 000 MDR-TB patients will be treated with regimens including second-line drugs. HIV testing and counseling will be provided to 29 million TB patients, and antiretroviral therapy (ART) and co-trimoxazole preventive therapy offered to 3.2 million. Approximately 200 million people infected with HIV will be screened for TB, and 24 million will be offered IPT.

The potential impact of scenario 3, as compared with scenarios 1 and 2, has been evaluated with a mathematical transmission model describing, as in previous models [38–41], how the planned interventions determine incidence, prevalence and death rates through time. Model calculations show that scenarios 2 and 3 should both satisfy MDG target 8, to ensure that the incidence rate of TB is falling globally. In fact, the annual incidence of new cases is expected to be in decline well before 2015, even under scenario 2. Notwithstanding the observations on impact in Section 1.3.3.3, ambitious plans for the South East Asia and Western Pacific regions are expected to generate relatively rapid declines in incidence rate of 7–9 % per year by 2015.

To halve prevalence and death rates between 1990 and 2015 will be more challenging. Projections suggest that these targets can be met globally with full implementation of the enhanced DOTS strategy (scenario 3), but not in Africa or Eastern Europe (Figure 1.5). Based on the calculated rate of decline in mortality from 2006 to 2015 in the African countries most affected by HIV (Africa – high HIV), the target death rate would not be reached before 2025. If the rate of decline in mortality slows, as it has in Europe and North America, then the target will be reached even later than 2025.

In Eastern Europe, but not in Africa, prevalence rates are also expected to remain high compared with 1990 levels. In Eastern Europe, a relatively high proportion of patients have chronic TB, which is commonly multidrug resistant. In Africa, patients that are infected with HIV do not suffer from TB for long; their illness typically progresses quickly, and they are either cured or die [42]. This bleak outlook for TB control in Africa and Eastern Europe arises in large part from the choice of 1990 as the MDG reference year. In that year, TB incidence rates in these two regions were close to their lowest levels for at least half a century, and most of the recent rise in incidence occurred during the 1990s.

While not ignoring the epidemiology of the recent past, more relevant here is the impact of interventions in the near future. The same projections also show that, over the 10 years from 2006 to 2015, the impact of the enhanced DOTS strategy, assuming

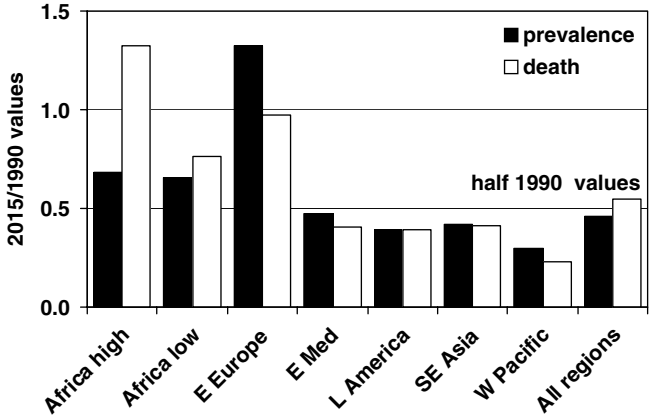

Figure 1.5 Expected reductions in prevalence (black bars) and death (white bars) rates by 2015, as compared with the estimated rates in the MDG baseline year, 1990. The analysis divides the world into seven regions, excluding the low-incidence indutrialized countries. The labels 'high' and 'low' used with reference to Africa refer to levels of HIV infection, see Figure 1.1 [11].

full implementation, would be almost as great in Africa and Eastern Europe as in other regions of the world: a reasonable goal in all regions would be to halve prevalence and death rates between 2005 and 2015. To that end, the implementation of the enhanced DOTS strategy will be especially important in Africa and Eastern Europe, where the incremental benefits of enhanced DOTS (scenario 3) compared with sustained DOTS (scenario 2) are greatest. Indeed, the proportional reduction in TB cases under scenario 3 (as compared with scenario 2) would be greater in Eastern Europe than in any other region. The proportional reduction in deaths would be greatest in Africa (countries with high HIV prevalence) and Eastern Europe.

