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Cover design by Tom Hiatt, Stop TB Department. The image depicts the remarkable decline in TB incidence, prevalence and mortality in China between 1990 and 2010. See Box 2.5.

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Contents

Abbreviations

ACSM	advocacy, communication and social mobilization
AFB	acid-fast bacilli
AFR	WHO African Region
AIDS	acquired immunodeficiency syndrome
AMR	WHO Region of the Americas
ARI	annual risk of infection
ART	antiretroviral therapy
BRICS	Brazil, the Russian Federation, India, China, South Africa
CDR	case detection rate
CPT	co-trimoxazole preventive therapy
CBC	community-based TB care
DOTS	the basic package that underpins the Stop TB Strategy
DRS	drug resistance surveillance or survey
DST	drug susceptibility testing
ECDC	European Centre for Disease Prevention and Control
EMR	WHO Eastern Mediterranean Region
EQA	external quality assurance
ERR	electronic recording and reporting
EU	European Union
EUR	WHO European Region
FIND	Foundation for Innovative New Diagnostics
GLC	Green Light Committee
GLI	Global Laboratory Initiative
Global Fund	The Global Fund to fight AIDS, Tuberculosis and Malaria
Global Plan	Global Plan to Stop TB, 2011–2015
GNI	gross national income
HBC	high-burden country of which there are 22 that account for approximately 80% of all new TB cases arising each year
HIV	human immunodeficiency virus
ICD-10	International Classification of Diseases (tenth revision)
IPT	isoniazid preventive therapy
IRR	incidence rate ratio
LED	light-emitting diode
LPA	line-probe assay
MDG	Millennium Development Goal
MDR-TB	multidrug-resistant tuberculosis (resistance to, at least, isoniazid and rifampicin)
NGO	nongovernmental organization
NTP	national tuberculosis control programme or equivalent
PAL	Practical Approach to Lung Health
PPM	public–private and public-public mix
SEAR	WHO South-East Asia Region
TB	tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNITAID	international facility for the purchase of diagnostics and drugs for diagnosis and treatment of HIV/AIDS, malaria and TB
USAID	United States Agency for International Development
VR	vital registration
WHA	World Health Assembly
WHO	World Health Organization
WPR	WHO Western Pacific Region
XDR-TB	extensively drug-resistant TB

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Executive summary

This is the sixteenth global report on tuberculosis (TB) published by WHO in a series that started in 1997. It provides a comprehensive and up-to-date assessment of the TB epidemic and progress in implementing and financing TB prevention, care and control at global, regional and country levels using data reported by 198 countries that account for over 99% of the world's TB cases.

The introductory chapter (**Chapter 1**) provides general background on TB as well as an explanation of global targets for TB control, the WHO's Stop TB Strategy and the Stop TB Partnership's Global Plan to Stop TB 2011–2015. The main findings and messages about the six major themes covered in the rest of the report are provided below.

The burden of disease caused by TB (Chapter 2)

In 2010, there were 8.8 million (range, 8.5–9.2 million) incident cases of TB, 1.1 million (range, 0.9–1.2 million) deaths from TB among HIV-negative people and an additional 0.35 million (range, 0.32–0.39 million) deaths from HIV-associated TB.

Important new findings at the global level are:

- The absolute number of TB cases has been falling since 2006 (rather than rising slowly as indicated in previous global reports);
- TB incidence rates have been falling since 2002 (two years earlier than previously suggested);
- Estimates of the number of deaths from TB each year have been revised downwards;
- In 2009 there were almost 10 million children who were orphans as a result of parental deaths caused by TB.

Updates to estimates of disease burden follow the completion of a series of consultations with 96 countries between 2009 and 2011, including China, India and 17 African countries in the past year, and much greater availability and use of direct measurements of TB mortality. Ongoing efforts to further improve measurement of TB cases and deaths under the umbrella of the WHO Global Task Force on TB Impact Measurement, including impressive progress on TB prevalence surveys and innovative work to strengthen surveillance, are summarized.

At country level, dramatic reductions in TB cases and deaths have been achieved in China. Between 1990 and 2010, prevalence rates were halved, mortality rates fell by almost 80% and TB incidence rates fell by 3.4% per year. Methods used to measure trends in disease burden in China – nationwide prevalence surveys, a sample vital registration system and a web-based case notification system – provide a model for many other countries.

