Tuberculosis 1

Tuberculosis control and elimination 2010–50: cure, care, and social development

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This is the first in a Series of eight papers about tuberculosis

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Rapid expansion of the standardised approach to tuberculosis diagnosis and treatment that is recommended by WHO allowed more than 36 million people to be cured between 1995 and 2008, averting up to 6 million deaths. Yet tuberculosis remains a severe global public health threat. There are more than 9 million new cases every year worldwide, and the incidence rate is falling at less than 1% per year. Although the overall target related to the Millennium Development Goals of halting and beginning to reverse the epidemic might have already been reached in 2004, the more important long-term elimination target set for 2050 will not be met with present strategies and instruments. Several key challenges persist. Many vulnerable people do not have access to affordable services of sufficient quality. Technologies for diagnosis, treatment, and prevention are old and inadequate. Multidrug-resistant tuberculosis is a serious threat in many settings. HIV/AIDS continues to fuel the tuberculosis epidemic, especially in Africa. Furthermore, other risk factors and underlying social determinants help to maintain tuberculosis in the community. Acceleration of the decline towards elimination of this disease will need invigorated actions in four broad areas: continued scale-up of early diagnosis and proper treatment for all forms of tuberculosis in line with the Stop TB Strategy; development and enforcement of bold health-system policies; establishment of links with the broader development agenda; and promotion and intensification of research towards innovations.

Introduction

Global control of tuberculosis is far from complete. There were 9·4 million estimated new cases of tuberculosis in 2008;[1,2] multidrug-resistant (MDR) tuberculosis remains a severe threat;[3,4] and HIV continues to fuel the epidemic, especially in Africa.[1,5] With 1·8 million estimated deaths every year, tuberculosis still takes a huge toll, especially for the poorest people. It is a leading cause of death in people in the most economically productive age-groups.[6] People who are cured from this disease can be left with lifetime sequelae that substantially reduce their quality of life.[7] The direct and indirect costs of tuberculosis, and the social consequences, are often catastrophic for the individual patient, the family, and the wider community.[8]

Fortunately, available drug regimens can cure most patients,[1] and tuberculosis treatment is among the most cost-effective health interventions.[9] If applied early in the disease course it can effectively cut transmission and prevent the disease from spreading. It can also yield economic benefits that are ten times the cost of the investment.[10] Therefore, concerted action to ensure universal access to high-quality tuberculosis diagnosis and treatment is being pursued by almost all countries, in line with WHO's Stop TB Strategy (panel 1)[11] and the Stop TB Partnership's Global Plan to Stop TB.[12,13] The medium-term target of these actions, set for 2015 in the

Key messages

- Rapid expansion of a standardised approach to tuberculosis diagnosis and treatment cured more than 36 million people between 1995 and 2008, averting up to 6 million deaths. However, tuberculosis remains a huge global public health concern, with more than 9 million new cases occurring every year.
- The Millennium Development Goal target to halt and begin to reverse tuberculosis incidence by 2015 is estimated to have been reached in 2004 globally. However, the decline is less than 1% per year.
- With present efforts, the targets to halve prevalence and death rates by 2015, compared with 1990 rates, will probably be met in most regions, but might not be met worldwide.
- The long-term elimination target, to reduce incidence to less than one case per million by 2050, will not be reached with existing technologies and approaches.
- Intensified case detection approaches are needed, linked to general health-system strengthening, ensuring universal access to high-quality early diagnosis, treatment, and care for all forms of this disease, including people infected with HIV and those affected by multidrug-resistant tuberculosis.
- Emphasis should be put on preventions, including preventive therapy, development of better vaccines, and actions to address direct tuberculosis risk factors (eg, HIV, undernutrition, diabetes, smoking, and drug and alcohol misuse), and underlying social determinants (eg, poverty, and poor living and working conditions).
- Acceleration of the present decline towards tuberculosis elimination will need invigorated actions in four broad areas: continued scale-up of early diagnosis and proper treatment in line with the Stop TB Strategy; development and enforcement of bold health-system policies; establishment of links with the broader development agenda; and promotion and intensification of research.

Search strategy and selection criteria

We searched PubMed, the Cochrane library, and the email send-list TB-Related News and Journal Items Weekly Update (prepared by the Centers for Disease Control and Prevention, Atlanta, GA, USA). No predefined inclusion or exclusion criteria were used. We purposively selected the publications that were judged most relevant for the review, with a preference for high-quality systematic reviews. We favoured publications in the past 5 years, but did not exclude highly regarded older publications.

context of the Millennium Development Goals (MDGs), is to halt and to begin to reverse incidence of this disease. Additional 2015 targets set by the Stop TB Partnership are to halve tuberculosis prevalence and death rates compared with 1990. A more long-term goal is to eliminate the disease as a public health concern by reducing incidence to less than one case per 1 million of the population by 2050.[14]

In the first paper in the Series, we assess progress towards reaching these targets, with particular focus on the 22 countries with a high burden of tuberculosis that together have more than 80% of the world's cases. We then scrutinise the present model for global tuberculosis control, and review the main challenges related to weak health systems, inadequate medical technologies, MDR tuberculosis, the HIV epidemic, other tuberculosis risk factors, and social determinants. Finally, we identify additional entry points for interventions and describe a way forward towards more effective tuberculosis control.

Methods

This paper draws on three categories of data: a review of published work; routine data submitted to WHO from member states; and epidemiological estimates produced by WHO based on data from routine surveillance, surveys, and systematic literature reviews. Methods used by WHO to estimate prevalence, rates of death, and incidence, and related data limitations, are described in detail elsewhere.[1,2]

Tuberculosis programme implementation and surveillance data for 2008 were submitted to WHO by member states in 2009. Of 204 countries and territories from which data were requested, 198 responded, representing more than 99% of the world's total population. In most countries, the reported data were obtained from a standardised recording and reporting system.[15] To supplement this information, we undertook a survey of present control policies and health systems, as reported by the managers of the national tuberculosis programmes (NTPs) in the 22 high-burden countries. Table 1 and table 2 summarise key indicators of data sources for burden estimates, progress towards targets, NTP performance, and health-system context for the 22 countries with high tuberculosis burden.

The country data presented in this paper largely rely on self-reported programme implementation and surveillance data. Doubts have been raised about the reliability of such data, which could be affected by political pressure and conflicts of interest.[17] WHO has put in place a transparent process of data validation, which includes close scrutiny of data at various levels by national and international surveillance experts before submission, and frequent external NTP reviews and data validation missions. The methods used to derive estimates for every country are available to the public.[1,2,18]

Nevertheless, the availability and quality of the required surveillance data are often unsatisfactory because of general health information deficiencies,[19] and trends might therefore be difficult to interpret.[17,18,20] Although in most countries tuberculosis is a notifiable disease by law, including in 15 of the 22 high-burden countries (table 2), the compliance with such laws varies greatly. Cases diagnosed outside NTPs—eg, in the private sector—are not systematically notified.[21] Cause-of-death registration is often non-existent or incomplete, and has been used as a means to improve estimates of tuberculosis burden for only four of the high-burden countries (table 1). The indirect method to estimate incidence, through an assumed fixed relation between the annual risk of tuberculosis infection and the incidence of new sputum-smear-positive disease, is too uncertain and no longer recommended.[22] At the same time, only few population-based epidemiological studies, such as surveys to establish the prevalence of disease, have been undertaken. Between 1990 and mid-2009, only six of the 22 high-burden countries had completed national surveys, and only two had done repeated surveys to assess trends (table 1). Finally, although a unique global initiative for drug-resistance surveillance has been in place since 1994, several countries still have insufficient information about drug resistance. 12 of the 22 countries had national data for drug-resistance surveillance by 2009. Another six had subnational information (table 1).

Substantial uncertainties thus surround estimates of tuberculosis incidence, prevalence, and mortality. Additionally, one of the traditional NTP performance indicators, the case detection rate, is difficult to estimate because of limitations with accuracy of both the numerator (number of new cases of smear-positive tuberculosis notified in the country in a year) and the denominator (estimated national incidence of new smear-positive tuberculosis).[23] The other traditional NTP performance indicator, the treatment success rate in new sputum-smear-positive cases treated in NTPs, can be correctly assessed through cohort analysis on the basis of standardised treatment registers. However, such data are not routinely analysed for sputum-smear-negative cases or for the large proportion of patients who are treated outside NTPs—eg, in the private sector.[21]

Ultimately, comprehensive and reliable vital registration and notification systems are needed to generate valid estimates.[24] Although most countries are far from such a situation,[25] much work is being done to improve estimates, including prevalence surveys and validation mechanisms for notification systems.[1]

Scale-up of diagnosis and treatment

Treatment and case detection rates

In 2008, 180 countries (91% of total countries reporting) and all 22 high-burden countries reported that they were implementing at least the essential directly observed therapy, short course (DOTS) component of the Stop TB Strategy (panel 1) through NTP or equivalent structures. In all high-burden countries apart from one (Brazil),

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Panel 1: The Stop TB Strategy