In regions of the world other than Africa and Eastern Europe, a higher proportion of the benefits to be obtained over the next ten years come from sustaining what has been achieved over the past ten. And TB epidemiology in these other regions, notably Asia, governs the global trend. Thus, enhanced DOTS (scenario 3), as compared with sustained DOTS (scenario 2) would save only 2.7 million deaths globally over the next decade (the difference between scenarios 2 and 3). But if scenario 3 is considered to be the logical extension of the program of global DOTS expansion that began in the early 1990s, then enhanced DOTS will save 13.7 million deaths between 2006 and 2015 (the difference between scenarios 1 and 3). In continuing this program of DOTS expansion, most cases and deaths saved will be in the South East Asia and Western Pacific regions.

1.5
Eliminating TB in the 21st Century

This discussion of control via the Stop TB Strategy has necessarily focused on the chemotherapy of active disease, because drug treatment is likely to remain the

principal option for combating TB over the next decade. In the longer term, TB elimination might be achieved through a combination of measures to prevent infection, to stop progression from infection to active disease, and to treat active disease. An examination of the principles of TB elimination shows how we may exploit, or even drive, the development of new drugs, diagnostics and vaccines [43–45].

Mathematical modeling shows that with the diagnosis and treatment of 70 % of new infectious cases arising each year and a cure rate of 85 %, the incidence rate is expected to fall from a steady state at around 4–5 % annually for the first 10 years, and then more slowly thereafter [46]. This is about the same as the additional rate of decline in TB incidence seen in Western European countries after effective TB drugs became available during the 1950s. The net effect is to halve the incidence rate by 2050. A reduction of this magnitude would be an important achievement for public health, but it leaves an incidence rate mid-century that is still far above the elimination threshold of one per million population (as does scenario 3 of the Global Plan to Stop TB; Section 1.4).

To eliminate TB by 2050 (outside sub-Saharan Africa), the incidence rate must fall at an average of 16 % annually from 2007 onwards. This rate of decline might be achieved for a few years, but it is unlikely to be sustainable. The reason, as observed in Section 1.2, is that when transmission and incidence fall, a growing proportion of cases arise from the slow reactivation of long-standing latent infections, rather than from the rapid progression of recent infections. Thus, the initial rate of decline in incidence is controlled by primary progression and reinfection, but the long-term rate of decline is governed by reactivation.

Combinations of interventions can, in principle, push TB closer to elimination, but some combinations are more effective than others. Figure 1.6A shows the expected incidence rate in 2050 when pre-exposure vaccination (to prevent infection) is combined with the treatment of TB patients. The effects of the two approaches are similar when used alone, and intensifying either control method yields sharply diminishing returns. The two methods are somewhat more effective in combination, but the additional impact is small. This is because drug treatment to stop transmission at source has effects that are similar to vaccination, which protects those who are exposed to infection. One intervention partly substitutes for the other; they do not act independently or synergistically. Therefore, a pre-exposure vaccine will be most useful in addition to treatment when the detection rate of active TB cases is low, and vice versa.

The campaign to eliminate TB will be more effective if two interventions attack different etiological pathways, that is, both the fast (transmission, infection and progressive primary disease) and slow (reactivation of latent infection) routes to developing active TB. The treatment of latent TB, either by preventive drug therapy or post-exposure vaccination, is relatively ineffective when used alone (Figure 1.6B and C), but powerful in combination with the treatment of active TB (Figure 1.6B and D) or with pre-exposure vaccination (Figure 1.6C). When these combined approaches are implemented intensively, the incidence of TB may be reduced to close to or below the elimination threshold by 2050. In the examples shown in Figure 1.6B and C, incidence is reduced to 0.14 per million by 2050,

