# Global tuberculosis control: lessons learnt and future prospects

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Abstract | Tuberculosis (TB) is an ancient disease, but not a disease of the past. After disappearing from the world public health agenda in the 1960s and 1970s, TB returned in the early 1990s for several reasons, including the emergence of the HIV/AIDS pandemic and increases in drug resistance. More than 100 years after the discovery of the tubercle bacillus by Robert Koch, what is the status of TB control worldwide? Here, we review the evolution of global TB control policies, including DOTS (directly observed therapy, short course) and the Stop TB Strategy, and assess whether the challenges and obstacles faced by the public health community worldwide in developing and implementing this strategy can aid future action towards the elimination of TB.

*"The struggle [against tuberculosis] has caught hold along the whole line and enthusiasm for the lofty aim runs so high that a slackening is no longer to be feared. If the work goes on in this powerful way, then the victory must be won."*

It is with these powerful and optimistic words that Robert Koch, discoverer of the tubercle bacillus, concluded his Nobel Lecture on December 12, 1905. Armed only with the conviction of the infectious nature of the disease and the importance of isolating infected individuals to decrease transmission, and convinced of the need to improve the social environment of patients with tuberculosis (TB), Koch was confident that society could win the battle against this disease. More than 100 years on (TIMELINE), how has TB control changed? Are we any closer to seeing this scourge eliminated in the foreseeable future? In this Review, we discuss the challenges and obstacles associated with global TB control, particularly those associated with the development of DOTS (directly observed therapy, short course) and the WHO Stop TB Strategy, and assess how the lessons learnt can aid future action towards elimination of the disease.

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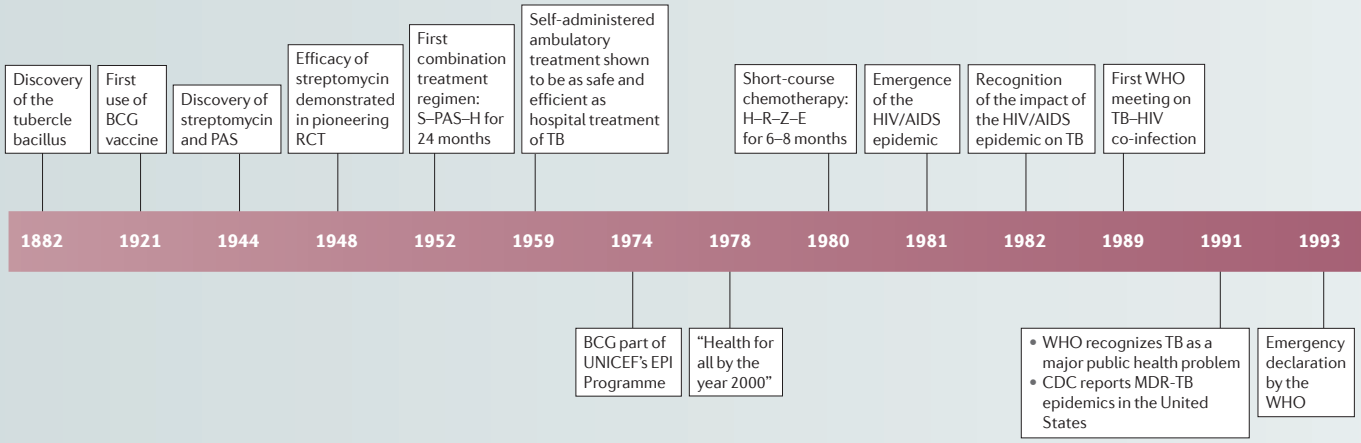
## Early TB control policies

Throughout the 20th century, TB mortality declined steadily in most industrialized countries, with interruptions during the two World Wars[1]. In England and Wales, the decline in reported mortality from TB that began to be observed in the mid-nineteenth century continued steadily until the 1960s[1], most probably as a result of improved socioeconomic conditions, better nutrition and living standards, and the isolation of infectious patients[2] (FIG. 1a). In the Netherlands, mortality due to TB fell by ~3% annually from 1900–1920 and by ~5.5% in the 1920s and 1930s[3] (FIG. 1b). The data for developing countries, especially in the pre-chemotherapy era, are scarce, but information can be obtained from tuberculin surveys that were carried out by the WHO between the 1950s and 1970s[4]. In Uganda, the annual risk of infection decreased by 1.4% from 1950 to 1970, which equated to halving the incidence of TB in more than 50 years, whereas in the Netherlands the annual risk of TB infection decreased by 14% over the same period, leading to a halving of the incidence of TB in 5 years[3].

The development of the *Mycobacterium bovis* bacillus Calmette–Guérin (BCG) vaccine generated high hopes for TB prevention. First administered in 1921, it was used increasingly in Europe following early evidence of its efficacy from studies of student nurses in Norway[5]. After the Second World War, the re-emergence of TB became a major public health concern, and mass BCG vaccination campaigns were encouraged in many countries within and outside of Europe, stimulated by UNICEF, the Scandinavian Red Cross Societies and the WHO[5]. Routine BCG vaccinations were established in many countries worldwide using various schedules, and the vaccine was incorporated into UNICEF's expanded programme on immunization of infants in 1974.

The discovery of streptomycin by Waksman in 1944, and the nearly simultaneous development of para-aminosalicylic acid (PAS) by Lehmann led to an effective

Timeline | **Landmarks in TB control**




BCG, *Mycobacterium bovis* bacillus Calmette–Guérin; DOTS, directly observed therapy, short course; EPI, expanded programme of immunization; FIND, Foundation for Innovative New Diagnostics; H–R–Z–E, isoniazid–rifampicin–pyrazinamide–ethambutol; MDR-TB, multidrug-resistant TB; PAS, para-aminosalicylic acid; RCT, randomized controlled trial; S–PAS–H, streptomycin–PAS–isoniazid; TB, tuberculosis; XDR-TB, extensively drug-resistant TB.

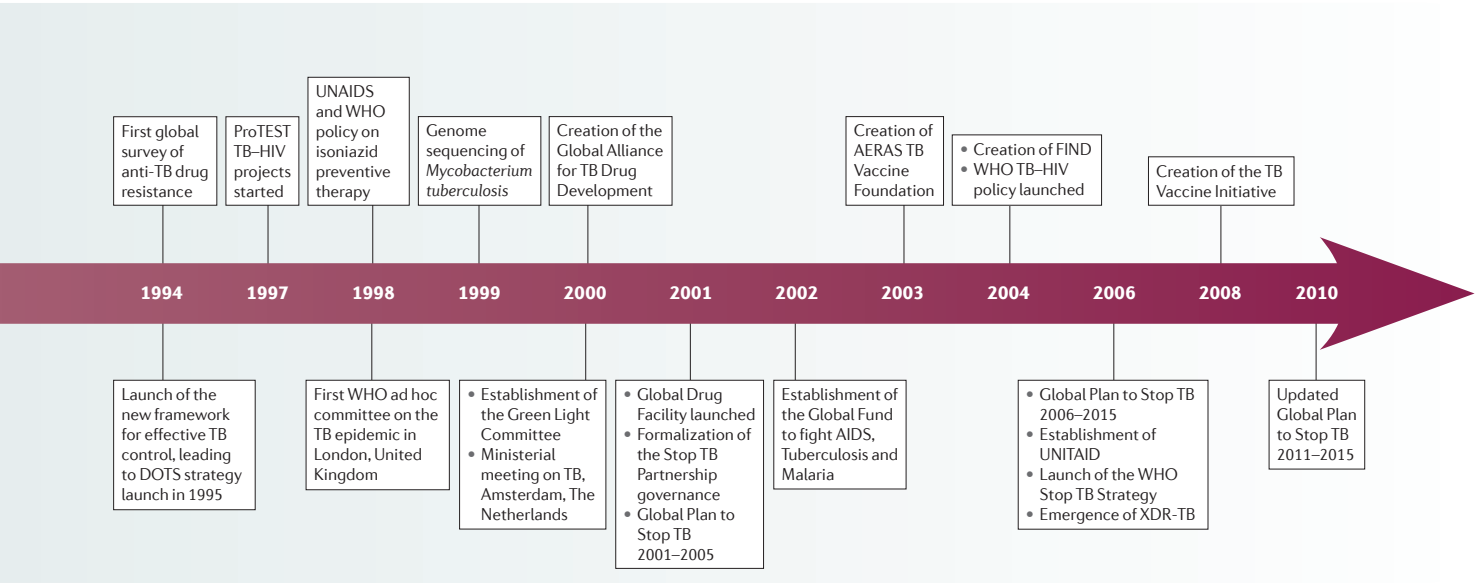
treatment that had a marked effect on TB mortality, ending the sanatorium era. The establishment of the first multi-therapy approach combining streptomycin and PAS was based on the results of a landmark clinical trial carried out by the UK Medical Research Council that showed the superiority of the combined treatment over either agent alone[6]. The discovery of isoniazid in 1951 completed the armamentarium of what became the first triple therapy for an infectious disease[7], curing patients with TB in 18–24 months. PAS was replaced by ethambutol in the early 1960s. The addition of rifampicin in the 1970s and the replacement of streptomycin by pyrazinamide in the 1980s were key to the development of the short-course chemotherapy of 6–8 month duration that became the pivotal element of modern TB control[8].