The Stop TB Strategy

Vision

A tuberculosis-free world

Goal

To substantially reduce the global burden of tuberculosis by 2015 in line with the MDGs and the Stop TB Partnership targets

Objective

- Achieve universal access to quality diagnosis and patient-centred treatment
- Reduce the human and socioeconomic burden associated with tuberculosis
- Protect vulnerable populations from tuberculosis, tuberculosis and HIV, and drug-resistant tuberculosis
- Support development of new methods and enable their timely and effective use
- Protect and promote human rights in tuberculosis prevention, care, and control

Targets

- MDG 6, target 8: halt and begin to reverse the incidence of tuberculosis by 2015
- Targets linked to the MDGs and endorsed by Stop TB Partnership:
  - 2015: reduce prevalence of and deaths due to tuberculosis by 50% relative to 1990
  - 2050: eliminate tuberculosis as a public health problem (less than one case per million population)

Components of the strategy and implementation approaches

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 standardised treatment with supervision, and patient support
- Ensure effective drug supply and management
- Monitor and assess performance and effect

Address tuberculosis/HIV, MDR tuberculosis, and the needs of poor and vulnerable populations

- Scale up collaborative tuberculosis/HIV activities
- Scale up prevention and management of MDR tuberculosis
- Address the needs of tuberculosis contacts and of poor and vulnerable populations

Contribute to health-system strengthening 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 the practical approach to lung health
- Adapt successful approaches from other areas and sectors, and foster action on the social determinants of health

Engage all care providers

- Involve all public, voluntary, corporate, and private providers through public-private mix approaches
- Promote use of the international standards for tuberculosis care

Empower people with tuberculosis and communities through partnership

- Pursue advocacy, communication, and social mobilisation
- Foster community participation in tuberculosis care, prevention, and health promotion
- Promote use of the Patients' Charter for Tuberculosis Care

Enable and promote research

- Undertake programme-based operational research
- Advocate for and participate in research to develop new diagnostics, drugs, and vaccines

MDG=Millennium Development Goal. DOTS=directly observed therapy, short course. MDR=multidrug resistant.

more than 90% of the population lived in areas in which DOTS was the official strategy (table 1).

The target of a treatment success rate of at least 85% for new smear-positive cases treated in NTPs was reached globally for the first time in the 2007 cohort.[2] However, there were large variations across regions and countries. The WHO eastern Mediterranean region (88%), the southeast Asian region (88%), and the western Pacific region (92%) surpassed the target. The region of the Americas was close at 82%. The African region (79%) and the European region (67%) both reported high death and default rates, whereas the treatment failure rate was also high in the European region.[2] Nine of the 22 high-burden countries did not reach the treatment success target in 2007 (table 1). High prevalence of HIV and MDR tuberculosis constitute specific challenges impeding high success rates in Africa and Europe, respectively. Health-system weaknesses, poor health-care access, and several patient-related factors, including financial barriers, create challenges for treatment adherence in many countries.[1,26]

The global case detection rate increased six-fold between 1995 and 2008. However, after a period of acceleration between 2001 and 2005, the rate stabilised around 60% between 2006 and 2008.[2] The target of 70%, which was originally set for 2000 and then postponed for 2005, has thus not yet been reached globally. Estimated case detection rates vary widely between countries and regions (figure 1). Only six of 22 high-burden countries had reached the 70% target for smear-positive tuberculosis in 2008 according to the best estimate (table 1).

The combination of increased case detection rates and improved rates of treatment success has resulted in more than 43 million patients having been treated under the DOTS and Stop TB Strategy principles worldwide, with 36 million patients cured between 1995 and 2008.[2] The case fatality rate halved from 8% to 4% in this time. Up to 6 million deaths are estimated to have been averted through scaling up DOTS, compared with a scenario in which the situation before 1995 would have continued.[2] Nevertheless, the scope is huge to further reduce burden, death, and transmission of tuberculosis, especially by closing the case detection gap of nearly 40% and reducing diagnostic delay. Globally, the margin of possible improvement is less for treatment success rates within NTPs, although efforts to reduce treatment interruption, treatment failure, and case fatality are crucial in many settings.

Programmatic management of MDR tuberculosis

Globally there were an estimated 440 000 new cases of MDR tuberculosis in 2008 (95% CI 390 000–510 000). However, in that year less than 30 000 cases (7% of the estimated global cases) were notified to WHO, and only around 6000 of them were treated in programmes approved by the Green Light Committee (a body that aims to increase access to high-quality, low-cost, second-

	Sources for TB burden estimates				Progress towards epidemiological targets*					Diagnosis and treatment within national TB programmes*							
	National prevalence survey since 1990 (year)	In-depth analysis of routine surveillance data in past 3 years	Analysis of vital registration data in past 3 years	Drug-resistance surveillance (most recent year)	Estimated incidence, all forms, per 100 000, 2008†	Yearly change in estimated incidence, all forms, 1990–2008 (%)‡	Estimated prevalence in 2008 *vs* 1990 (%)§	Estimated death rate in 2008 *vs* 1990 (%)¶	MDR-TB prevalence in new cases (year of DRS, %)	Pop living in districts with DOTS, 2007 (%)	Notified under NTP, of estimated new ss+ cases, 2008 (%)‖	Yearly change 1998–2008 in proportion notified in NTP, new ss+ (%)**	NTP treatment success rate, new ss+, 2007 cohort (%)††	Notified TB patients tested for HIV, 2008 (%)	HIV-positive notified TB cases receiving ART, 2008 (%)	MDR-TB cases notified/ estimated number, 2008 (%)	Treated under GLC/ estimated MDR-TB cases, 2008 (%)
Afghanistan	N	Y	N	N	190	0·0%	96%	100%	..	97%	61%	21%	87%	..	..	..	0·0%
Bangladesh	2008	Y	N	N	220	0·0%	75%	79%	..	100%	61%	13%	92%	..	..	..	1·1%
Brazil	N	Y	Y	1996	46	–3·3%	30%	47%	0·9%	75%	75%	3·1%	72%	49%	91%	25%	0·0%
Burma	N	Y	N	2007	400	0·0%	43%	57%	4·2%	95%	43%	21%	79%	3%	28%	5·4%	0·0%
Cambodia	2002	N	N	2001	490	–1·0%	48%	60%	0·0%	100%	56%	8·0%	94%	54%	22%	1·4%	1·9%
China	1990, 2000	Y	N	2007	97	–1·0%	34%	42%	5·7%	100%	72%	12%	87%	8%	20%	..	0·0%
DR Congo	N	Y	N	1999‡‡	380	4·7%	240%	240%	5·8%	100%	66%	5·4%	84%	19%	20%	2·3%	2·6%
Ethiopia	N	Y	N	2005	370	4·7%	960%	570%	1·6%	95%	32%	13%	91%	23%	44%	2·5%	0·0%
India	N	Y	N	2006‡‡	170	0·0%	54%	69%	2·8%	100%	70%	9·6%	87%	2%	..	0·3%	0·0%
Indonesia	2004	Y	N	2004‡‡	190	0·0%	46%	56%	2·0%	100%	80%	17%	85%	..	..	4·8%	0·0%
Kenya	N	Y	N	1995‡‡	330	6·0%	99%	270%	0·0%	100%	68%	5·6%	94%	83%	30%	3·1%	0·8%
Mozambique	N	Y	N	2006	420	4·7%	240%	440%	3·5%	100%	47%	5·9%	85%	81%	30%	5·1%	0·0%
Nigeria	N	Y	N	N	300	4·7%	190%	260%	..	91%	24%	20%	82%	62%	45%	0·21%	0·0%
Pakistan	N	Y	N	N	230	0·0%	47%	54%	..	99%	58%	22%	91%	3%	100%	0·26%	0·0%
Philippines	1997, 2007	N	Y	2004	280	–1·8%	55%	170%	4·0%	100%	67%	5·5%	89%	1%	..	7·2%	4·0%
Russia	N	Y	Y	2006‡‡	110	0·0%	30%	60%	13·0%	100%	73%	0·3%	58%	100%	23%	18%	4·0%
South Africa	N	Y	Y	2002	960	6·4%	200%	590%	1·8%	100%	68%	0·97%	83%	39%	25%	48%	0·0%
Thailand	N	Y	N	2006	140	0·0%	92%	100%	1·7%	100%	64%	16%	88%	96%	38%	12%	0·0%
Uganda	N	N	N	1997	310	3·6%	270%	200%	0·5%	100%	54%	5·0%	75%	63%	19%	3·6%	0·0%
Tanzania	N	Y	N	2007	190	–1·0%	41%	64%	1·1%	100%	70%	2·5%	92%	77%	30%	2%	0·0%
Vietnam	2007	Y	N	2006	200	–0·1%	73%	81%	2·7%	100%	62%	2·9%	74%	11%	32%	..	0·0%
Zimbabwe	N	Y	N	1995‡‡	760	4·7%	170%	230%	1·9%	100%	24%	6·0%	78%	9%	23%	..	0·0%