Other results reinforce the findings of previous global reports:

- The world and all of WHO's six regions are on track to achieve the Millennium Development Goal target that TB incidence rates should be falling by 2015;
- TB mortality rates have fallen by just over a third since 1990, and the world as well as five of six WHO regions (the exception being the African Region) are on track to achieve the Stop TB Partnership target of halving 1990 mortality rates by 2015;
- The Stop TB Partnership target of halving TB prevalence rates by 2015 compared with 1990 is unlikely to be achieved globally, although the target has already been reached in the Region of the Americas and the Western Pacific Region is very close to reaching the target;
- There were 3.2 million (range, 3.0–3.5 million) incident cases of TB and 0.32 million (range, 0.20–44 million) deaths from TB among women in 2010;
- About 13% of TB cases occur among people living with HIV.

Case notifications and treatment outcomes (Chapter 3)

In 2010, there were 5.7 million notifications of new and recurrent cases of TB, equivalent to 65% (range 63–68%) of the estimated number of incident cases in 2010. India and China accounted for 40% of the world's notified cases of TB in 2010, Africa for a further 24% and the 22 high-TB burden countries (HBCs) for 82%. At global level, the treatment success rate among new cases of smear-positive pulmonary TB was 87% in 2009.

Between 1995 and 2010, 55 million TB patients were treated in programmes that had adopted the DOTS/Stop TB Strategy, and 46 million were successfully treated. These treatments saved almost 7 million lives.

Alongside these achievements, diagnosis and appropriate treatment of multidrug-resistant TB (MDR-TB) remain major challenges. Less than 5% of new and previously treated TB patients were tested for MDR-TB in

most countries in 2010. The reported number of patients enrolled on treatment has increased, reaching 46 000 in 2010. However, this was equivalent to only 16% of the 290 000 cases of MDR-TB estimated to exist among notified TB patients in 2010.

Financing TB care and control (Chapter 4)

In 97 countries with 92% of the world's TB cases for which trends can be assessed, funding from domestic and donor sources is expected to amount to US$ 4.4 billion in 2012, up from US$ 3.5 billion in 2006. Most of this funding is being used to support diagnosis and treatment of drug-susceptible TB, although funding for MDR-TB is growing and expected to reach US$ 0.6 billion in 2012. Countries report funding gaps amounting to almost US$ 1 billion in 2012.

Overall, domestic funding accounts for 86% of total funding, with the Global Fund accounting for 12% (82% of all international funding) and grants from other agencies for 2%, but striking contrasts between BRICS (Brazil, the Russian Federation, India, China and South Africa) and other countries are highlighted:

- BRICS invested US$ 2.1 billion in TB control in 2010, 95% of which was from domestic sources;
- In the other 17 HBCs, total expenditures were much lower (US$ 0.6 billion) and only 51% of funding was from domestic sources.

Most of the funding needed to scale up the treatment of MDR-TB towards the goal of universal access is needed in BRICS and other middle-income countries (MICs). If BRICS and other MICs fully finance the scale-up of treatment for MDR-TB from domestic sources, current levels of donor financing for MDR-TB would be almost sufficient to fund the scale-up of MDR-TB treatment in low-income countries.

Donor funding for TB is expected to reach US$ 0.6 billion in 2012, a 50% increase compared with US$ 0.4 billion in 2006, but far short of donor funding for malaria (US$ 1.8 billion in 2010) and HIV (US$ 6.9 billion in 2010).

New diagnostics and laboratory strengthening (Chapter 5)

The first data on the roll-out of Xpert MTB/RIF, a new rapid molecular test that has the potential to substantially improve and accelerate the diagnosis of TB and drug-resistant TB, are presented. By 30 June 2011, six months after the endorsement of Xpert MTB/RIF by WHO in December 2010, 26 of the 145 countries eligible to purchase GeneXpert instruments and Xpert MTB/RIF cartridges at concessional prices had done so. This shows that the transfer of technology to developing countries can be fast.

The continued inadequacy of conventional laboratory capacity is also illustrated:

- In 2010, 8 of the 22 HBCs did not meet the benchmark of 1 microscopy centre per 100 000 population;
- Among the 36 countries in the combined list of 22 HBCs and 27 high MDR-TB burden countries, 20 had less than the benchmark of 1 laboratory capable of performing culture and drug susceptibility testing per 5 million population.

Overall, laboratory strengthening needs to be accelerated, as is currently happening in 27 countries through the EXPAND-TB project supported by UNITAID.