In 1947, based on the expected high impact of mass BCG vaccination campaigns, and the discovery of the first anti-TB drugs, the WHO declared TB a priority and established a TB section to assist governments in developing effective control programmes[9]. This inaugurated the era of large vertical control programmes (1948–1963), based on mass vaccination, mass radiological screening and TB case management[10] (vertical programmes are single-purpose programmes that are independent of both the general health infrastructure and the structure of other vertical programmes, and are staffed with specialized personnel from the central level to the local level at which the technical control activities are delivered). This approach, which took place in an era of sustained economic development, was successful in many industrialized countries, thereby accelerating the decline in the incidence of TB[3,11].

However, it was not easily transferred to developing countries[1]; large-scale mass BCG vaccinations did not have a long-lasting effect on TB epidemiology[5,12], and anti-TB campaigns could not be sustained outside of the general health services in resource-poor settings. This led to a radical move towards integration of TB programmes into general health services in the mid-1960s, based on pilot studies carried out in India[13,14]. This new policy was formalized in the eighth report of the WHO Expert Committee in 1964 (REF. 15), which emphasized the integration of service delivery, using simple standardized diagnostics and treatment approaches. Unfortunately, in most resource-poor settings, the transfer of responsibilities from vertical to general health services was not accompanied by an increase in resources, leading to weakened TB control with almost no effect on TB indicators. To remedy this, when the WHO embraced primary healthcare (PHC) in the late 1970s, a second wave of integration occurred, aimed at further integration of service delivery and full managerial functions, dismantling the remains of the vertical approaches[10]. This resulted in severe weakening of case-finding and treatment activities in many developing countries, mainly owing to the deterioration of public health infrastructure, compounded by a series of economic crises. The neglect of TB control worldwide was further accelerated in the late-1980s with the promotion of health sector reforms that involved decentralization of authority and managerial integration of programmes[16]. This shift in the overall concept of health management had a staggering effect on disease control programmes, which temporarily disappeared as specific entities[10,17].

## The resurgence of TB in the 1990s

The 1990s saw major disruptions in the world, with the end of the Cold War, the dissolution of the former Soviet Union and the inexorable expansion of the HIV/AIDS pandemic. New global TB estimates in 1989–1990 revealed a huge burden of disease in developing countries, accounting for an estimated 7.1 million out of 8 million new cases globally, with TB becoming a leading cause of mortality in sub-Saharan Africa[18]. The driving forces were the HIV/AIDS pandemic, which produced sharp increases in notifications of TB cases, particularly in sub-Saharan Africa[19], associated with insufficient case detection and low cure rates within disorganized and




insufficiently resourced TB control programmes[1,20]. In parallel, TB started re-emerging in several industrialized countries. In the USA, after years of decline, the number of newly reported cases began to increase in 1986, peaking in 1992 (REF. 21). A similar situation was observed in most western European countries, and in Eastern Europe the crisis resulting from the collapse of the former Soviet Union led to a major increase in TB incidence and mortality in practically all the newly established states[20].

***The development of DOTS.*** This alarming situation led to a re-appraisal and reinvigoration of global TB control activities. After decades of neglect, a new strategy was promoted by the WHO, based on the approach developed by Karel Styblo and the International Union Against Tuberculosis and Lung Disease in Tanzania and Malawi in the 1980s[3], which involved moving away from strict integration management theories and emphasized the need for specialized managerial functions at all levels of health care[9,10,22,23]. In 1991, the 44th World Health Assembly (WHA) adopted a resolution that recognized TB as a major public health problem[24]. Two global targets were set for the year 2000: detecting 70% of infectious cases and curing 85% of them. As poor adherence to, and premature interruption of, treatment contribute to prolonged infectiousness and drug resistance, the newly developed strategy, which centred around direct supervision of drug intake by patients, was labelled DOTS, and was characterized by a package of five elements (BOX 1) that constituted a framework for effective TB control[25]. A key element of this strategy was the supervision of drug intake. This approach relied on early work by Wallace Fox, who investigated the possibility of ambulatory (that is, outpatient) self-administration of drugs in the 1950s[26]. The results of a controlled trial in Chennai, India, showed that "the merits of domiciliary therapy [were] comparable to those of sanatorium treatment" (REF. 27). However, to be succesful, domiciliary therapy required an adequate supply of drugs, proper staffing, adequate transport, availability of hospital beds for referrals, supervision of drug intake by members of the patient's family or neighbours, and surprise visit checks. This notion was further embraced in the United States as a fundamental component of proper TB care and named directly observed therapy (DOT)[28].

In 1995, after the establishment of a TB global surveillance and monitoring system, in principle 23% of the world's population had access to DOTS[29]. This figure reached 56% by 1998 (REF. 30), and by 1999 127 countries had adopted this approach, including the 22 highest burden countries, which collectively were responsible for 80% of global TB mortality[31–33]. By 2005, 89% of the world's population was living in areas where DOTS services were available[34]. However, in 2000 it was estimated that only 27% of smear-positive cases worldwide were reported and managed by DOTS programmes[35]. Furthermore, the effectiveness of DOTS was questioned, particularly in areas of high HIV prevalence and in resource-poor settings[36–39]. Indeed, DOTS expansion in the early years was limited by many factors, including the lack of uniform and complete coverage within countries, the high variability of interventions incorporated in TB control practices, the perceived lack of flexibility and adaptability of the strategy, and the lack of explicit reference to social support to facilitate access and adherence to treatment[38–41]. This called for a revision that would allow wider access for all infected individuals, particularly for the underprivileged in the poorest countries[10], and became the foundation for the development of the new Stop TB Strategy in the mid-2000s (see below).