TB=tuberculosis. MDR-TB=multidrug-resistant tuberculosis. DRS=drug-resistant surveillance. Pop=population. DOTS=directly observed therapy, short course. NTP=national tuberculosis programme. ss+=sputum-smear positive. ART=antiretroviral treatment. GLC=Green Light Committee. N=no. Y=yes. DR=Democratic Republic. *Only best estimates are reported here. Ranges for several of these indicators are reported in WHO's Global Tuberculosis Control Report.[2] †Stop TB Partnership tuberculosis elimination target: to reduce incidence to less than 0·1 case per 100 000 population and per year by 2050. ‡Incidence is assumed to follow a linear trend on the log scale during 1990–2008. Millennium Development Goal (MDG) 6, target 8, is to have halted and begun to reverse the incidence of tuberculosis by 2015. §Expressed as the ratio of estimated prevalence in 2008 over 1990, as a percentage. MDG indicator 23a. The related Stop TB Partnership target is to halve prevalence in 2015 compared with 1990.[12] ¶Expressed as the ratio of estimated mortality (excluding HIV-positive individuals) in 2008 over 1990. MDG indicator 23b. The related Stop TB Partnership target is to halve death rate in 2015 compared with 1990.[12] ‖Also called the case detection rate. MDG indicator 24a. The related Stop TB Partnership target set for 2005 was 70%.[12] **The ratio of notified over estimated incident cases is assumed to follow a linear trend on the log scale during 1990–2008. ††MDG indicator 24b. The related Stop TB Partnership target set for 2005 was 85%.[12] ‡‡Subnational. §§Countries that together have 80% of the estimated global number of tuberculosis cases.

Table 1: **Epidemiological situation and tuberculosis programme implementation in 22 countries with high tuberculosis burden§§**

	Free TB diagnosis, 2009*	Sputum-smear microscopy availability ≥1 per 100 000 pop, 2008†	CDS test lab availability ≥1 per 5 million pop, 2008†	Free first-line drugs in NTP, 2009	Free second-line drugs in NTP, 2009	Stock-outs of first-line drugs peri-peral level, 2008	Paediatric formulation available, 2009	NTP expenditure per head, 2010 (US$)	Government health expenditure per head, 2006 (US$)‡	NTP expenditure of total government health expenditure, 2010 (%)	NTP funding gap (% of budget)	Private health expenditure of total health expenditure, 2006 (%)‡	Proportion of listed private providers engaged by NTP, 2008 (%)	TB drugs available in private pharmacies, 2009	TB drugs available without prescription, 2009	TB is a notifiable disease by law, 2009
Afghanistan	N	Y	N	Y	N	N	N	0·36	9	4·0%	3%	68%	1%	Y	Y	N
Bangladesh	N	N	N	Y	Y	N	N	0·10	4	2·5%	1%	68%	20%	Y	Y	Y
Brazil	Y	Y	N	Y	Y	N	Y	0·27	204	0·1%	24%	52%	NA§	N	N	Y
Burma	N	N	N	Y	Y	N	Y	0·08	1	8·1%	75%	87%	7%	Y	Y	Y
Cambodia	N	Y	N	Y	Y	N	Y	0·70	8	8·7%	36%	74%	23%	N	N	N
China	N¶	N	N	Y	Y	N	N	0·16	38	0·4%	13%	59%	NA§	Y	Y	Y
DR Congo	Y	Y	N	Y	Y	..	Y	0·23	2	11·7%	77%	81%	65%	N	N	Y
Ethiopia	N	Y	N	Y	..	N	N	0·19	4	4·6%	50%	41%	..	Y	N	N
India	Y	Y	N	Y	Y	N	Y	0·08	7	1·2%	17%	75%	17%‖	Y	Y	N
Indonesia	N	Y	N	Y	Y	N	Y	0·22	20	1·1%	31%	50%	2%	Y	Y	Y
Kenya	N	Y	N	Y	Y	N	Y	0·34	14	2·4%	61%	52%	..	Y	Y	Y
Mozambique	Y	Y	N	Y	Y	N	Y	0·67	11	6·1%	56%	29%	..	N	N	Y
Nigeria	N	N	N	Y	N	Y	Y	0·17	10	1·7%	59%	70%	..	Y	Y	N
Pakistan	Y	N	N	Y	N	N	Y	0·11	3	3·8%	69%	84%	6%	Y	Y	N
Philippines	N	Y	N	Y	Y	Y	Y	0·49	17	2·9%	0%	67%	13%	Y	Y	Y
Russia	Y	Y	Y	Y	Y	Y	Y	8·68	232	3·7%	2%	37%	NA§	Y	Y	Y
South Africa	Y	N	Y	Y	Y	N	Y	7·30	160	4·6%	0%	62%	20%	Y	N	Y
Thailand	Y	Y	Y	Y	Y	N	Y	0·72	73	1·0%	6%	36%	19%	Y	N	Y
Uganda	Y	Y	N	Y	N	N	N	0·25	6	4·2%	67%	75%	..	N	N	N
Tanzania	N	Y	N	Y	Y	N	Y	0·48	13	3·7%	32%	42%	8%**	N	N	Y
Vietnam	N	N	N	Y	Y	N	N	0·14	15	0·9%	0%	68%	30%	Y	Y	Y
Zimbabwe	N	N	N	Y	..	Y	Y	0·48	35	1·4%	35%	51%	..	N	N	Y

TB=tuberculosis. pop=population. CDS=culture and drug susceptibility. lab=laboratory. NTP=national tuberculosis programme. N=no. Y=yes. NA=not appliable. DR=Democratic Republic. *Smear, radiography, and culture free for all people suspected of tuberculosis, as needed. †Benchmark for population coverage of diagnostic facilities as defined in Global Plan to Stop TB, 2006–2015.[12] ‡Data from World Health Statistics, 2009.[35] §Not applicable. In these countries, private sector is small and/or not involved in tuberculosis diagnosis or treatment. ¶Diagnostic smear microscopy and radiography are free if suspects present to a tuberculosis dispensary, but not in general hospitals or tuberculosis hospitals. Free culture in a few selected sites only. ‖Refers to proportion of private doctors registered with the medical association. The proportion would be much lower if the denominator also included other types of private providers, but the number is unknown. **Refers to private hospitals only. ††Countries that together have 80% of the estimated global number of tuberculosis cases.

Table 2: **Health-systems context in 22 countries with high tuberculosis burden††**

line antituberculosis drugs for the treatment of MDR tuberculosis among providers who comply with WHO's guidelines).[1] 16 of the 22 high-burden countries had no cases of MDR tuberculosis treated in programmes approved by the Green Light Committee in 2007, whereas five did not report any notified MDR tuberculosis cases (table 1). Further scale-up of programmatic management of MDR tuberculosis is thus crucial, and is discussed by Gandhi and colleagues in this Series.[27]

Tuberculosis and HIV collaboration

In 2008, HIV status was known for 22% of all notified cases of tuberculosis globally. However, the worldwide total of about 357 000 HIV-positive patients with tuberculosis who were identified in 2008 represent only 25% of the estimated 1·4 million incident HIV-infected tuberculosis cases. About 254 000 of them received co-trimoxazole prophylaxis, and about 114 000 were enrolled on antiretroviral treatment (ART). This proportion represents only about a third of the targets for 2008 in the Global Plan to Stop TB, 2006–2015.[2,12] Screening for tuberculosis in HIV-positive individuals more than doubled from 0·6 million to 1·4 million people between 2007 and 2008, but still represents only 4% of the estimated 35 million people with HIV infection worldwide. Only about 50 000 of those screened negative for active tuberculosis were provided with isoniazid preventive therapy in 2008.[2] Thus, despite progress in the implementation of tuberculosis and HIV interventions, greatly increased collaboration between programmes and services is needed for these diseases, and is discussed by Harries and colleagues in this Series.[28]

Epidemiological effect

Estimated global tuberculosis prevalence and death have decreased during most of the past decade (figure 2). However, with the present rate of decline, the targets for prevalence and death rate set for 2015 might not be met globally, mainly because of the rapid increase in prevalence and death rate in Africa during the 1990s, which only recently reverted to a modest fall.[2]

The estimated number of incident cases in the world increased from 9·3 million to 9·4 million between 2007 and 2008, and the number of deaths associated with tuberculosis increased from 1·77 million to 1·82 million.[2] These increases are the net effect of a growing world population, offsetting modest reductions in global incidence and death rates per head. Global incidence was estimated at 139 cases (range 131–148) per 100 000 population in 2008, which had decreased from 143 cases (136–151) per 100 000 population in the apparent peak year of 2004 (figure 2). Incidence seems to be falling in all six WHO regions (figure 3) and in eight of nine epidemiological subregions (figure 4). If these trends are sustained, the world as a whole and most regions are on track to achieve the MDG target to begin to reverse the trend in incidence. Even if that is the case, the estimated global decline between 2004 and 2008 is very modest at –0·7% per year, and will need to be substantially accelerated to get even close to the elimination target that is set for 2050.