Addressing the co-epidemics of TB and HIV (Chapter 6)

Progress in scaling up interventions to address the co-epidemics of TB and HIV has continued:

- In 2010, HIV testing among TB patients reached 34% globally, 59% in the African Region and ≥75% in 68 countries;
- Almost 80% of TB patients known to be living with HIV were started on cotrimoxozole preventive therapy (CPT) and 46% were on antiretroviral therapy (ART) in 2010;
- A large increase in screening for TB among people living with HIV and provision of isoniazid preventive therapy to those without active TB disease occurred in 2010, especially in South Africa.

Impressive improvements in recent years notwithstanding, much more needs to be done to reach the Global Plan targets that all TB patients should be tested for HIV and that all TB patients living with HIV should be provided with CPT and ART.

Research and development (Chapter 7)

The topic of research and development is discussed for the first time in the global report. There has been considerable progress in diagnostics in recent years, including the endorsement of Xpert MTB/RIF at the end of 2010; other tests including point-of-care tests are in the pipeline. There are 10 new or repurposed TB drugs in clinical trials that have the potential to shorten the treatment of drug-susceptible TB and improve the treatment of MDR-TB. Results from three Phase III trials of 4-month regimens for the treatment of drug-susceptible TB are expected between 2012 and 2013, and results from two Phase II trials of new drugs for the treatment of MDR-TB are expected in 2012. There are 9 vaccine candidates in Phase I or Phase II trials. It is hoped that one or both of the candidates currently in a Phase II trial will enter a Phase III trial in the next 2–3 years, with the possibility of licensing at least one new vaccine by 2020.

CHAPTER 1

Introduction

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis*. It typically affects the lungs (pulmonary TB) but can affect other sites as well (extrapulmonary TB). The disease is spread in the air when people who are sick with pulmonary TB expel bacteria, for example by coughing. In general, a relatively small proportion of people infected with *Mycobacterium tuberculosis* will go on to develop TB disease; however, the probability of developing TB is much higher among people infected with the human immunodeficiency virus (HIV). TB is also more common among men than women, and affects mostly adults in the economically productive age groups; around two-thirds of cases are estimated to occur among people aged 15–59 years.

The most common method for diagnosing TB worldwide is sputum smear microscopy (developed more than 100 years ago), in which bacteria are observed in sputum samples examined under a microscope. In countries with more developed laboratory capacity, cases of TB may also be diagnosed via culture methods (the current gold standard) or, increasingly, using rapid molecular tests.

Without treatment, mortality rates are high. In studies of the natural history of the disease among sputum smear-positive and HIV-negative cases of pulmonary TB, around 70% died within 10 years; among culture-positive (but smear-negative) cases, 20% died within 10 years.[1] Treatment using combinations of anti-TB drugs developed in the 1940s and 1950s can dramatically reduce mortality rates. In clinical trials, cure rates of above 90% have been documented; the treatment success rate among smear-positive cases of pulmonary TB reported to WHO reached 87% at the global level in 2009.

Despite the availability of highly efficacious treatment for decades, TB remains a major global health problem. In 1993, the World Health Organization (WHO) declared TB a global public health emergency, at a time when an estimated 7–8 million cases and 1.3–1.6 million deaths occurred each year. In 2010, there were an estimated 8.5–9.2 million cases and 1.2–1.5 million deaths (including deaths from TB among HIV-positive people).[2] TB is the second leading cause of death from an infectious disease worldwide (after HIV, which caused an estimated 1.8 million deaths in 2008).[3]

WHO has published a global report on TB every year since 1997 (**Figure 1.1**). The main aim of the report is to provide a comprehensive and up-to-date assessment of the TB epidemic and progress made in prevention, care and control of the disease at global, regional and country levels, in the context of global targets set for 2015 and WHO's recommended strategy for achieving these targets.

BOX 1.1

Goals, targets and indicators for TB control

Millennium Development Goals set for 2015

Goal 6: Combat HIV/AIDS, malaria and other diseases

Target 6c: Halt and begin to reverse the incidence of malaria and other major diseases

Indicator 6.9: Incidence, prevalence and death rates associated with TB

Indicator 6.10: Proportion of TB cases detected and cured under DOTS

Stop TB Partnership targets set for 2015 and 2050

By 2015: Reduce prevalence and death rates by 50%, compared with their levels in 1990

By 2050: Reduce the global incidence of active TB cases to <1 case per 1 million population per year

The 2015 global targets for reductions in disease burden (**Box 1.1**) are that TB incidence should be falling (MDG Target 6.c) and that prevalence and death rates should be halved compared with their levels in 1990. WHO's recommended strategy for achieving these targets is the Stop TB Strategy[4] (**Box 1.2**), which was launched in 2006 as an enhancement of the DOTS

[1] Tiemersma EW et al. Natural history of tuberculosis: duration and fatality of untreated pulmonary tuberculosis in HIV-negative patients: A systematic review. *PLoS ONE* 2011 6(4): e17601.