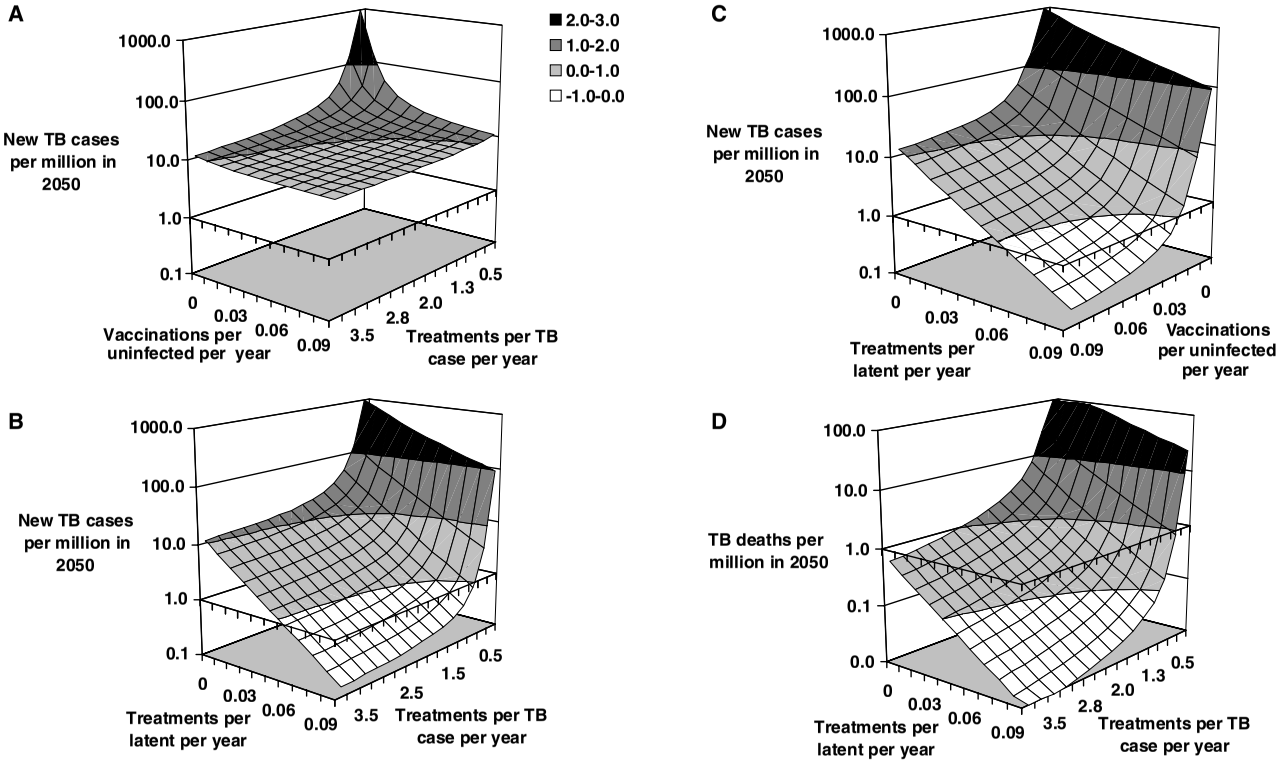

Figure 1.6 Pair-wise combinations of three control methods to eliminate TB, starting from an annual incidence of approximately 1000 per million of the population. Surfaces show the expected incidence rates in 2050 with (A) pre-exposure vaccination and treatment of active TB, (B) treatment of latent infection and active TB, (c) treatment of latent infection and pre-exposure vaccination. (D), as for (B), but with TB death rate as the outcome. Shading in (A)–(C) indicates ranges of incidence rates per million population reached by 2050: <1 (white, below elimination threshold), <10 (light gray), <100 (dark gray), ≥ 100 (black). Because there are fewer TB deaths than cases, the gray scale in (D) is shifted by a factor of 10 [46].

about 7 times lower than expected if the effects were independent. The proportional effect on the TB death rate is still greater (cf. Figure 1.6B and D).

1.6 Conclusions

The countries of sub-Saharan Africa and Eastern Europe (mainly the former Soviet Union) suffered large increases in TB during the 1990s, but there are indications that the incidence rates in these two regions are now stable or falling. If the TB epidemics in these two regions are indeed on the decline, then the global incidence rate is almost certainly declining too, along with prevalence and mortality. This means that MDG Target 8, as related to TB, has already been satisfied, 10 years in advance of the 2015 deadline.