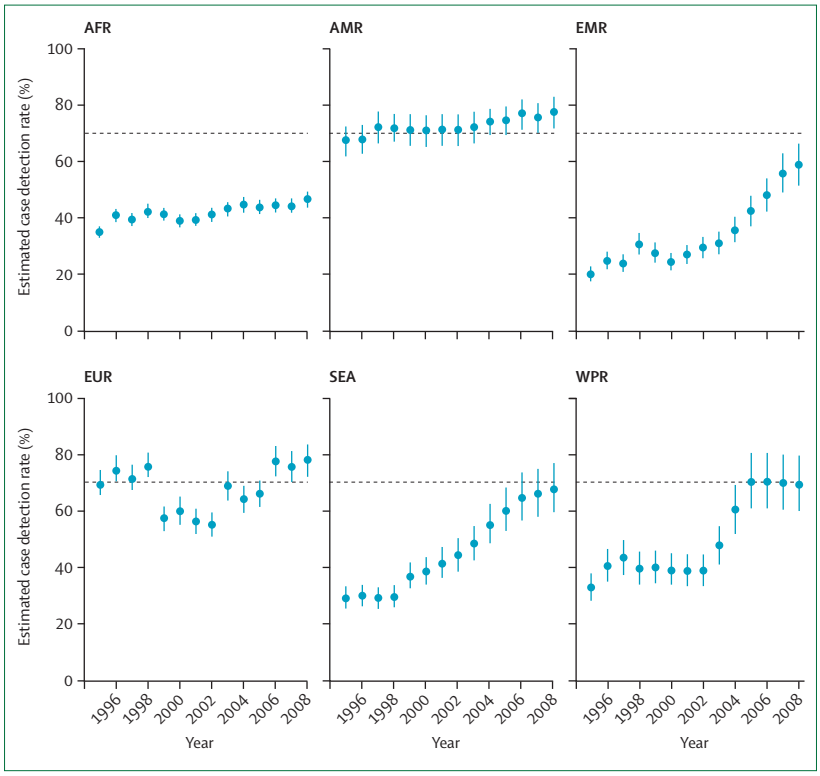

Figure 1: **Estimated case detection rate (new smear-positive tuberculosis), by WHO region, 1995–2008**
Vertical segments represent 95% CIs. The horizontal line shows the 70% target set for 2005. AFR=African region. AMR=American region. EMR=eastern Mediterranean region. EUR=European region. SEA=southeast Asian region. WPR=western Pacific region.

Estimated trends in incidence vary widely between regions (figures 3 and 4), and these trends are not clearly correlated with trends in NTP performance indicators. Eastern European and former Soviet Union countries had an increase in incidence in the 1990s (figure 4).[29] The recent stabilisation of this trend is associated with improved NTP performance, but other factors have contributed, such as general socioeconomic improvements.[30] The rapid increase and subsequent stabilisation and then decrease in incidence from 2004 in sub-Saharan African countries (figures 3 and 4) is strongly correlated with trends in HIV prevalence,[5,31] whereas NTP performance indicators have improved only marginally in these countries since 2003.[1,2]

The eastern Mediterranean, southeast Asian, and western Pacific WHO regions improved average NTP performance substantially between the end of the 1990s and 2008. Case detection rates increased (figure 1), and treatment success rates were greater than 80% in the past 10 years. Yet, comparing 1995–99 and 2006–08, the rates of decrease in incidence have remained stable at low levels in these regions (figure 4).[1] In the 22 high-burden

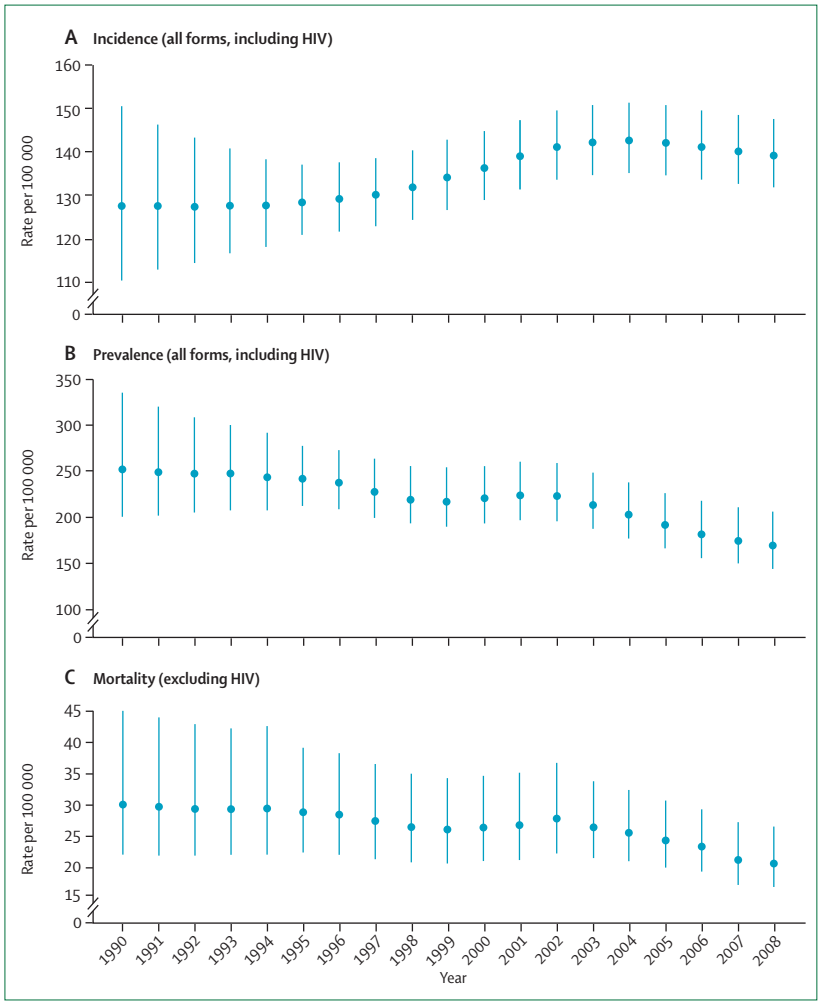

Figure 2: **Estimated global rates of tuberculosis incidence (A), prevalence (B), and mortality (C), 1990–2008**
Vertical segments represent 95% CIs.

countries, the estimated incidence decreased between 1990 and 2008 in only six countries, and only two had an average yearly decrease of more than 1%.

Two studies[32,33] suggest that changes in estimated national tuberculosis incidence are more strongly associated with changes in national socioeconomic indices and the general health status of the population than with NTP performance. Several examples of epidemiological effect associated with DOTS implementation exist, including in China,[34] Cuba,[35] parts of south India,[36] Peru,[37] Chile,[38] and Uruguay.[39] However, distinguishing the effects of DOTS from those of social and economic improvements has been difficult.[33,40] Other countries—including Vietnam,[41] Morocco,[42] Burma, some states in India, and Sri Lanka[43]—have not yet had the expected effect despite apparent long-term good programme performance. Many of the high-burden countries that achieved substantial improvements in programme performance over the past 10 years have recorded very modest decreases in estimated incidence (table 1).

Expansion of the control model

The apparent modest effect on tuberculosis incidence contrasts with mathematical modelling studies, suggesting that detecting at least 70% of the incident cases of highly infectious tuberculosis and curing at least 85% of them would lead to a 5–10% reduction per year in incidence, and that the rate of decline would be substantial also at lower case detection rates.[44–46] However, recent analyses suggest that reaching these targets leads to a rapid decline in incidence over a short period only.[47,48] For sustained rapid decline, both targets need to be exceeded, and combined with additional interventions.[40,47] In this section we discuss how the present tuberculosis control model could be further expanded to achieve the acceleration in tuberculosis incidence decline that is needed to approach the elimination target set for 2050.

Effective reduction of transmission

To cut transmission effectively, the duration of infectiousness has to be kept to a minimum through early diagnosis and treatment.[49–51] There are no targets for reduction of treatment delay, nor is delay routinely measured and reported.[1,50] However, much research has shown that long treatment delays are a common problem, which relate to insufficient knowledge about tuberculosis in the population, stigma, poor access to health care, missed diagnosis by health-care workers, and inadequate diagnostic instruments.[52] Addressing these factors is essential to ensure early diagnosis and cure.

Findings from three population-based tuberculosis prevalence surveys draw attention to additional challenges for early case detection. In these surveys, in which all participants were tested for tuberculosis irrespective of symptoms, 47%, 57%, and 61% of those with bacteriologically confirmed pulmonary tuberculosis did not report symptoms that corresponded to the commonly used criteria (such as cough for more than 3 weeks) for suspecting disease and prompting diagnostic investigation.[53–55] Most were not previously diagnosed, and thus constituted a large proportion of untreated patients with infectious tuberculosis who could be detected early only through more active screening approaches than by screening for chronic cough in people who actively seek health care.

Much attention has been given to smear-positive tuberculosis, because it is the most infectious form of this disease. However, the risk of transmission from sputum-smear-negative cases is not negligible,[56] and smear-negative tuberculosis could become smear-positive as the disease progresses. Early case detection of all types of tuberculosis might further reduce transmission.