[2] These deaths are classified as HIV deaths in the *International statistical classification of diseases and related health problems, 10th revision (ICD-10)*, 2nd ed. Geneva, World Health Organization, 2007.

[3] **http://apps.who.int/ghodata**. These HIV deaths include 0.4 million deaths from TB.

[4] *The Stop TB Strategy: building on and enhancing DOTS to meet the TB-related Millennium Development Goals*. Geneva, World Health Organization, 2006 (WHO/HTM/TB/2006.368).

BOX 1.2

The Stop TB Strategy at a glance

THE STOP TB STRATEGY

VISION	A TB-free world
GOAL	To dramatically reduce the global burden of TB by 2015 in line with the Millennium Development Goals (MDGs) and the Stop TB Partnership targets
OBJECTIVES	• Achieve universal access to high-quality care for all people with TB
	• Reduce the human suffering and socioeconomic burden associated with TB
	• Protect vulnerable populations from TB, TB/HIV and drug-resistant TB
	• Support development of new tools and enable their timely and effective use
	• Protect and promote human rights in TB prevention, care and control
TARGETS	• MDG 6, Target 6.c: Halt and begin to reverse the incidence of TB by 2015
	• Targets linked to the MDGs and endorsed by the Stop TB Partnership: – 2015: reduce prevalence of and deaths due to TB by 50% compared with a baseline of 1990 – 2050: eliminate TB as a public health problem

COMPONENTS

1. **Pursue high-quality DOTS expansion and enhancement**
   a. Secure political commitment, with adequate and sustained financing
   b. Ensure early case detection, and diagnosis through quality-assured bacteriology
   c. Provide standardized treatment with supervision, and patient support
   d. Ensure effective drug supply and management
   e. Monitor and evaluate performance and impact
2. **Address TB/HIV, MDR-TB, and the needs of poor and vulnerable populations**
   a. Scale-up collaborative TB/HIV activities
   b. Scale-up prevention and management of multidrug-resistant TB (MDR-TB)
   c. Address the needs of TB contacts, and of poor and vulnerable populations
3. **Contribute to health system strengthening based on primary health care**
   a. Help improve health policies, human resource development, financing, supplies, service delivery and information
   b. Strengthen infection control in health services, other congregate settings and households
   c. Upgrade laboratory networks, and implement the Practical Approach to Lung Health
   d. Adapt successful approaches from other fields and sectors, and foster action on the social determinants of health
4. **Engage all care providers**
   a. Involve all public, voluntary, corporate and private providers through public–private mix approaches
   b. Promote use of the International Standards for Tuberculosis Care
5. **Empower people with TB, and communities through partnership**
   a. Pursue advocacy, communication and social mobilization
   b. Foster community participation in TB care, prevention and health promotion
   c. Promote use of the Patients' Charter for Tuberculosis Care
6. **Enable and promote research**
   a. Conduct programme-based operational research
   b. Advocate for and participate in research to develop new diagnostics, drugs and vaccines

FIGURE 1.1

Fifteen annual WHO reports on TB in 14 years, 1997–2010

strategy. DOTS was a five-point package that remains the first component and foundation of the Stop TB Strategy. The other components of the Stop TB Strategy highlight the need to address the challenge of drug-resistant TB and the co-epidemics of TB and HIV, the importance of engaging all care providers in TB care and control and of contributing to strengthening health systems, the role of communities and people with TB, and the fundamental role of research and development for new diagnostics, new drugs and new vaccines. The Stop TB Partnership's Global Plan to Stop TB for 2011–2015 has set out the scale at which interventions included in the Stop TB Strategy need to be implemented to achieve the 2015 targets for reductions in disease burden.[1] The plan comes with a price tag of US$ 47 billion and the main indicators and associated baselines and targets are summarized in **Table 1.1**.

This 2011 edition of WHO's annual global TB report – the 16th in the series – continues the tradition of previous reports. It is based primarily on data compiled in annual rounds of global TB data collection in which countries are requested to report a standard set of data to WHO.[2] In 2011, data were requested on the following topics: case notifications and treatment outcomes, including breakdowns by age, sex and HIV status; an overview of services for the diagnosis and treatment of TB; laboratory diagnostic services; drug management; monitoring and evaluation; surveillance and surveys of drug-resistant TB; management of drug-resistant TB; collaborative TB/HIV activities; human resource development; TB control in vulnerable populations and high-risk groups; TB infection control; the Practical Approach to Lung Health;[3] engagement of all care providers in TB control; advocacy, communication and social mobilization; the budgets of national TB control programmes (NTPs) in 2011 and 2012; utilization of general health services (hospitalization and outpatient visits) during treatment; and NTP expenditures in 2010. A shortened version of the online questionnaire was used for high-income countries (that is, countries with a gross national income per capita of ≥US$ 12 276 in 2010, as defined by the World Bank)[4] and/or low-incidence countries (defined as countries with an incidence rate of <20 cases per 100 000 population or <10 cases in total).