***The new challenges: HIV infection and MDR-TB.*** The link between TB and HIV was reported soon after the first descriptions of AIDS in 1981 (REFs 42,43). HIV infection rapidly emerged as the strongest risk factor for the development of TB in individuals infected with *Mycobacterium tuberculosis*[19,44], with the risk up to

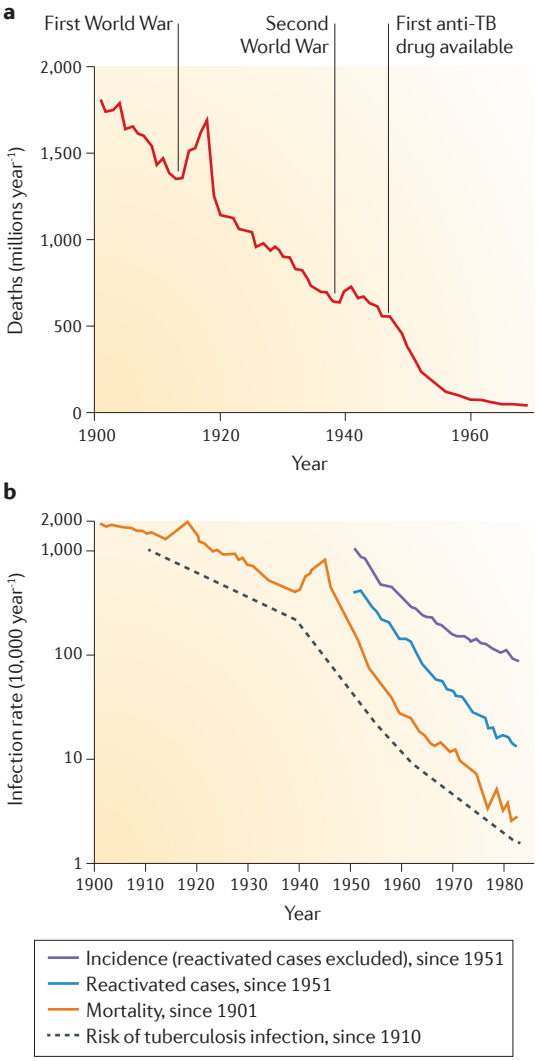



Figure 1 | **Early declines in TB mortality in Europe.** **a** | Decline in tuberculosis (TB) mortality in England and Wales for the period 1900–1960. Data from REF. 101. **b** | TB incidence, reactivation and death rates (per 100,000) and the average annual risk of TB infection (per 10,000) in the Netherlands for the period 1901–1983. Data from REF. 3.

37 times higher than in HIV-negative patients infected with the bacterium[45]. This resulted in an increase in TB case notifications in HIV-prevalent countries, particularly in sub-Saharan Africa, which mirrored the increase in the prevalence of HIV infection with a 4–7-year delay[45]. TB control faced increasing challenges, with rising case notifications, difficulties in diagnosis, drug-related side effects, high case-fatality rates, increased recurrence rates and increased transmission of *M. tuberculosis* within crowded settings[44,46]. In response to this, in 1997 the WHO launched the ProTEST initiative, an operational research project to address the unprecedented scale of the epidemic of HIV-related TB and develop a district-based strategy for joint TB–HIV control efforts. This initiative promoted voluntary HIV testing as the point of entry for access to HIV and TB interventions, including intensified TB case finding and isoniazid preventive therapy[47]. Evaluation of pilot projects conducted in Malawi, South Africa and Zambia[48] and elsewhere in Africa and Asia by organizations such as Family Health International and the CDC[49] showed that HIV/AIDS and TB control programmes can work together effectively and that such collaborative activities are necessary to improve the care available for people co-infected with TB and HIV. The rapid expansion of access to antiretroviral therapy (ART) through the 3 by 5 initiative (which aimed to provide 3 million people living with HIV/AIDS in low- and middle-income countries with ART by the end of 2005) has accelerated the implementation of the "policy on collaborative TB/HIV activities" (REF. 50).

At the same time, in the early 1990s, outbreaks of multidrug-resistant (MDR) TB (that is, strains resistant to isoniazid and rifampicin) were reported in the United States, mainly among HIV-infected individuals[51–54]. By the end of the 1990s, virtually all countries participating in a global survey of anti-TB drug resistance reported MDR-TB cases[55]. This emerging problem was linked to improper prescribing practices, lack of patient adherence to treatment and irregular supply and low quality of drugs, all of which reflected poor TB control practices[56]. In addition, ongoing primary transmission was found to contribute to rising rates of MDR-TB[55,56].

Building on the DOTS strategy, a new programme-based approach was devised to address the rise in MDR-TB around the world[57]. In June 2000, the WHO, together with other partners (Harvard Medical School, the CDC, Médecins Sans Frontières, the Royal Dutch Tuberculosis Foundation and the National TB Programme of Peru) established a pooled procurement mechanism to increase the availability of quality second-line drugs at low cost, named the Green Light Committee (GLC)[58]. The objective was to allow countries in which TB is endemic to access concessionally priced and quality-assured second-line anti-TB drugs[59], while ensuring safe and rational drug use.

***How TB control reappeared on the global public health agenda.*** By 1998, only a handful of countries had achieved the 70% case detection and 85% treatment success targets that had been set by the 44th WHA, so the WHO convened an ad-hoc committee in London, United Kingdom, to address the delays in implementation of the DOTS strategy. The committee made several key recommendations that modified the approach to worldwide TB control[60]. First, it established that the response to the TB epidemic had to be based on a new coalition with common aims of all partners and governments worldwide. Subsequently, the Stop TB Initiative, a coalition of stakeholders in the global fight against TB, was launched at the World TB Conference in Bangkok, Thailand, in November 1998. It called for the development of a global action plan for TB control focusing on high-burden countries, and addressing drug-resistant and HIV-associated TB[61]. Second, the committee called for a central mechanism of drug procurement and supply that would address the serious issue of first-line drugs being out of stock in numerous developing countries.

In accordance with this, the Global TB Drug Facility (GDF) was established in 2001 and delivered its first drugs to Moldova in May of that year[62]. Third, the committee called on the governments of the 22 high-burden countries to commit to TB control. Following a ministerial meeting in Amsterdam, the Netherlands, on World TB Day in 2000, a declaration for action was issued, stating the strategic directions and targets that were to be achieved by a new deadline of 2005 (REF. 63). This was endorsed by the WHA 2 months later[64].

The original Stop TB Initiative did not function immediately. However, by the year 2000, a new environment was created by a change of leadership, the goodwill of key partners and the agreement reached around the GDF. In February 2001, in Bellagio, Italy, under the auspices of the Rockefeller Foundation, a new governance was approved based on a secretariat located at the WHO, a permanent coordinating board and several technical working groups. The Stop TB Partnership was established[61], and the first coordinating board meeting was held in 2001 in Annapolis, Maryland, United States.

A business plan was needed to describe the strategic directions that the Stop TB Partnership would take to make a difference in TB control. The 'Global Plan to Stop TB 2000–2005' defined strategies and activities to expand DOTS coverage, address HIV-associated TB and MDR-TB, and pursue innovative research for new TB diagnostics, drugs and vaccines[65]. This was followed by a second plan that set the global goals to halve TB prevalence and mortality compared with 1990 levels by 2015, the deadline year for the Millennium Development Goals (MDG), and to achieve TB elimination, defined as less than one case per million population per year, by 2050 (REF. 66).

In parallel, talks were held at the G8 Summit in Okinawa, Japan, in 2000, about a "new global partnership to address the infectious diseases of poverty, including TB". Moroever, at the UN General Assembly in June 2001, the then Secretary-General of the UN, Kofi Annan, called for the creation of a global fund to fight HIV/AIDS. The merging of the two concepts led to the establishment of a Global Fund to fight AIDS, Tuberculosis and Malaria, which was announced at the G8 Summit in Genoa, Italy, in 2001 (REF. 67) and began operating formally in early 2002 (REF. 68). The first disbursements were made in 2004, and TB control budgets began to increase dramatically. Later in the decade, other international financing mechanisms were created, including UNITAID, a funding initiative proposed by France, Brazil and Chile based on a tax levy on air flights to support essential commodities for the fight against HIV/AIDS, TB and malaria (see UNITAID website). Support for TB control greatly increased in the 2000s, and by 2011, US$3.1 billion was invested in TB control, approximately three times more than was invested in 2002.