The rate of transmission is also determined by the environment in which transmission takes place. Infection-control measures affect the risk of transmission in health-care facilities and congregate settings.[57] Poverty, urbanisation, crowded living conditions, increased population density, and migration constitute societal forces

that favour transmission, and changes in these factors can have a substantial effect on tuberculosis trends.[40,58,59]

Reduction in the risk of progression from infection to active disease

Preventive therapy with isoniazid is recommended by WHO for people with HIV who are at risk of tuberculosis, and for young children who have had contact with a person with infectious disease.[60] This intervention needs to be urgently scaled up.[1,28,60] Potentially, preventive therapy can be expanded to additional risk groups, but further research is needed to establish cost-effectiveness and feasibility, especially in low-income and middle-income countries.

Modelling studies suggest that interventions to stop progression from latent infection to active disease might be of particular importance for future tuberculosis control. If tuberculosis transmission can be effectively reduced, the number of tuberculosis cases arising from recent infections will be kept to a minimum, while an increasing proportion of incident cases will be generated from the huge number of people with latent tuberculosis infection.[47,61] The 2 billion individuals who are estimated to be already latently infected will continue to generate tuberculosis for decades, unless reactivation to active disease can be prevented. Therefore, even with the most optimistic scenario of a substantially reduced transmission through full scale-up of early diagnosis and treatment, the projected incidence in 2050 may still be 100 times higher than the elimination target.[47,62]

A crucial question for global tuberculosis control is therefore how immune competence can be improved within populations. One approach would be to develop improved medical technologies for prevention. For example, the combination of a new highly effective pre-exposure vaccine,[63] combined with a more effective preventive therapy,[64] would potentially have a dramatic effect on incidence.[47] A highly effective vaccine[63] after exposure would in principle have the same effect as would preventive treatment. Unfortunately, these methods are not yet available, and the funding for innovative research in this area is far behind what is needed.[65]

A second approach consists of preventive actions that are aimed at reducing the prevalence of factors that increase the risk of progression from infection to disease. HIV is the most potent risk factor within individuals,[66] with a relative risk of more than 20.[2] HIV is an important factor within populations in countries where HIV prevalence is moderate to high, such as those in sub-Saharan Africa. Less potent but more common risk factors might also have an important and underappreciated role.[62] Systematic reviews have shown that undernutrition,[67,68] smoking,[69,70] diabetes,[71–73] and alcohol misuse[74,75] are individual risk factors that can double or triple the risk of development of active tuberculosis (table 3). Indoor air pollution is a possible causal factor, but the evidence base is still incomplete.[70] Mathematical modelling studies have shown the potential importance of these factors; findings have suggested that a large part of the tuberculosis burden in India can be attributed to smoking (40%)[82] and diabetes (15%),[83] and that gradual reductions in the prevalence of smoking and exposure to indoor air pollution in China could reduce incidence by an additional 14–52% by 2033, which is in excess of the expected effect of sustained good NTP performance.[84]

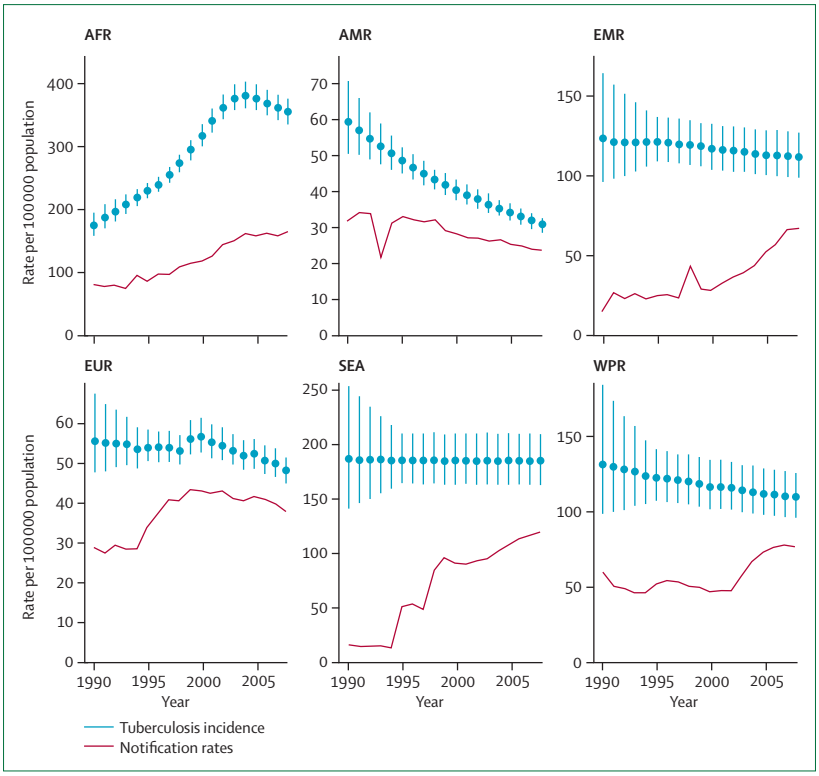

Figure 3: **Estimates of tuberculosis incidence (all forms) and notification rates, by WHO region, 1990–2008**
Vertical segments represent 95% CIs. Accidents in notification time series are generally the result of errors and inconsistencies in reporting from national tuberculosis programmes. AFR=African region. AMR=American region. EMR=eastern Mediterranean region. EUR=European region. SEA=southeast Asian region. WPR=western Pacific region.

A wide range of comparatively uncommon medical disorders (eg, silicosis, malignant diseases, and chronic systemic illnesses), and immunosuppressive treatments, are established risk factors for tuberculosis.[59,85] These risk factors have important implications for individuals, but are of less public health relevance. Furthermore, a set of common factors, such as chronic helminth infections, depression or mental illness, pregnancy and the post-partum period, and outdoor air pollution have been postulated as risk factors for tuberculosis, but very little research has been done to test these hypotheses.

Table 3 shows the estimated relative risk, prevalence, and corresponding population attributable fractions of selected risk factors for tuberculosis in high-burden countries. Table 3 includes only factors that are common, can be changed, have a strong or growing evidence base for a causal relation with tuberculosis, and for which there are quantitative data for the strength of the association. In

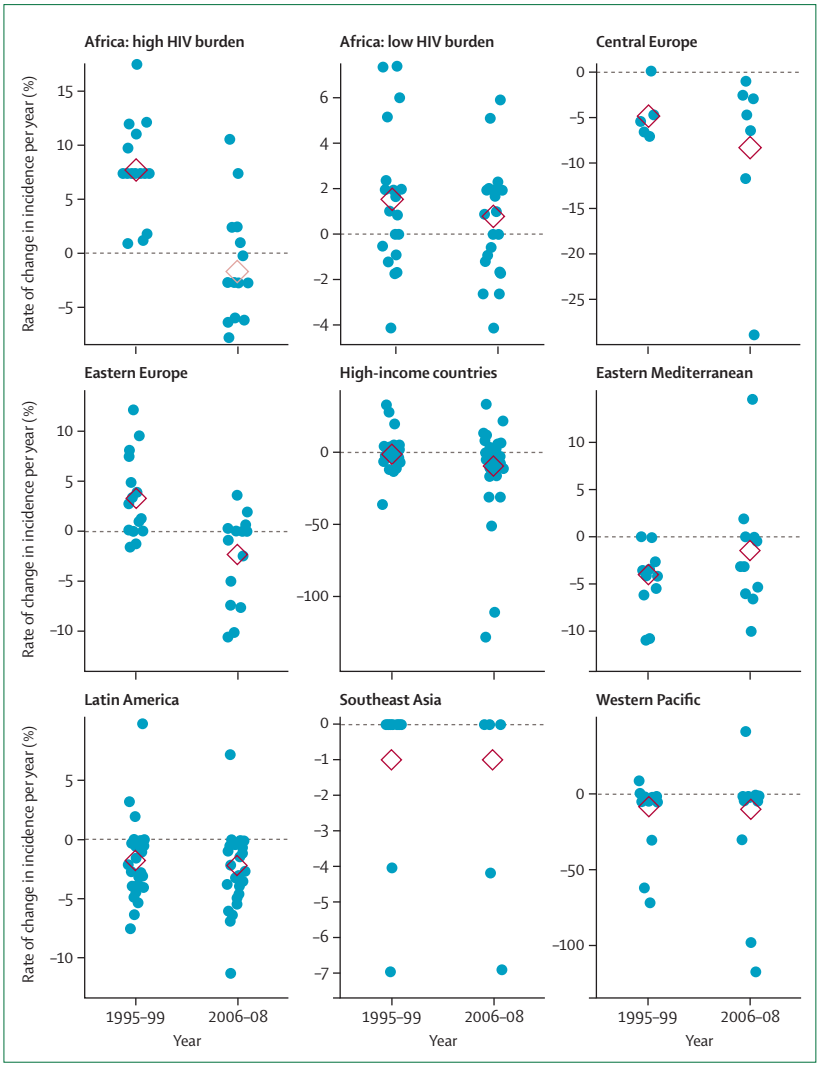

Figure 4: **Rates of change in estimated tuberculosis incidence during 1995–99 and 2006–08, in nine epidemiological subregions**
The open red diamonds denote group mean rates of change.

the high-burden countries, undernutrition and smoking seem to contribute the highest proportion of cases, but the variation in relative importance of different risk factors is large across countries. Indoor air pollution has a high population attributable fraction, but a causal relation is not yet proven. HIV, alcohol misuse, and diabetes are important factors, especially in adults. In most African high-burden countries, HIV is a leading attributable factor. Alcohol misuse and diabetes are predicted to increase in low-income and middle-income countries and might be crucial factors in coming decades.[73,86]

Genetic factors are also important determinants of host defence. Natural selection might be part of the explanation of a decrease in tuberculosis burden in industrialised countries.[87] Furthermore, some populations in present high-burden countries might have, on average, weaker host defences because of genetic predisposition, possibly linked to shorter history of exposure to *Mycobacterium tuberculosis*. Age and sex are strong determinants, with highest risks in elderly people, those who are very young, and in men older than 20 years.[59] Although not possible to change, increased understanding of genetic and age-related factors is important to develop case detection strategies, to interpret and predict future tuberculosis trends,[47,61] and to advance the basic knowledge of immunity against this disease that is needed for the development of improved vaccines and treatments.