Since 2009, data have been reported using an online web-based system.[5] In 2011, the online system was opened for reporting on 15 March, with a deadline of 17 May for all WHO regions except the Region of the Americas (31 May) and the European Region (15 June). A total of 198 countries and territories accounting for over 99% of the world's estimated cases of TB reported data by the deadlines, including all or almost all countries in five of WHO's six regions (**Table 1.2**). Data were reviewed, and followed up with countries where appropriate, by a team of reviewers from WHO (headquarters and regional offices) and the Global Fund. Validation of data by respondents was also encouraged via a series of inbuilt and real-time checks of submitted data as well as a summary report of apparent inconsistencies or inaccuracies that can be generated at any time within the online system. The data contained in the global TB database on 21 June 2011 were used for the main part of this report. The detailed data in **Annex 2** and **Annex 3** reflect the data available on 2 September, the final deadline for receipt

[1] *The Global Plan to Stop TB, 2011–2015*. Geneva, World Health Organization, 2010 (WHO/HTM/STB/2010.2).

[2] The annual data collection form is designed for collecting aggregated national data. It is not recommended for collection of data within countries. WHO recommendations for recording and reporting within countries are described at: **www.who.int/tb/dots/r_and_r_forms/en/index.html**

[3] The Practical Approach to Lung Health (PAL) is a patient-centred approach to improving the quality of diagnosis and treatment for common respiratory illnesses in primary health-care facilities.

[4] **http://data.worldbank.org/about/country-classifications**

[5] **www.stoptb.org/tme**. Countries in the European Union submit notification data to a system managed by the European Centre for Disease Prevention and Control (ECDC). Data from the ECDC system were uploaded into WHO's online system.

TABLE 1.1

Summary of main indicators, baselines and targets set in the Global Plan to Stop TB 2011–2015

PLAN COMPONENT AND INDICATORS	BASELINE (2009)	TARGET (2015)
DOTS/laboratory strengthening		
Number of cases diagnosed, notified and treated according to the DOTS approach (per year)	5.8 million	6.9 million
Treatment success rate (in annual cohort)	86%	90%
Number of countries with ≥1 laboratory with sputum-smear microscopy services per 100 000 population	≥75	149
Drug-resistant TB/laboratory strengthening		
Percentage of previously treated TB patients tested for MDR-TB	7%	100%
Percentage of new bacteriologically-positive patients tested for MDR-TB	7%	20%
Number of countries among the 22 HBCs and 27 high MDR-TB burden countries with ≥1 culture laboratory per 5 million population	18–21	36
Percentage of confirmed cases of MDR-TB enrolled on treatment according to international guidelines	36%	100%
Number of confirmed cases of MDR-TB enrolled on treatment according to international guidelines	11 000	~270 000
Treatment success rate among confirmed cases of MDR-TB	60%	≥75%
TB/HIV/laboratory strengthening		
Percentage of AFB smear-negative, newly notified TB cases screened using culture and/or molecular-based test	<1%	≥50%
Percentage of TB patients tested for HIV	26%	100%
Percentage of HIV-positive TB patients treated with CPT	75%	100%
Percentage of HIV-positive TB patients treated with ART	37%	100%
Percentage of people living with HIV attending HIV care services who were screened for TB at their last visit	~25%	100%
Percentage of people living with HIV attending HIV care services who were enrolled on IPT; among those eligible	<1%	100%
Laboratory strengthening (additional to those above)		
Percentage of national reference laboratories implementing a quality management system (QMS) according to international standards	<5%	≥50%

AFB, acid-fast bacilli; ART, antiretroviral therapy; CPT, co-trimoxazole preventive therapy; HBC, high TB burden country; HIV, human immunodeficiency virus; IPT, isoniazid preventive therapy; MDR-TB, multidrug-resistant tuberculosis.