Box 1 | **The five components of DOTS**

- Generating government commitment to mobilize sufficient resources for tuberculosis (TB) control.
- Case detection through passive case finding using sputum smear microscopy in patients with respiratory symptoms.
- Treatment using standard short-course chemotherapy regimens containing rifampicin, administered under direct observation for at least the first 2 months of treatment.
- Securing a regular supply of essential anti-TB drugs.
- Establishing a reliable monitoring, recording and reporting system for programme supervision and evaluation.

DOTS, directly observed therapy, short course.

## The development of the Stop TB Strategy

The increased political commitment from high-burden countries and their national and international partners led to progress in global TB control. By 2004, more than 20 million patients had been treated in DOTS programmes around the world, and more than 16 million of them had been cured[69]. However, although the implementation of DOTS helped achieve good progress, it was insufficient to accomplish the international targets of halving TB mortality and prevalence by 2015 (REF. 70). Urgent action was needed, particularly in parts of the world where the epidemic was becoming worse, notably in Africa, Eastern Europe and Asia. In these areas, identifying and reaching those in need of care required concomitant progress of efforts to control TB and efforts to strengthen health services as a whole. Thus, in 2005, based on crucial reports[71,72], the WHA passed a resolution advocating for "sustainable financing for TB control and prevention", with countries making a commitment to strengthen efforts to achieve the TB-related international targets[73].

Since the development and initial promotion of DOTS, the WHO and other international partners had been exploring complementary approaches to address the major constraints in TB control, particularly the new challenges of TB–HIV co-infection and MDR-TB. Together with the rapid expansion of access to antiretrovirals, collaborative TB–HIV activities were defined and implemented[50]. Strategies for programme-based management of MDR-TB were developed and tested[74], and effective ways of undertaking community care to support patients and expand access were identified[75]. In addition, there was increased recognition of the crucial part played by patients and their community members in the design and implementation of policies and programmes, both globally and nationally[76,77]. The WHO and its partners developed evidence-based strategies to engage diverse public, voluntary, corporate and private providers to widen the network of TB services offered[78], and formulated and published the International Standards for TB Care to ensure quality of care across all providers[79]. Moreover, they piloted initiatives that strengthened primary respiratory care while expanding quality services for TB[80].

In addition to mechanisms such as the GDF and GLC, which aimed to improve access to quality drugs for TB and MDR-TB, respectively[59,62], options for tackling poverty in TB care and control were investigated[81]. New resources were becoming available for health systems and disease control from domestic and

Box 2 | **Components of the Stop TB Strategy and implementation approaches**

**1. Pursue high-quality DOTS expansion and enhancement**
- Secure political commitment, with adequate and sustained financing.
- Ensure early case detection and diagnosis through quality-assured bacteriology.
- Provide standardized treatment, with supervision, and patient support.
- Ensure effective drug supply and management.
- Monitor and assess performance and effect.

**2. Address TB–HIV, MDR-TB and the needs of poor and vulnerable populations**
- Scale up collaborative tuberculosis (TB)–HIV activities.
- Scale up prevention and management of multidrug-resistant (MDR) TB.
- Address the needs of contacts of patients with TB and of poor and vulnerable populations.

**3. Contribute to strengthening the health system based on primary health care**
- Help to improve health policies, human resource development, financing, supplies, service delivery and information.
- Strengthen infection control in health services, other congregate settings and households.
- Upgrade laboratory networks and implement practical approaches to lung health.
- Adapt successful approaches from other areas and sectors, and foster action on the social determinants of health.

**4. Engage all care providers**
- Involve all public, voluntary, corporate and private providers through public–private mix approaches.
- Promote the use of the international standards for TB care.

**5. Empower people with TB and communities through partnership**
- Pursue advocacy, communication and social mobilization.
- Foster community participation in TB care, prevention and health promotion.
- Promote use of the Patients' Charter for TB Care.

**6. Enable and promote research**
- Undertake programme-based operational research.
- Advocate for and participate in research to develop new diagnostics, drugs and vaccines.

DOTS, directly observed therapy, short course.

international sources, including: the Global Fund to fight AIDS, Tuberculosis and Malaria; bilateral agencies; and philanthropic organizations. This created a favourable environment to build a new strategy, expanding beyond DOTS and drawing attention to the need for comprehensive action on several fronts (BOX 2). The new Stop TB Strategy was formally launched on World TB Day in 2006. Building on the expansion of high-quality DOTS, this strategy integrated the need to address the new challenges posed by TB–HIV co-infection and MDR-TB, the need to reach out to poor and vulnerable populations and foster private sector and community involvement in TB care and control, and the need to address the health system[82]. It provided the basis and the context for the Global Plan to Stop TB 2006–2015.

### The role of research and development

TB research and development stagnated for several decades, as the prevailing concept was that the essential tools were available and that better application of these tools would suffice. However, most developing countries in the 1990s and 2000s were using old tools that had found their limits with TB–HIV co-infection and the emergence of anti-TB drug-resistance: sputum microscopy and traditional solid culture when and where available as diagnostics; the four-drug treatment regimen that was developed in the 1970s; and the same, largely ineffective BCG vaccine that has been in use since the 1920s.

The need for research to develop new tools for optimal diagnosis, prevention and treatment of all forms of TB in people of all ages (including children and those living with HIV) was evident. The establishment of the Bill & Melinda Gates Foundation coincided with the establishment of other public–private partnerships that have played a major part in resurrecting TB research and development. The Global Alliance for TB Drug Development was created in New York, United States, in 2000, with support from the Rockefeller Foundation, with the aim of facilitating research and development of new TB drugs. A decade later, and with salient investment from various pharmaceutical companies, there are several promising compounds in the pipeline, and a few new drugs belonging to new classes of anti-TB molecules might be released for clinical use in 2012–2013 (REFs 83,84). For TB diagnostics, FIND (Foundation for Innovative New Diagnostics) was established in 2004 in Geneva, Switzerland, with grants from the Bill & Melinda Gates Foundation and other donors to facilitate the development of new diagnostics. Only a few years after its creation, FIND has facilitated the development of new, effective diagnostics, such as innovative nucleic acid amplification tests[85], and a series of new strategies for diagnostics have been endorsed by the WHO[86]. Finally, in the field of vaccines, with the involvement of several academic groups, research institutions and public–private partnerships such as AERAS and the TB Vaccine Initiative (TBVI), a pipeline exists that contains at least 10 vaccine candidates, including modified and strengthened BCG vaccines, as well as novel vaccines designed to be used in prime-boost vaccination strategies[87]. This reinvigorated role of research was reflected in the revised Global Plan to Stop TB 2011–2015 (REF. 88). Overall, TB research and development increased substantially over the past decade, thanks to the involvement of key donors, and today's annual investment is more than $0.6 billion[89]. However, according to the estimates in the Global Plan 2011–2015, expenditure on TB research and development should be ~$2 billion per year to deliver according to expectations[88].

### Impact of TB control since 1995

The reductions in the burden of disease achieved to date are the result of more than 15 years of intensive efforts to improve TB care and control. Between 1995 and 2010, 46 million patients with TB were successfully treated in DOTS programmes, and up to 7 million lives were saved, including 2 million women and children[90]. Overall, the treatment success rate has increased from 57% in 1995 to 87% in 2009 among sputum smear-positive cases.