The way forward: action on four fronts

Continued scale-up of early diagnosis and treatment in line with the Stop TB Strategy

Countries should aim to diagnose and treat successfully as close as possible to 100% of all estimated tuberculosis cases—ie, all forms of the disease and all age-groups. Most high-burden countries have far to go to close the case detection gap. In 2008, 39% of all estimated new cases and 97% of the estimated incident cases of MDR tuberculosis were not detected by NTPs,[2] and many were detected after long delays.[52]

Some of the missing cases are already being managed, but not notified. Many people with tuberculosis seek and receive care in the private sector and in public facilities that are not linked to NTPs.[21] These providers, who rarely follow the International Standards for Tuberculosis Care (ISTC)[88] or notify cases to health authorities, should be actively encouraged to collaborate with NTPs through public-private mix approaches.[89]

Others access health services, but are not diagnosed. The WHO recommendation to test all individuals with chronic cough (2–3 weeks) who seek health care[60] is not followed consistently throughout the health-care system.[26] Improvement of basic laboratory and radiography services is the first essential step.[60] Actively asking all patients about chronic cough, particularly those at increased risk for tuberculosis, can yield additional cases.[90,91] Furthermore, use of a duration of cough shorter than 3 weeks as a cutoff point for active tuberculosis investigations increases yield.[92] Cough screening can be strengthened through the practical approach to lung health, which promotes screening for tuberculosis in all patients with respiratory diseases.[93,94] Screening of all people with HIV for tuberculosis yields a substantial number of additional tuberculosis cases.[1] Active screening in health facilities of other high-risk groups—such as people affected by diabetes,[95] smoking-related diseases,[69] alcohol misuse,[75] and undernutrition[67]—could further increase the yield, but more research is needed to examine feasibility and cost-effectiveness.

To help with increased detection, the definition of smear-positive tuberculosis has been changed, such that one positive sputum smear of two is sufficient for the diagnosis of smear-positive tuberculosis.[96] The two smears can be done on the same day to simplify diagnosis for the patient and to reduce costs.[97] To simplify the

	HIV*			Undernutrition†		Diabetes‡			Alcohol misuse§			Smoking¶			Indoor air pollution‖	
	P >15 y (%)	PAF >15 y (%)	PAF total pop (%)	P total pop (%)	PAF total pop (%)	P >15 y (%)	PAF >15 y (%)	PAF total pop (%)	P >15 y (%)	PAF >15 y (%)	PAF total pop (%)	P >15 y (%)	PAF >15 y (%)	PAF total pop (%)	P total pop (%)	PAF total pop (%)
Afghanistan	0·1%	2·5%	1·5%	23·0%	33·6%	6·6%	12·2%	6·8%	0·1%	0·2%	0·1%	21·0%	17·4%	10·0%	95·0%	27·5%
Bangladesh	0·1%	2·5%	0·2%	27·0%	37·3%	3·5%	6·8%	4·6%	0·9%	1·7%	1·1%	26·0%	20·6%	14·5%	88·0%	26·0%
Brazil	0·6%	13·4%	8·9%	6·0%	11·7%	6·0%	11·2%	8·3%	11·1%	17·4%	13·2%	16·0%	13·8%	10·3%	12·0%	4·6%
Burma	0·7%	15·2%	11·2%	19·0%	29·5%	2·8%	5·6%	4·1%	1·2%	2·2%	1·6%	29·0%	22·5%	17·5%	95·0%	27·5%
Cambodia	0·8%	17·0%	11·8%	26·0%	36·4%	3·5%	6·8%	4·4%	4·1%	7·2%	4·7%	28·0%	21·9%	15·0%	95·0%	27·5%
China	0·1%	2·5%	1·3%	9·0%	16·5%	4·5%	8·6%	6·9%	8·3%	13·6%	11·1%	34·5%	25·7%	21·4%	80·0%	24·2%
DR Congo	1·4%	20·9%	12·3%	76·0%	62·6%	2·6%	5·2%	2·8%	5·3%	9·1%	5·1%	8·0%	7·4%	4·1%	95·0%	27·5%
Ethiopia	2·1%	29·2%	18·8%	46·0%	50·3%	2·0%	4·0%	2·3%	5·3%	9·1%	5·3%	5·0%	4·8%	2·7%	95·0%	27·5%
India	0·3%	7·2%	5·0%	21·0%	31·6%	7·1%	13·0%	9·1%	5·8%	9·9%	6·9%	19·0%	16·0%	11·3%	74·0%	22·8%
Indonesia	0·2%	4·9%	2·9%	17·0%	27·2%	4·6%	8·8%	6·5%	1·2%	2·2%	1·6%	34·0%	25·4%	19·7%	72·0%	22·4%
Kenya	8·6%	62·8%	47·7%	32·0%	41·3%	2·8%	5·6%	3·2%	5·3%	9·1%	5·4%	14·0%	12·3%	7·4%	81·0%	24·5%
Mozambique	12·5%	71·0%	57·9%	38·0%	45·5%	3·3%	6·5%	3·7%	5·3%	9·1%	5·3%	12·0%	10·7%	6·3%	80·0%	24·2%
Nigeria	3·9%	43·3%	25·6%	9·0%	16·5%	3·5%	6·8%	4·0%	26·1%	33·2%	21·7%	7·0%	6·5%	3·8%	67·0%	21·1%
Pakistan	0·1%	2·5%	1·5%	23·0%	33·6%	7·6%	13·8%	9·3%	0·1%	0·2%	0·2%	21·0%	17·4%	11·8%	72·0%	22·4%
Philippines	0·1%	2·5%	0·2%	16·0%	26·0%	6·7%	12·3%	8·3%	4·1%	7·2%	4·7%	33·0%	24·8%	17·4%	47·0%	15·8%
Russia	1·1%	17·7%	11·4%	3·0%	6·2%	9·0%	15·9%	13·8%	33·3%	38·8%	35·0%	49·0%	32·9%	29·4%	7·0%	2·7%
South Africa	18·1%	78·0%	69·7%	2·5%	5·2%	4·5%	8·6%	6·0%	15·2%	22·4%	16·4%	19·0%	16·0%	11·4%	18·0%	6·7%
Thailand	1·4%	21·5%	15·8%	17·0%	27·2%	7·7%	13·9%	11·3%	18·6%	26·1%	21·8%	23·0%	18·7%	15·4%	72·0%	22·4%
Uganda	5·4%	51·4%	37·4%	15·0%	24·8%	1·7%	3·4%	1·8%	5·3%	9·1%	4·9%	12·0%	10·7%	5·8%	95·0%	27·5%
Tanzania	6·2%	54·9%	40·4%	35·0%	43·5%	2·6%	5·2%	3·0%	5·3%	9·1%	5·3%	14·0%	12·3%	7·3%	95·0%	27·5%
Vietnam	0·5%	11·4%	7·9%	14·0%	23·5%	2·9%	5·7%	4·1%	4·1%	7·2%	5·2%	23·0%	18·7%	14·0%	70·0%	21·9%
Zimbabwe	15·3%	75·0%	65·6%	40·0%	46·8%	4·1%	7·9%	5·0%	5·3%	9·1%	5·8%	19·0%	16·0%	10·4%	73·0%	22·6%
Weighted average	0·8%	16·0%	11·0%	16·7%	26·9%	5·4%	10·2%	7·5%	8·1%	13·4%	9·8%	26·5%	20·9%	15·8%	71·2%	22·2%