TABLE 1.2

Reporting of data in the 2011 round of global TB data collection

WHO REGION OR SET OF COUNTRIES	NUMBER OF COUNTRIES AND TERRITORIES	NUMBER OF COUNTRIES AND TERRITORIES REPORTING DATA[a]
African Region	46	45
Eastern Mediterranean Region	22	21
European Region	55	42
Region of the Americas	46	46
South-East Asia Region	11	10
Western Pacific Region	36	34
High-burden countries	22	22
WORLD	**216**	**198**

[a] Countries that did not report data included Comoros (African Region), Libyan Arab Jamahiriya (Eastern Mediterranean Region), Timor-Leste (South-East Asia Region), Japan and Wallis and Futuna Islands (Western Pacific Region). Countries that did not report in the European Region were mostly in Western Europe.

of data from countries in the European Union.[1] Besides the data reported through the standard TB questionnaire, the report uses data about screening for TB among people living with HIV and provision of isoniazid preventive therapy to those without active TB that are collected annually by the HIV department in WHO, as well as data and information that are available to WHO through separate mechanisms.

The report is structured in six major chapters. Each chapter is intended to stand alone, but links to other chapters are highlighted where appropriate. The six chapters are:

- **Chapter 2: The burden of disease caused by TB.** This chapter presents estimates of the numbers of TB cases and deaths caused by TB in 2010, estimates of trends in cases and deaths since 1990, and an assessment of whether the 2015 targets for reductions in cases and deaths will be achieved. This is done for the world as a whole, for WHO's six regions and for

[1] Countries can edit their data at any time. After the global report is published, the most up-to-date data can be downloaded from WHO's global TB database (**www.who.int/tb/data**). For most countries, there are few updates after the global report is published.

each of the 22 high TB burden countries (HBCs) that have been prioritized at global level since 2000.[1] The chapter also puts the spotlight on China, highlighting new evidence on impressive reductions in disease burden between 1990 and 2010. Progress in improving measurement of the burden of disease under the umbrella of the WHO Global Task Force on TB Impact Measurement is also discussed, covering efforts to strengthen TB surveillance and to implement national population-based surveys of the prevalence of TB disease in around 20 global focus countries.

- **Chapter 3: Case notifications and treatment outcomes.** This chapter includes data reported by NTPs on the number of TB cases diagnosed and treated, both overall and for multi-drug resistant TB (MDR-TB) specifically. Numbers of cases diagnosed and treated are compared with the targets included in the Global Plan to Stop TB. Progress in engaging the full range of care providers in diagnosis and treatment is illustrated, and estimates of the proportion of estimated incident cases of TB that were reported to NTPs in 1995, 2000, 2005 and 2010 – the so-called case detection rate (CDR) – are presented. The last part of the chapter summarizes data on treatment outcomes, both overall and for MDR-TB.
- **Chapter 4: Financing TB care and control.** This chapter presents breakdowns of funding for TB prevention, diagnosis and treatment from both domestic and donor sources for the 22 HBCs from 2002 to 2012, and for a total of 97 countries for which trends can be assessed since 2006. Breakdowns are provided for categories of expenditure and by source of funding. Funding gaps are quantified, and available resources are compared with both the funding requirements set out in the Global Plan to Stop TB and levels of international funding for HIV and malaria. Country-specific estimates of the cost per patient treated, and how these are related to levels of average income, are also featured.
- **Chapter 5: New diagnostics and laboratory strengthening for TB.** Laboratory strengthening including the roll out of new diagnostic tests and policies are recognized as top priorities for TB care and control. This chapter describes laboratory capacity in the 22 HBCs as well as 27 high MDR-TB burden countries (a total of 36 countries, given overlap between the two groups). It also assesses progress in efforts to strengthen laboratories, with particular attention to the EXPAND-TB project[2] and the uptake of recent WHO policy guidance on diagnostics. Following the endorsement by WHO of a new molecular diagnostic test for the rapid diagnosis of TB and rifampicin-resistant TB at the end of 2010 – Xpert MTB/RIF – progress in the roll-out of this test is assessed. New policies on TB diagnostics in 2011 and the evidence on which they are based are also summarized.
- **Chapter 6: Addressing the co-epidemics of TB and HIV.** Besides diagnosis and treatment of TB among HIV-positive people, WHO recommends a range of other interventions to jointly address the co-epidemics of TB and HIV. These include HIV testing among all TB patients, provision of co-trimoxazole preventive therapy and antiretroviral therapy for HIV-positive TB patients, intensified case-finding for TB among people receiving HIV care and isoniazid preventive therapy for HIV-positive people without active TB. Progress in

BOX 1.3

What's new in this report?