In 2010, there were 5.7 million official case notifications of TB cases worldwide, up from 3.4 million in 1995, and there were an estimated 8.8 million incidents

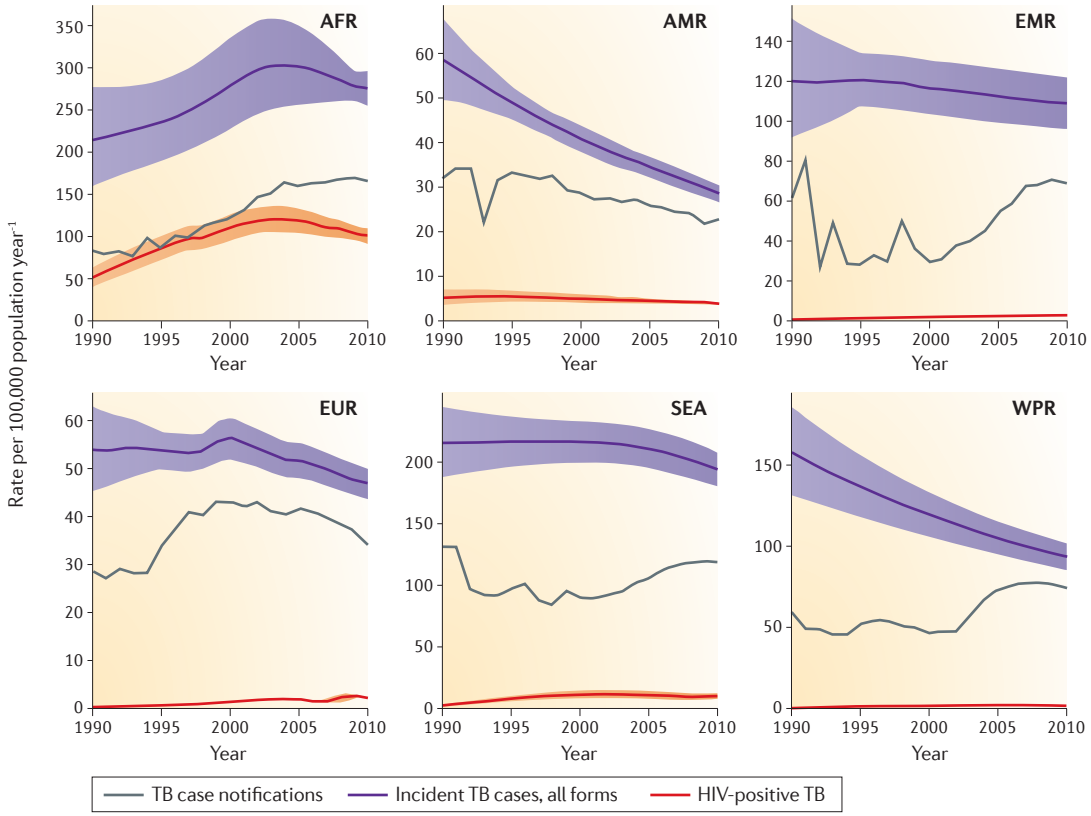



Figure 2 | **Recent trends in TB incidence and case notification rates.** The graphs show trends in case notification rates (new and relapse cases, all forms), estimated incidence rates, including HIV-positive tuberculosis (TB) and estimated incidence rates of HIV-positive TB cases in the WHO regions for the period 1990–2010. The shaded areas represent uncertainty bands. AFR, Africa Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; SEA, South East Asia Region; WPR, Western Pacific Region. Data from REF. 91.

(8.5 million–9.2 million) of TB globally (equivalent to 128 cases per 100,000 population)[91]. Global TB incidence rates have been falling since 2002, and the number of case notifications has been falling since 2006 (REF. 91) (FIG. 2). If these trends are sustained, the MDG target will be achieved. However, global incidence is falling too slowly for TB elimination to be reached by 2050. Also in 2010, there were an estimated 0.9 million–1.2 million TB-related deaths among HIV-negative individuals globally and 0.32 million–0.39 million TB-related deaths among HIV-infected individuals. Global TB mortality rates fell by around 40% between 1990 and 2010 (REF. 91), and the target of a 50% reduction by 2015 could be achieved if the current rate of decline is sustained (FIG. 3); this target could be achieved in five out of the six WHO regions, the exception being the African Region.

HIV infection has markedly increased the number of TB cases reported annually from sub-Saharan Africa, and in 2010 the African Region accounted for 74% of the world's HIV-positive TB cases. Overall, 34% of patients with TB in 2010 knew their HIV status (up from 28% in 2009)[91], including 59% of patients in the African Region. Globally, a total of 300,000 HIV-positive patients with TB were enrolled on co-trimoxazole preventive therapy, and almost 200,000 on ART (77% and 46%, respectively, of patients with TB who were HIV positive). However, the use of isoniazid to prevent the development of TB remains an inconsistently implemented global policy, and only 180,000 people living with HIV received prophylactic treatment in 2010 (REF. 91). In 2010, there were an estimated 460,000–870,000 prevalent cases of MDR-TB, mostly in China, India, the Russian Federation and South Africa. By November 2011, 58 countries and territories had reported at least one case of extensively drug-resistant TB (XDR-TB). Among TB case notifications in 2010, an estimated 290,000 patients had MDR-TB. Of these, slightly more than 46,000 patients (16%) were diagnosed with MDR-TB and put on treatment[91].

## Future prospects

As the international community continues to make strides to reach the TB control targets set for 2015, attention is gradually shifting towards TB elimination. Based on the progress made to date, the experiences arising from more than 50 years of global TB control and the lessons learnt, we suggest that actions will be required on four distinct but synergistic fronts to achieve this ambitious goal[92].

***Securing the core functions.*** Ensuring full and continued funding and implementation of all components of the Stop TB Strategy is the highest priority for all

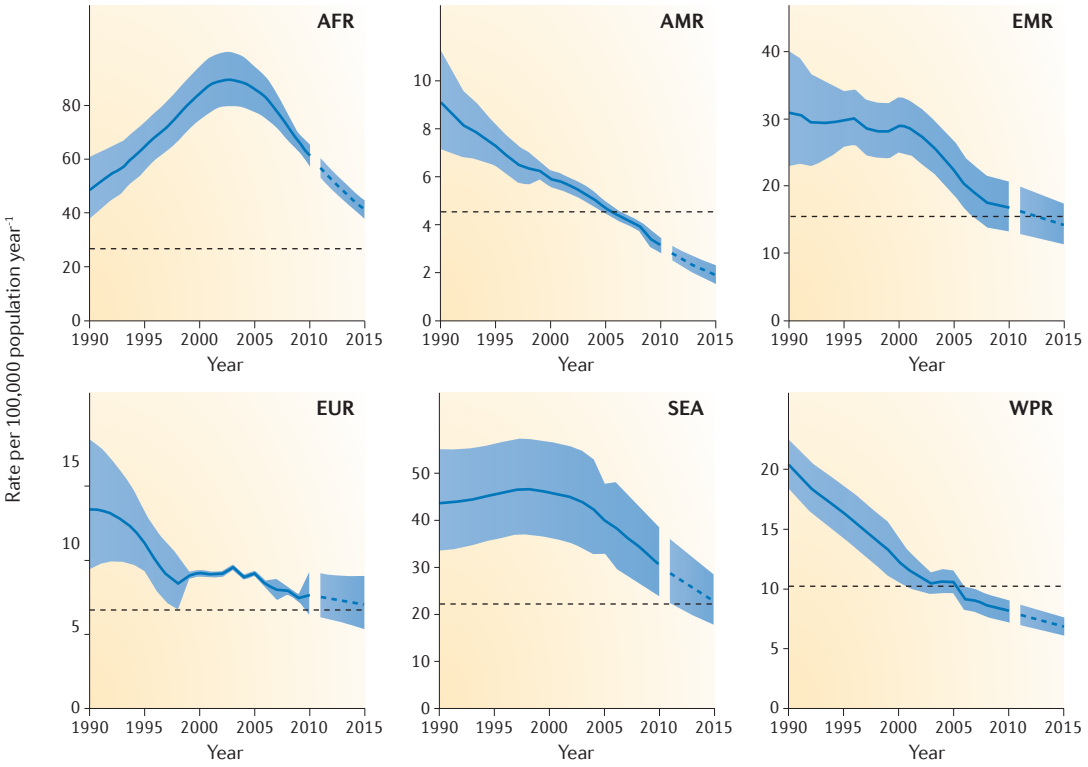



Figure 3 | **Recent trends in TB mortality.** The graphs show tuberculosis (TB)-related mortality, including deaths in HIV-infected individuals, for the period 1990–2010 and projected mortality for the period 2011–2015, for the WHO regions. The shaded areas represent uncertainty bands. Uncertainty is comparatively lower when the data come from vital registration records. AFR, Africa Region; AMR, Region of the Americas; EMR, Eastern Mediterranean Region; EUR, European Region; SEA, South East Asia Region; WPR, Western Pacific Region. The dashed line represents the Stop TB Partnership target of 50% reduction in the mortality rates by 2015 compared with 1990 levels. Data from REF. 91.

countries. When and where the fundamentals of TB care and control are not yet in place, efforts should first focus on establishing these principles, and when they are in place, should focus on sustaining them. In particular, it will be crucial to improve access and intensify action to reach out to those who are not diagnosed early enough through passive case-finding approaches. This includes intensified screening of TB among people seeking healthcare using sensitive tools and algorithms, as well as active case finding among TB contacts and other high-risk groups[92].