Point estimate of relative risk was used. When prevalence was available only for adults, the prevalence in adults was adjusted for proportion of population younger than 15 years to estimate the total population PAF. PAF estimates presented here do not account for interaction between risk factors, nor for prevention of secondary cases. Uncertainty limits for PAF (not shown) are large, since they are determined by the confidence limits for the relative risk estimate, as well as the confidence limits for prevalence estimates. P=prevalence. y=years. PAF=population attributable fraction, which is equal to [prevalence×(relative risk–1)]/[prevalence×(relative risk–1)+1]. pop=population. DR=Democratic Republic. *HIV: relative risk=26·7, 95% CI 20–35. Point estimate is for low HIV prevalence settings (0·1–1%), lower bound is for high HIV prevalence setting (>1%), and upper bound is for very low HIV prevalence settings (<0·1%). Relative risk estimates are from WHO, 2009.[1,2] Different estimates have been applied according to HIV prevalence in respective country. Prevalence data are from UNAIDS, 2008.[76] †Undernutrition: relative risk=3·2, 95% CI 3·1–3·3 for body-mass index 16 kg/m^2 versus 25 kg/m^2, based on average reduction in tuberculosis incidence of 13·8% (95% CI 13·4–14·2) per unit increase in body-mass index, as reported in a meta-analysis by Lönnroth and colleagues.[68] Prevalence data are from prevalence of undernourishment as reported in: The State of Food Insecurity in the World 2008.[77] ‡Diabetes: relative risk=3·1, 95% CI 2·3–4·3. Point estimate and 95% CI are from pooled estimate in meta-analysis by Jeon and Murray (2008).[72] Prevalence data are from IDF, 2010.[78] §Alcohol misuse: relative risk=2·9, 95% CI 1·9–4·6. Point estimate and 95% CI are from pooled estimate in meta-analysis by Lönnroth and colleagues (2008).[74] Prevalence data are from average of prevalence of heavy drinking in men and women (>40 g alcohol per day for men and >20 g per day for women). China, Brazil, India, Nigeria, Pakistan, Russia, South Africa, and Thailand data from Rehm and colleagues.[75] Other data are based on regional estimates reported in WHO, 2004.[79] ¶Smoking: relative risk=2·0, 95% CI 1·6–2·5. Point estimate and 95% CI are from pooled estimate comparing risk of pulmonary tuberculosis in current versus never smokers, in meta-analysis by Lin and colleagues (2007).[70] Prevalence data are from WHO, 2008.[80] ‖Indoor air pollution: relative risk=1·4, 95% CI 0·6–3·4. Point estimate and 95% CI from pooled estimate comparing risk of pulmonary tuberculosis in studies controlling for smoking, in meta-analysis by Lin and colleagues (2007).[70] Prevalence data are from WHO, 2006.[81]

Table 3: **Prevalence and population attributable fractions of selected tuberculosis risk factors, in 22 high-burden countries**

diagnostic algorithm for sputum-smear-negative cases, diagnosis based on initial radiography has been recommended for people with HIV.[98]

The sensitivity of conventional sputum-smear microscopy is low,[99] but can be improved through various sputum processing techniques, fluorescent microscopy, and new techniques such as light-emitting-diode (LED) fluorescent microscopy.[100] Replacement of solid with liquid cultures increases sensitivity and reduces delay.[45] New diagnostics are available or under development, but most need to be further assessed and field tested.[101] A rapid and simple point-of-care test would improve early case detection substantially.[100] These approaches do not help people who do not access health services. The poorest and most vulnerable groups are well known to face the largest access barriers,[8,40] and in many settings this includes women because of disempowerment, stigma, and few financial resources.[102,103] These problems need specific actions to improve access for poor people.[104] Health-care seeking behaviour can also be improved through engagement of various partners, including community organisations, in awareness campaigns.[105]

Active case finding outside health facilities might also be warranted. Since contacts of cases are at substantially increased risk of contracting tuberculosis,[106] contact investigation is a logical first step. A systematic review of the effects of investigations in tuberculosis contacts in low-income and middle-income countries showed that 4·5% of

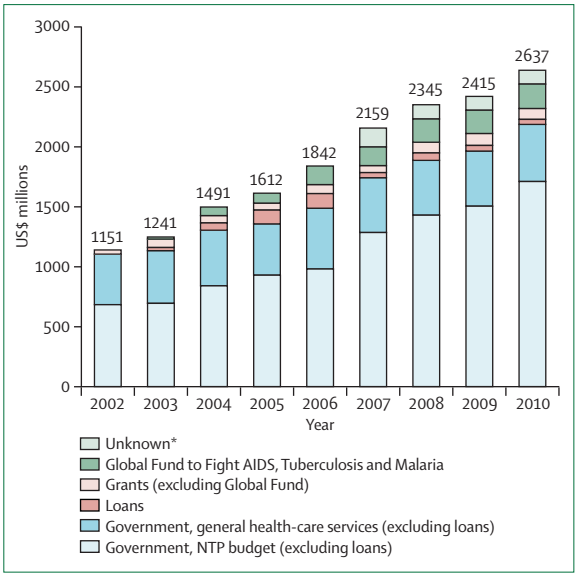

Figure 5: **Funding for tuberculosis control by source of funding in 22 high-burden countries, 2002–10**
NTP=national treatment programme. *Unknown source applies only to a proportion of the budget for multidrug-resistant tuberculosis hospitals in South Africa.

identified household contacts had active tuberculosis at the time of screening, and additional contacts subsequently developed disease.[107] Mass radiography screening was historically a standard element of control programmes in industrialised countries,[108] but was later strongly discouraged because of low cost-effectiveness.[109,110] Nonetheless, several alternatives to mass screening are available, which are more targeted and potentially more cost effective, although rigorous analysis is still necessary. These options include screening of subpopulations with a particularly high risk of exposure, such as health-care workers,[111] prisoners,[112] drug addicts,[113] homeless people,[114] slum dwellers, refugees, migrants, displaced populations,[115] or other high-risk groups.[116]

Strategies to improve treatment outcomes should be tailored to local situations, but ensuring that internationally recommended treatment regimens and quality-assured drug formulations are being consistently used is essential,[117] and avoiding drug stockouts is crucial. Drug management in NTPs has improved over the past two decades, but improvements can still be made. In 2008, four of the 22 high-burden countries had drug stockouts. Poor treatment adherence should be addressed through patient-friendly service delivery models and intensified patient support that addresses social and economic factors hindering treatment adherence,[8,104,118] while respecting human rights and ethical principles.[119] When case fatality is high, common causes need to be identified and addressed, including the possible effect of comorbidities. In the absence of ART, HIV increases the risk of death during tuberculosis treatment.[120] Both diabetes and smoking have been associated with increased tuberculosis case fatality, but the effect on mortality, failure, and relapse of these and other risk factors needs further study.[67,69,73,75] High rates of treatment failure should trigger careful assessment of treatment adherence and drug-resistance patterns.

Development and enforcement of bold health-system policies

An important reason for slow scale-up of quality tuberculosis diagnosis and treatment is that most NTPs operate within weak and underfunded health systems with generally poor infrastructure, an insufficient workforce, limited capacity to enforce policies, and poor governance functions.[18,121,122]

Funding for tuberculosis control in high-burden countries more than doubled between 2002 and 2009 (figure 5).[2] Nevertheless, large funding gaps remain. The funding shortfall expected in these countries in 2010 is US$0·5 billion, and in all countries the deficit in 2010 compared with the Global Plan to Stop TB is $2·1 billion.[2,12] Many countries are struggling to sustain basic diagnostic and treatment services. At the same time, they are trying to scale up management of MDR tuberculosis and collaborative tuberculosis and HIV activities, and to introduce new methods and strategies that increase complexity and cost. Therefore, despite increased resources, the gap between what is needed and what can be funded with available resources is increasing. Eight of the high-burden countries had funding gaps of more than 50% of the required NTP budget in 2009 (table 2). Although most high-burden countries have managed to increase national funding for tuberculosis control over recent years, many still rely heavily on international support.[2] With government health expenditure of $20 per head or less in 16 of the 22 countries, and on average 3·6% of government health expenditure used for NTPs (table 2), this finding is not surprising. International funding for tuberculosis control has increased over the past decade, especially from the Global Fund to Fight AIDS, Tuberculosis and Malaria (figure 5),[1,2] which contributed more than 60% of the external funding for tuberculosis control and provided treatment for 6 million people with this disease up to 2009.[123] However, the increasing acknowledgment of huge unmet needs in other health areas, combined with a global financial crisis, means that competition for scarce resources has intensified both nationally and internationally. This risks increased inequality, with the poorest and most affected people having potentially reduced access to preventive and treatment services, especially in areas in which social protection mechanisms are weak or non-existent.[124]

Within existing constraints, NTPs try to provide services that are free of charge or highly subsidised, with mixed success. Although NTPs in most high-burden countries provide free sputum-smear microscopy for all patients with suspected pulmonary tuberculosis, only nine of 22 also provide other diagnostic tests free of charge (table 2). Most

high-burden countries charge for radiography, culture, and drug-susceptibility testing (DST). Sufficient coverage of sputum-smear microscopy (≥one per 100 000 population) has been achieved in 14 of these countries, but the benchmark coverage (≥one per 5 million population) for culture and DST has been reached in only three (table 2). These deficiencies are an indicator of generally weak laboratory diagnostic services.