- The absolute number of TB cases arising each year is estimated to be falling globally
- Evidence of dramatic reductions in TB cases and deaths in China between 1990 and 2010
- Estimates of how many children become orphans as a result of parental deaths caused by TB
- Better estimates of TB mortality due to the greater availability and use of direct measurements from vital registration systems and mortality surveys
- An important update to estimates of TB cases and deaths in the African Region
- Discussion of how synergies between the work of the WHO Global Task Force on TB Impact Measurement and the new grant architecture of the Global Fund have the potential to substantially improve measurement of the burden of disease caused by TB
- Better data on the contribution of public-private and public-public mix (PPM) to TB notifications
- Analysis of the funding required to scale up diagnosis and treatment of multidrug-resistant TB (MDR-TB) in BRICS (Brazil, the Russian Federation, India, China and South Africa), other middle-income countries and low-income countries, combined with assessment of how donor funding could be better used to support this scale-up
- Data on the roll-out of Xpert MTB/RIF for the rapid diagnosis of TB and rifampicin-resistant TB following WHO's endorsement of the test in December 2010
- A chapter on the latest status of progress in developing new TB diagnostics, drugs and vaccines

[1] These countries are (in alphabetical order): Afghanistan, Bangladesh, Brazil, Cambodia, China, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, the Philippines, the Russian Federation, South Africa, Thailand, Uganda, the United Republic of Tanzania, Viet Nam and Zimbabwe.

[2] www.who.int/tb/publications/factsheet_expand_tb.pdf

scaling up provision of these services is described and discussed.

- **Chapter 7: Research and development.** The most commonly used diagnostic test for TB is over 100 years old, the anti-TB drugs used in first-line treatments are around 50 years old and the BCG vaccine to prevent TB is almost 100 years old. In the past decade, efforts to develop new drugs, new diagnostics and new vaccines have intensified. This chapter presents the current status of progress.

Annex 1 explains the methods that were used to produce estimates of the burden of disease caused by TB. **Annex 2** contains country profiles for the 22 HBCs and also highlights additional profiles that are available for all countries online.[1] **Annex 3** contains summary tables that provide data on key indicators for the world, WHO regions and individual countries.

[1] **www.who.int/tb/data**

CHAPTER 2

The burden of disease caused by TB

KEY MESSAGES

- There were an estimated 8.8 million incident cases of TB (range, 8.5 million–9.2 million) globally in 2010, 1.1 million deaths (range, 0.9 million–1.2 million) among HIV-negative cases of TB and an additional 0.35 million deaths (range, 0.32 million–0.39 million) among people who were HIV-positive.
- In 2009, there were an estimated 9.7 million (range, 8.5–11 million) children who were orphans as a result of parental deaths caused by TB.
- Globally, the absolute number of incident TB cases per year has been falling since 2006 and the incidence rate (per 100 000 population) has been falling by 1.3% per year since 2002. If these trends are sustained, the MDG target that TB incidence should be falling by 2015 will be achieved.
- TB mortality is falling globally and the Stop TB Partnership target of a 50% reduction by 2015 compared with 1990 will be met if the current trend is sustained. The target could also be achieved in all WHO regions with the exception of the African Region.
- Although TB prevalence is falling globally and in all regions, it is unlikely that the Stop TB Partnership target of a 50% reduction by 2015 compared with 1990 will be reached. However, the target has already been achieved in the Region of the Americas and the Western Pacific Region is very close to reaching the target.
- Dramatic reductions in TB cases and deaths have been achieved in China. Between 1990 and 2010, prevalence rates were halved, mortality rates were cut by almost 80% and incidence rates fell by 3.4% per year. In addition, methods for measuring trends in disease burden in China provide a model for many other countries.
- Between 2009 and 2011, consultations with 96 countries that account for 89% of the world's TB cases have led to a major updating of estimates of TB incidence, mortality and prevalence, particularly for countries in the African Region.
- Estimates of TB mortality have substantially improved in the past three years, following increased availability and use of direct measurements from vital registration systems and mortality surveys. In this report, direct measurements of mortality are used for 91 countries (including China and India for the first time).