***Health system support.*** The lack of progress in control efforts in recent years in some settings is largely due to the limitations of the health systems and services within which TB control programmes operate[93]. Inspiring statements about bold policy changes for health system strengthening must be urgently translated into action, including: increased public spending on health care; improved human resources for health care; universal coverage with free diagnosis and treatment; and full protection against the catastrophic direct and indirect cost of illness. Better intelligence on the TB burden requires improved health information systems. Alignment of care to best evidence across the health system requires much stronger collaboration with private practitioners, including increased education and technical assistance[78]. Prevention and management of drug-resistant TB requires enforced drug regulation, as well as rational prescribing and dispensing of drugs. Addressing all these barriers is a tall order and will require political will on the highest level, stimulated by forceful grassroots demands.

***Investing in research.*** Any realistic prospect of eliminating TB relies both on better and wider use of existing technologies and the development of new tools for TB diagnosis, treatment and prevention. Research must be accelerated across the continuum, from discovery (the basic science that underpins the development of new diagnostics, drugs and vaccines) to implementation research (ensuring that newly developed tools are rapidly and effectively taken up in areas where they are most needed). With this view, the TB Research Movement has been launched, with the aim of boosting TB research and accelerating progress in TB control towards international targets[94]. This is, however, insufficient. As suggested by a recent mathematical model, the elimination of TB by 2050 relies on the combined and synergistic implementation of several new strategies, including improved diagnosis of drug-susceptible and drug-resistant TB, shorter treatment of overt TB cases (≤2 months), scaled-up treatment of latently infected individuals (especially in high-risk populations) and

mass vaccination campaigns using a more effective vaccine[95]. The goal of eliminating TB will remain elusive without the much needed transformation in research to develop new technologies for diagnosis, treatment and prevention[94]. To catalyse this transformation and pave the way for future research, in 2011 the TB Research Movement produced the International Roadmap for TB Research[96], which outlines crucial priority areas for future scientific investment, with the aim of synergizing research efforts globally and catalysing the development of new research collaborations to address difficult and unanswered questions in TB research[97].

***Addressing the social determinants of TB.*** The social and economic forces behind TB infection and disease have remained the same for centuries. Poverty, undernourishment, and poor living and working conditions, maintained by social injustice, political instability and war, continue to create fertile ground for TB to spread and thrive. Rapid urbanization concentrates these conditions into large pockets of extreme poverty. Increased migration allows TB to be transmitted faster and over a wider area. Shifting lifestyles have brought many unhealthy choices to the developing world, with increasing prevalence of smoking[98] and diabetes[99], as well as alcohol and drug abuse[100], all of which are risk factors for TB. These risk factors are associated with economic progress, but disproportionally affect the lower social classes in all societies, making those already vulnerable to TB infection even more vulnerable, completing the vicious circle that links the disease and poverty[101].

Actions on social determinants can have a positive effect on TB control on at least three levels[92]. First, to improve TB treatment outcomes, treatment must be free of charge and delivered in a way that optimizes chances of full treatment adherence and minimizes direct and indirect costs. Second, to improve early case detection, access barriers need to be addressed within a broader health system strengthening agenda, and high TB risk populations must be targeted with intensified and proactive case detection efforts. Finally, socioeconomic conditions must be improved through social and economic reforms, and the prevalence of TB risk factors should be tackled through broad public health actions.

The fight against TB is becoming ever more multifaceted and has to be carried out on many fronts. The stakeholders involved in TB control need to become more diverse and grow in number. The health sector is but one of many sectors that need to be fully engaged. The research community needs better stimuli to take on new developments. All government sectors, non-governmental organizations, the private sector, civil society organizations and TB-affected communities have key parts to play in creating demand for, and ensuring effective delivery of, both medical and social interventions[102].

## Conclusions

To achieve maximum TB care and control, countries must move rapidly towards universal access to prevention, diagnostic and treatment services for all forms of TB. From a broader perspective, realizing the Stop TB Strategy's vision of a TB-free world will require policies and actions beyond the remit of TB control programmes and non-state health stakeholders, and will need contributions from other sectors to eradicate the key determinants of the epidemic. In the context of health and human development, research to accelerate progress in TB control is inextricably associated with efforts to alleviate poverty and promote social and economic development.