All high-burden countries report provision of free first-line tuberculosis drugs within NTPs (table 2). Second-line drugs for patients with MDR tuberculosis treated by the NTP are also, in principle, free of charge in most of these countries. However, since programmatic management of MDR tuberculosis has so far been implemented on a small scale, a very small proportion of patients have access to the drugs (table 2). Furthermore, NTPs in six high-burden countries have no paediatric formulations (table 2). Many patients purchase drugs in private pharmacies. Tuberculosis drugs can be bought in private pharmacies in 15 high-burden countries, and without a prescription in 12 of them (table 2), creating the conditions for uncontrolled and irrational use of drugs,[125] which are seldom produced by manufacturers that have been prequalified or quality assured.[126] It is estimated that half of the market for first-line drugs is in the private sector and that the private sector dominates the market for second-line drugs.[127] Irrational and expensive drug use in the private sector contributes to the development of drug resistance and to huge expenditure for patients.[21]

This situation stems from a wider health-system challenge, in which the gap created by small amounts of government investment in health is filled with largely unregulated private care. In high-burden countries, on average 60% of overall health expenditure is in the private sector; the figure is 50% or more in 17 of these countries (table 2), and much of this amount is out-of-pocket expenditure by patients. In many countries, especially in Asia, the private sector is the dominant health provider, and the first port of call for most people with tuberculosis. The quality of diagnostic and treatment services is often substandard. Diagnostic algorithms and drug regimens are not in line with international standards, tuberculosis drugs are often sold over the counter, patient support and supervision mechanisms are often absent, and treatment success rates are consequently low.[21] Active engagement of the private sector and promotion of care in line with the ISTC (including free, quality-assured drugs) can improve quality of care, achieve high cure rates, and substantially reduce costs to patients.[89] Even so, most high-burden countries have not actively and systematically engaged private providers (table 2). An underlying difficulty is weak regulatory framework for private health care, rendering NTPs powerless to impose standards on providers who are unwilling to collaborate. The necessary solution will have to include strengthened government stewardship of the private sector.[128]

Tuberculosis is associated with a wide range of comorbidities. Globally, about 15% of people with this disease are infected with HIV.[2] From the data in table 3 we can deduce that about 50% of patients with tuberculosis in high-burden countries are undernourished; in adults, about 50% are smokers, about 20% misuse alcohol, and about 15% have diabetes, with much higher numbers in some countries than in others. Services for these diseases are often underdeveloped in low-income and middle-income countries and, as a result, they are often not diagnosed.[95] Meeting the medical-care needs of patients with tuberculosis therefore requires access to basic primary health-care services, beyond good tuberculosis care. Within national health plans, NTPs should strengthen collaboration with other public health programmes to contribute to the prevention, treatment, and management of these conditions. Frameworks for such work are already well established for HIV, and are being developed for smoking-related diseases.[129]

Finally, the challenge of inadequate information about tuberculosis morbidity and mortality needs to be addressed in the context of broad efforts to tackle general deficiencies in health-information systems. Experience in China has shown how improvements in the general disease-notification system, combined with increased public health funding and regulatory interventions, improved both the quality of tuberculosis statistics and programme performance.[130]

Establishment of links with the broader development agenda

The positive effects of improved living conditions and nutritional status in industrialised countries over the past century,[131] the negative effects of the economic downturn in countries of eastern Europe and the former Soviet Union in the 1990s,[29,30] and the clear association between broad development indicators and tuberculosis incidence trends in the past century and in recent years[32,33,40] are examples of how socioeconomic factors can affect tuberculosis epidemics. Most of the proximate risk factors for tuberculosis are associated with social conditions. People from low socioeconomic status groups typically have more frequent contact with people with active disease, a higher likelihood of crowded living and working conditions, greater food insecurity, lower levels of health awareness or less power to act on existing knowledge concerning healthy behaviour, and less access to quality health care than do those from high socioeconomic groups.[40] Malnutrition, crowding, and exposure to indoor air pollution are direct markers of poverty. The prevalence of smoking is consistently highest in low socioeconomic groups in all regions worldwide. For HIV, alcohol misuse, and diabetes, the trend is not straightforward, but in middle-income and high-income countries these factors are more prevalent in low socioeconomic groups.[132]

Improved wealth, education, and social protection would greatly benefit tuberculosis control.[133] However, some

Panel 2: **Possible strategies to reduce costs for patients with tuberculosis and their families**

Provision of all tuberculosis services free of charge
- Sputum-smear microscopy
- Culture, radiography, and other tests
- Drugs (including second-line drugs)
- Consultation and registration fees

Reduction of diagnostic delay and health-care spending
- Decentralise diagnosis
- Improve referral routines
- Address access barriers
- Reduce stigma and discrimination

Further treatment decentralisation and patient supportive care
- Community-based treatment
- Engage all care providers

Introduction of enabling supportive packages
- Travel vouchers, cash transfer
- Food support

Promotion of continued work, compensation for lost earnings, and social welfare support
- Health education
- Livelihood support, vocational training
- Dialogues with employers and sickness insurance systems
- Enrolment in appropriate social welfare programmes

aspects of economic development might have a negative effect. Rapid industrialisation, urbanisation, and migration—dominant occurrences in most developing countries—can create ideal conditions for tuberculosis epidemics to flourish, unless accompanied by good urban planning, social reforms, environmental protection, and a strong and well coordinated health system. The incidence in urban areas is generally higher than in rural areas,[134] possibly because of a combination of high population density and lifestyle changes associated with urban living. Exposure to some tuberculosis risk factors such as smoking, alcohol misuse, and unhealthy diet can increase when absolute poverty falls at the same time as rapid sociocultural transition leads to changed patterns in health behaviour.[135]

What clearly emerges is a need for both public health interventions to tackle specific tuberculosis risk factors, and high-level political decisions to reduce poverty and promote social protection, education, and empowerment. The more upstream the intervention is implemented, the more widespread the effect for public health. Tuberculosis shares many social determinants with other key public health conditions, including the diseases that are direct risk factors for tuberculosis.[132] The Commission on Social Determinants of Health developed frameworks for action to address a wide range of social determinants.[136] Although the main responsibility to pursue health in all policies rests with the ministry of health and other ministries, the NTP and its international technical partners should lend support to the implementation of these frameworks, both through advocacy and by helping to address the social conditions of patients and their families.

First and foremost this approach entails ensuring that the costs of care for patients are kept to a minimum to minimise risk of further impoverishment (panel 2). The combined direct and indirect costs to patients during tuberculosis treatment in NTPs can range from $50 to $300, even when tuberculosis tests and drugs are provided free of charge.[8] Costs before treatment, for seeking care, are often even greater, and the total cost often constitutes more than 50% of the yearly income of patients with tuberculosis in developing countries. Out-of-pocket expenditure can be substantially reduced through elimination of user fees (eg, link to universal health coverage and the establishment of social insurance schemes), decentralisation of services, and community-based care.[8,137,138] Additionally, NTPs can provide support in the form of travel vouchers, food packages, conditional cash transfers, microcredit schemes, and vocational training, while advocating to employers and trade unions to protect the rights of workers affected by tuberculosis.

Political commitment—the first element of the Stop TB Strategy—should not only include commitment from governments to invest in and support tuberculosis diagnosis and treatment programmes, but also recognition by all political contributors, including civil society and health activists, that this disease is an expression of a development crisis that will be ultimately addressed by removal of the upstream drivers of the epidemic.

Promotion and intensification of research

An intensive effort is needed to develop new medical technologies for prevention, diagnosis, and treatment.[101,139,140] Further basic epidemiological research will be needed into risk factors and social determinants. Effectiveness and cost-effectiveness of new strategies for improved early case detection, treatment, and prevention need to be assessed. Operational research into how to rapidly transfer, introduce, and adapt new methods and strategies to local contexts is also needed. Finally, the data and methods used to assess tuberculosis burden and trends need to be further improved.[25] Tuberculosis research investments have increased in recent years, but from very low amounts. The present investments of about $0·5 billion per year are insufficient to accelerate research that is needed to pursue tuberculosis elimination.[141]

Conclusions

Proper tuberculosis care and control averted up to 6 million deaths and cured 36 million people between 1995 and 2008. However, this disease is still causing considerable burden and loss of productivity. Much intensified action is needed to control and ultimately eliminate the disease. Every country should now focus

action in the four areas of continued scale-up of early diagnosis and proper treatment, development and enforcement of bold health-system policies, establishment of links with the broad development agenda, and promotion and intensification of research efforts. Monitoring of key indicators, such as those presented in tables 1 and 2, and continuous assessment of determinants, such as those listed in table 3, will prove crucial for the understanding of the challenges, needs, and the progress towards achievement of the global targets.

Contributors

KL did the initial literature search, undertook the survey of tuberculosis control policies and health-systems context, did the analysis of population attributable fractions, wrote the first draft of the report, and coordinated its completion. KGC, JMC, and LSC undertook additional literature searches, and contributed to significant parts of the text. KF and PG coordinated the data collection, did the analysis, and produced the graphs of tuberculosis epidemiology and tuberculosis programme performance and funding. MCR conceptualised the paper, wrote parts of it, revised regularly, and guided its development and completion, including that of the tables. All authors reviewed drafts of the paper and approved the final report.

Steering committee

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Conflicts of interest

We declare that we have no conflicts of interest.

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