But there are two important caveats. First, the decline in incidence per capita was slower than the increase in human population in 2005; consequently, the total number of new cases was still rising each year. And second, prevalence and mortality rates are not being reduced quickly enough to meet the MDGs by 2015. These are sharp reminders that, despite having treated more than 26 million patients between 1994 and 2005, DOTS has so far had limited epidemiological impact.

It is clear, too, that the fall in case load in some countries is only partially due to the impact of DOTS. In sub-Saharan Africa, the incidence of HIV infection was probably at its highest during the 1990s, and the fall in HIV incidence has weakened the main driving force behind the TB epidemic. In Eastern European countries, many components of the TB control system (diagnostic services, drug supplies, etc.) have been restored after the collapse of the Soviet Union. But this is unlikely to be the full explanation for the stabilization in case notifications in Eastern Europe, because the initial resurgence could also have been due to changes in susceptibility among people who were malnourished, stressed and prove to other biological and social risk factors. In many countries of Latin America, the Eastern Mediterranean region and Asia, TB (all forms) case notification rates were falling well before the implementation of DOTS programs.

The epidemiological impact of DOTS has been discernible in a few countries (e.g. Peru, China), but remains a matter of conjecture in most. There will always be analytical difficulties in distinguishing the impact of a public health intervention outside a randomized controlled trial. Nonetheless, surveillance in India, Indonesia, Myanmar, Sri Lanka and Vietnam raises doubts about whether the fall in incidence in Asia will be as great as expected from the post-war experience in Europe [47], or as anticipated by mathematical models [48,49]. The causes of, for example, rising incidence rates among young adults, are not yet clear. HIV infection plays a part, but is unlikely to provide the full explanation. There is a strong case for re-examining some basic assumptions about TB epidemiology, such as the magnitude of reactivation and re-infection rates in relation to risk factors including indoor air pollution, drug resistance, malnutrition, diabetes and tobacco smoking [50–58].

None of these observations are reasons for abandoning DOTS or the Stop TB Strategy. Rather, the strategy must be reinforced as the only feasible mechanism for

achieving the MDGs by 2015. In evaluating progress towards those goals, it will be vital to measure epidemiological impact through a combination of survey methods and surveillance. Periodic population-based surveys of the prevalence of active disease and infection can reveal trends, which could be attributable to specific interventions. TB deaths need to be counted in more countries, and more accurately, either as a component of general cause-of-death surveys or through systems of routine death registration [58]. The evidence from surveys of prevalence and deaths should be supplemented by fuller analyses of the huge body of surveillance data that is routinely collected by national control programs (following the example of Peru).

Beyond the Stop TB Strategy, the Global Plan and the MDGs, TB elimination in the 21st century will require a new armory of diagnostics, drugs and vaccines. TB cannot be eliminated by 2050 solely by cutting transmission, no matter how well current programs of drug treatment are implemented. To eliminate TB on this time-scale it will be essential to stop the progression from latent infection to active disease, in addition to preventing new infections.

This is unlikely to be possible on a large scale unless existing procedures to carry out preventive therapy can be greatly simplified, or replaced. That will require, first, a diagnostic test for latent infection that is more sensitive and specific than the current tuberculin skin test but easy to administer and read. That need might be satisfied, in part, by interferon-γ release assays, though these need further evaluation [60,60a]. Preventive therapy also requires a course of treatment that is shorter than 9 months. In this context, a 3-month treatment regimen now appears feasible with combinations of drugs such as isoniazid with rifapentine [60]. A major step forward in preventive therapy would be a test to identify which infected people are at relatively high risk of progressing to active disease (from factor other than HIV co-infection).

TB control by immunization certainly requires a vaccine that is superior to the widely-used BCG (Bacille Calmette-Guérin), for which efficacy is variable and often negligible in preventing pulmonary disease in adults. Vaccines that prevent either new infections (pre-exposure), or the reactivation of latent infections (post-exposure), each have their advantages and disadvantages. Pre-exposure vaccines have a greater impact than post-exposure vaccines when used alone, but have the same effect as treating active TB. Therefore a pre-exposure vaccine will be most useful as an addition to treating patients when the detection rate of active TB cases is low, and vice versa. Post-exposure vaccines have a relatively small impact when used alone but, like IPT, act in synergy with the treatment of active TB [45,46].

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