1. Styblo, K. in *Selected Papers*, Vol. 24 (KNCV, 1991).
2. Lienhardt, C. From exposure to disease: the role of environmental factors in susceptibility to TB. *Epidemiol. Rev.* **23**, 288–301 (2001).
3. Styblo, K. Overview and epidemiological assessment of the current global tuberculosis situation with an emphasis on control in developing countries. *Rev. Infect. Dis.* **1**, S339–S346 (1989).
4. Roelsgaard, E., Iversein, E. & Blocher, C. Tuberculosis in tropical Africa. *Bull. World Health Organ.* **30**, 459–518 (1964).
5. Fine, P. E. M., Carneiro, I. A. M., Milstien, J. B. & Clements, C. J. *Issues Relating to the Use of BCG in Immunisation Programmes.* (WHO, 1999).
6. Medical Research Council. Treatment of pulmonary tuberculosis with para-aminosalicylic acid and streptomycin: a preliminary report. *BMJ* **2**, 1521 (1949).
7. Crofton, J. Chemotherapy of pulmonary tuberculosis. *BMJ* **1**, 1610–1664 (1959).
8. Fox, W., Ellard, G. A. & Mitchison, D. A. Studies on the treatment of tubeculosis undertaken by the British Medical Research Council Tuberculosis Units, 1946–1986, with relevant consequent publications. *Int. J. Tuberc. Lung Dis.* **10**, S231–S279 (1999).
9. World Health Organization. *Official Records of the World Health Organization, No 6.* (WHO, 1947).
10. Raviglione, M. D. & Pio, A. Evolution of WHO policies for tuberculosis control, 1948–2001. *Lancet* **359**, 775–780 (2002).
11. Styblo, K. Recent advances in epidemiological research in tuberculosis. *Adv. Tuberc.Res.* **20**, 1–63 (1980).
12. Styblo, K. & Meijer, J. Impact of vaccination programmes in children and young adults on the tuberculosis problem. *Tubercle* **57**, 17–43 (1976).
13. Mahler, H. The tuberculosis programme in the developing countries. *Bull. Int. Union Tuberc.* **37**, 77–82 (1966).
14. Banerji, D. Tuberculosis: a problem of social planning in developing countries. *Med. Care* **3**, 151–161 (1965).
15. WHO Expert Committee on Tuberculosis. *Eighth Report. World Health Organization Technical Report Series No. 290.* (WHO, 1964).
16. Berman, P. A. Health Sector Reform. Making health development sustainable. *Health Policy* **32**, 13–29 (1995).
17. Miller, B. Health sector reform: scourge or salvation for TB control in developing countries? *Int. J. Tuberc. Lung Dis.* **4**, 593–594 (2000).
18. Murray, C. J. L., Styblo, K. & Rouillon, A. Tuberculosis in developing countries: burden, intervention and cost. *Bull. Int. Union Tuberc. Lung Dis.* **65**, 6–24 (1990).
19. Narain, J. P., Raviglione, M. C. & Kochi, A. HIV-associated tuberculosis in developing countries: epidemiology and strategies for prevention. *Tubercle Lung Dis.* **73**, 311–321 (1992).
20. Raviglione, M. C., Snider, D. E. Jr & Kochi, A. Global epidemiology of tuberculosis. Morbidity and mortality of a worldwide epidemic. *JAMA* **273**, 220–226 (1995).
21. Bloom, B. & Murray, C. J. L. Tuberculosis: commentary on a re-emergent killer. *Science* **257**, 1055–1064 (1992).
22. Enarson, D. A. Principles of IUATLD collaborative tuberculosis progammes. *Bull. Int. Union Tuberc. Lung Dis.* **66**, 195–200 (1991).
23. Kochi, A. The global tuberculosis situation and the new control strategy of the World Health Organization. *Tubercle* **72**, 1–6 (1991).
24. World Health Organization. *Forty-fourth World Health Assembly: Resolutions and Decisions. Resolution WHA 44.8. WHA44/1991/REC/1.* (WHO, 1991).
25. World Health Organisation. *Framework for Effective Tuberculosis Control. WHO Tuberculosis Programme.* (WHO, 1994).
26. Fox, W. The problem of self-administration of drugs, with particular reference to pulmonary tuberculosis. *Tubercle* **39**, 269–274 (1958).
27. Tuberculosis Chemotherapy Center, Madras. *A concurrent comparison of home and sanatorium treatment of pulmonary tuberculosis in South India. Bull. World Health Organ.* **21**, 51–144 (1959).
28. Iseman, M. D., Cohn, D. L. & Sbarbaro, J. A. Directly oberved therapy: we can't afford not to do it. *N. Engl. J. Med.* **328**, 576–578 (1993).
29. Raviglione, M. C., Dye, C., Schmidt, S. & Kochi. A. Assessment of worldwide tuberculosis control. *Lancet* **350**, 624–629 (1997).
30. World Health Organisation. *Global Tuberculosis Control. WHO Report 2001, Document WHO/CDS/TB/2001.287.* (WHO, 2001).
31. China Tuberculosis Control Collaboration. The effect of tuberculosis control in China. *Lancet* **364**, 417–422 (2004).
32. Netto, E. M., Dye, C. & Raviglione, M.C. Progress in global tuberculosis control 1995–1996, with emphasis on 22 high-incidence countries. *Int. J. Tuberc. Lung Dis.* **3**, 310–320 (1999).
33. Suarez, P. G. *et al*. The dynamics of tuberculosis in response to 10 years of intensive control effort in Peru. *J. Infect. Dis.* **184**, 473–478 (2001).
34. World Health Organization. *WHO Report 2007: Global Tuberculosis Control (Surveillance, Planning, Financing).* (WHO, 2008).

35. Dye, C., Watt, C. J. & Bleed, D. Low access to a highly effective therapy: a challenge for international tuberculosis control. *Bull. World Health Organ.* **80**, 437–444 (2002).
36. Zwarenstein, M., Schoeman, J. H., Vundule, C., Lombard, C. J. & Tatley, M. Randomised controlled trial of self-supervised and directly observed treatment of tuberculosis. *Lancet* **352**, 1340–1343 (1998).
37. De Cock, K. M. & Chaisson, R. E. Will DOTS do it? A reappraisal of tuberculosis control in countries with high rates of HIV infection. *Int. J. Tuberc. Lung Dis.* **3**, 457–465 (1999).
38. Volminck, J., Matchaba, P. & Garner, P. Directly observed therapy and treatment adherence. *Lancet* **355**, 1345–1350 (2000).
39. Walley, J. D., Khan, A. N., Newell, J. N. & Khan, M. H. Effectiveness of the direct observation component of DOTS for tuberculosis: a randomised controlled trial in Pakistan. *Lancet* **357**, 664–669 (2001).
40. Khan, M. A., Walley, J. D., Witter, S. N., Imran, A. & Safdar, N. Costs and cost-effectiveness of different DOT strategies for the treatment of tuberculosis in Pakistan. Directly observed treatment. *Health Policy Plan* **17**, 178–186 (2002).
41. Lienhardt, C. & Ogden, J. A. Tuberculosis control in resource-poor countries: have we reached the limits of the universal paradigm? *Trop. Med. Int. Hlth* **9**, 833– 841 (2004).
42. Pitchenik, A. E. & Fischl, M. A. Disseminated tuberculosis and the acquired immunodeficiency syndrome. *Ann. Intern. Med.* **98**, 112 (1983).
43. Mann, J. *et al.* Association between HTLV-III LAV infection and tuberculosis in Zaire. *JAMA* **256**, 346 (1986).
44. De Cock, K. M., Coulibaly, S. I. M. & Lucas, S. B. Tuberculosis and HIV infection in sub-Saharan Africa. *JAMA* **268**, 1581–1587 (1992).
45. Getahun, H., Gunneberg, C., Granich, R. & Nunn, P. HIV infection-associated tuberculosis: the epidemiology and the response. *Clin. Infect. Dis.* **50**, S201–S207 (2010).
46. Harries, A. *et al.* Tuberculosis 3. *Lancet* **375**, 1906– 1919 (2010).
47. Godfrey-Faussett, P. *et al.* How human immunodeficiency virus voluntary testing can contribute to tuberculosis control. *Bull. World Health Organ.* **80**, 939–945 (2002).
48. World Health Organization. *Report of a 'Lesson Learnt' Workshop on the Six ProTEST Pilot Projects in Malawi, South Africa and Zambia.* (WHO, 2004).
49. Getahun, H., Scano, F. & Nunn, P. in *Tuberculosis, a Comprehensive Clinical Reference*. (eds Schaaf, H. S. & Zumla, A.) (Saunders Elsevier, 2009).
50. World Health Organization. *Interim Policy on Collaborative TB/HIV Activities*. (WHO, 2004).
51. Iseman, M. D. & Madsen, L. A. TB isolates resistant to the two principal drugs, isoniazid and rifampicin, or to those and additional drugs are referred to as multidrug-resistant strains. *Clin. Chest Med.* **10**, 341 (1989).
52. Centers for Disease Control. Nosocomial transmission of multidrug-resistant tuberculosis among HIV-infected persons— Florida and New York, 1988–1991. *JAMA* **266**, 1483–1485 (1991).
53. Edlin, B. R. *et al.* An outbreak of multidrug-resistant tuberculosis among hospitalized patients with the acquired immunodeficiency syndrome. *N. Engl. J. Med.* **326**, 1514–1521 (1992).
54. Frieden, T. *et al.* The emergence of drug-resistant tuberculosis in New York City. *N. Engl. J. Med.* **328**, 521–526 (1993).
55. Pablos-Mendez, A. *et al.* Global surveillance for antituberculosis-drug resistance, 1994–1997. *N. Eng. J. Med.* **338**, 1641–1649 (1998).
56. Cohn, D., Bustreo, F. & Raviglione, M. Drug-resistant tuberculosis: review of the worldwide situation and the WHO/IUATLD global surveillance project. *Clin. Inf. Dis.* **24**, S121–S130 (1997).
57. World Health Organization. *Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of Multidrug-Resistant Tuberculosis (MDR-TB)* (WHO, 2001).
58. Gupta, R. *et al.* Responding to market failure in tuberculosis control. *Science* **293**, 1049–1051 (2001).
59. Gupta, R. *et al.* Increasing transparency in partnerships for health-introducing the Green Light Committee. *Trop. Med. Intern. Health* **7**, 970–976 (2002).
60. World Health Organization. *Global Tuberculosis Programme. Report of the Ad Hoc Committee on the Tuberculosis Epidemic. London, March 17–19, 1998.* (WHO, 1998).
61. Kumaresan, J., Heitkamp, P., Smith, I & Billo, N. Global Partnership to Stop TB: A model of an effective public health partnership. *Int. J. Tuberc. Lung Dis.* **8**, 120–129 (2004).
62. Kumaresan, J., Smith, I., Arnold, V. & Evans, P. The global TB drug facility. Innovative global procurement. *Int. J. Tuberc. Lung Dis.* **8**, 130–138 (2004).
63. World Health Organization. *Stop TB Initiative. Amsterdam. Declaration to Stop TB: a Call for Accelerated Action against Tuberculosis.* (WHO, 2000).
64. World Health Organization. *Fifty-third World Health Assembly. Resolutions and Decisions. Resolution WHA 53.1. WHA53/2000/REC/.* (WHO, 2000).
65. World Health Organization. *The Global Plan to Stop Tuberculosis – Stop TB Partnership. WHO/CDS/STB/2001.16.* (WHO, 2001).
66. Stop TB Partnership and WHO. *Global Plan to Stop TB 2006–2015. Actions for Life—Towards a World Free of Tuberculosis. WHO/HTM/STB/2006.35.* (WHO, 2006).
67. Brugha, R. & Walt, G. A global health fund: a leap of faith? *BMJ* **323**, 152–154 (2001).
68. Brugha, R. *et al.* The Global Fund: managing great expectations. *Lancet* **364**, 95–100 (2004).
69. Uplekar, M., Weil, D., Raviglione, M. C. in *Reichman and Hershfield's Tuberculosis: A Comprehensive, International Approach* (Informa Healthcare, 2006)
70. Dye, C. *et al.* Evolution of tuberculosis control and prospects for reducing tuberculosis incidence, prevalence, and deaths globally. *JAMA* **293**, 2767– 2775 (2005).
71. World Health Organization. *Macroeconomics and Health: Investing in Health for Economic Development. Report of the Commission on Macroeconomics and Health.* (WHO, 2001).
72. World Health Organization. *Report on the Meeting of the Second Ad-Hoc Committee on the TB Epidemic—Recommendations to Stop TB partners—Montreux, Switzerland, Sept. 2003. WHO/CDS/STB/2004.28.* (WHO, 2004).
73. World Health Organization. *Fifty-eighth World Health Assembly. WHA58/2005/REC/1.* (WHO, 2005).
74. World Health Organization. *Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. WHO/HTM/TB/2006.361.* (WHO, 2006).
75. World Health Organization. *Community Contribution to TB care: Practice and Policy. WHO/CDS/TB/2002.318.* (WHO, 2002).
76. Achmat, Z. Science and social justice: the lessons of HIV/AIDS activism in the struggle to eradicate tuberculosis. *Int. J. Tuberc. Lung Dis.* **10**, 1312–1317 (2006).
77. Harrington M. From HIV to tuberculosis and back again: a tale of activism in 2 pandemics. *Clin. Infect. Dis.* **50**, S260–S266 (2010).
78. Lönnroth, K. *et al.* Public-private mix for implementation: what makes it work? *Bull. World Health Organ.* **82**, 580–586 (2004).
79. Hopewell, P. C., Pai, M., Maher, D., Uplekar, M. & Raviglione, M. C. International standards for tuberculosis care. *Lancet Infect. Dis.* **6**, 710–725 (2006).
80. World Health Organization. *Practical Approach to Lung Health (PAL). A Primary Health Care Strategy for the Integrated Management of Respiratory Conditions in People Five Years of Age or Over. WHO/HTM/TB/2005.351.* (WHO, 2005).
81. [No authors listed]. Tackling poverty in tuberculosis control. *Lancet* **366**, 5 (2005).
82. Raviglione, M. C. & Uplekar, M. WHO's new stop TB strategy. *Lancet* **367**, 952–955 (2006).
83. Lienhardt, C., Vernon, A. & Raviglione, M. C. New drugs and new regimens for the treatment of tuberculosis: review of the drug development pipeline and implications for national programmes. *Curr. Opin. Pulm. Med.* **16**, 186–193 (2010).
84. Ma, Z. *et al.* Global tuberculosis drug development pipeline: the need and the reality. *Lancet* **375**, 2100– 2109 (2010).
85. Boehme, C. C. *et al.* Rapid molecular detection of tuberculosis and rifampicin resistance. *N. Engl. J. Med.* **363**, 1005–1015 (2010).
86. Wallis, R. S. *et al.* Biomarkers and diagnostics for tuberculosis: progress, needs, and translation into practice. *Lancet* **375**, 1920–1937 (2010).
87. Kaufmann, S. H. E., Hussey, G. & Lambert, P.-H. New vaccines for tuberculosis. *Lancet* **375**, 2110–2119 (2010).
88. Stop TB Partnership and WHO. *Global Plan to Stop TB, 2011-2015: Transforming the Fight Towards Elimination of Tuberculosis.* (WHO, 2010).
89. Treatment Action Group. *2011 Report on Tuberculosis Research Funding Trends, 2005–2010.* (Treatment Action Group, 2012).
90. Glaziou, P. *et al.* Lives saved by tuberculosis control and prospects for achieving the 2015 global target for reducing tuberculosis mortality. *Bull. World Health Organ.* **89**, 573–582 (2011).
91. World Health Organization. *Global tuberculosis control: WHO Report 2011.* (WHO, 2011).
92. Lönnroth, K. *et al.* Tuberculosis control and elimination 2010-50: cure, care, and social development. *Lancet* **375**, 1814–1829 (2010).
93. Atun, R., Weil, D. E., Eang, M. T. & Mwakyusa, D. Health-system strengthening and tuberculosis control. *Lancet* **375**, 2169–2178 (2010).
94. Lienhardt, C., Espinal, M., Maher, D., Pai, M. & Raviglione, M. What research is needed to stop TB? Introducing the TB Research Movement. *PLoS Med.* **8**, e1001135 (2011).
95. Abu-Raddad, L. J. *et al.* Epidemiological benefits of more effective tuberculosis vaccines, drugs and diagnostics. *Proc. Natl Acad. Sci. USA* **106**, 13980– 13985 (2009).
96. Stop TB Partnership and WHO. *The International Roadmap for Tuberculosis Research - Towards a World Free of TB.* (WHO, 2011).
97. Lienhardt, C. Why is research critical to stop tuberculosis? *PLoS Med. community blog* [online], http://blogs.plos.org/speakingofmedicine/2012/01/26/why-is-research-critical-to-stop-tuberculosis (2012).
98. Lin, H., Ezzati, M. & Murray, M. Tobacco smoke, indoor air pollution and tuberculosis: a systematic review and meta-analysis. *PLoS Med.* **4**, e142 (2007).
99. Jeon, C. Y. & Murray, M. B. Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS Med.* **5**, e152 (2008).
100. Lönnroth, K., Williams, B. G., Stadlin, S., Jaramillo, E. & Dye, C. Alcohol use as a risk factor for tuberculosis—a systematic review. *BMC Public Health* **8**, 289 (2008).
101. Lönnroth, K., Jaramillo, E., Williams, B. G., Dye, C. & Raviglione, M. Drivers of tuberculosis epidemics: the role of risk factors and social determinants. *Soc. Sci. Med.* **68**, 2240–2246 (2009).
102. Getahun, H. & Raviglione, M. Transforming the global tuberculosis response through effective engagement of civil society organizations: the role of the World Health Organization. *Bull. World Health Organ.* **89**, 616–618 (2011).



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