The burden of disease caused by TB can be measured in terms of incidence (defined as the number of new and relapse cases of TB arising in a given time period, usually one year), prevalence (defined as the number of cases of TB at a given point in time) and mortality (defined as the number of deaths caused by TB in a given time period, usually one year). It can also be expressed in terms of the years of life lost or, to account for illness as well as mortality, the disability-adjusted life years (DALYs) lost. WHO publishes estimates of the burden of disease by major cause and risk factor using all of these metrics.[1]

The first three parts of this chapter present estimates of TB incidence, prevalence and mortality (absolute numbers and rates) between 1990 and 2010 and (for prevalence and mortality) forecasts up to 2015. These data are used to assess progress towards achieving the global targets set for 2015: that incidence should be falling (MDG Target 6.c) and that prevalence and death rates should be halved by 2015 compared with their levels in 1990 (**Box 1.1** in **Chapter 1**). Key aspects of the methods used to produce the estimates are provided at the beginning of each section; a detailed description is provided in **Annex 1**.[2] **Section 2.4** focuses on multidrug-resistant TB (MDR-TB), providing estimates of the number of cases of MDR-TB in 2010 and a new analysis of trends in such cases at global and regional levels.

There is uncertainty in all estimates of the burden of disease caused by TB (**Box 2.1**). The final part of the chapter profiles efforts to improve measurement of the burden of disease caused by TB under the umbrella of the WHO Global Task Force on TB Impact Measurement. These include efforts to strengthen surveillance of cases and deaths via notification and vital registration (VR) systems, and national surveys of the prevalence of TB disease in global focus countries.

The chapter also puts the spotlight on China, where considerable efforts to measure the burden of disease

[1] World Health Statistics 2010. Geneva, World Health Organization, 2010 (WA 900.1).

[2] Methods were fully updated in 2009 following 18 months of work by an expert group convened by the WHO Global Task Force on TB Impact Measurement. Improvements included systematic documentation of expert opinion and uncertainty intervals, simplification of models, updates to parameter values based on the results of literature reviews and much greater use of mortality data from vital registration systems. For further details, see the Task Force web site at: **www.who.int/tb/advisory_bodies/impact_measurement_taskforce**

BOX 2.1

Uncertainty in estimates of TB incidence, prevalence and mortality

TB incidence has never been directly measured at national level, since this would require long-term studies among large cohorts of people (hundreds of thousands) at high cost and with challenging logistics. In countries with a high burden of TB, prevalence can be directly measured in nationwide surveys using sample sizes of around 50 000 people and costs in the range of US$ 1–4 million per survey.[1] Relatively few countries with a high burden of TB have conducted prevalence surveys in recent years (although this is now changing), and sample sizes and costs become prohibitive in low and medium-burden countries. TB mortality among HIV-negative people can be directly measured if national vital registration (VR) systems of high coverage in which causes of death are accurately coded according to the latest revision of the international classification of diseases (ICD-10) are in place (and sample VR systems covering representative areas of the country provide an interim solution). Mortality surveys can also be used to directly measure deaths caused by TB. In 2010, most countries with a high burden of TB lacked national or sample VR systems and few had conducted mortality surveys. TB mortality among HIV-positive people is hard to measure even when VR is in place, since deaths among HIV-positive people are coded as HIV deaths and contributory causes (such as TB) are often not reliably recorded.

For all these reasons, the estimates of TB incidence, prevalence and mortality included in this chapter are presented with uncertainty intervals. When ranges are presented, the lower and higher numbers correspond to the 2.5th and 97.5th centiles of the outcome distributions (generally produced by simulations). The methods used to produce best estimates and uncertainty intervals are described in detail in **Annex 1**. Improvements to the estimates published in this report compared with previous years are profiled in **Box 2.2** and **Box 2.3**.

[1] *TB prevalence surveys: a handbook*. Geneva, World Health Organization, 2011 (WHO/HTM/TB/2010.17).

caused by TB have been made over the past 20 years. The impressive results and the methods used to produce them – which provide a model for many other countries – are highlighted as a special case study.

2.1 Estimates of the incidence of TB

The incidence of TB cannot be measured directly (**Box 2.1**). For 96 countries that account for 89% of the world's TB cases, estimates were thoroughly reviewed and updated between 2009 and 2011 in either regional or country workshops (**Figure 2.1**). This was done using a framework (**Figure 2.2**) and associated tools developed by the WHO Global Task Force on TB Impact Measurement. In-depth analyses of the available surveillance, survey and programmatic data were undertaken, and expert opinion about the fraction of cases diagnosed but not reported, or

FIGURE 2.1

Progress in applying the Task Force framework for assessment of TB surveillance data, as of July 2011[a]

[a] All countries shown in orange participated in regional workshops held from April 2009 to June 2010, with the exception of the United Republic of Tanzania where a country mission was undertaken in October 2009 and India where three country missions were undertaken between April and July 2011. As follow-up to the regional workshop held for countries in the Western Pacific Region in June 2010, a national workshop was also held in China in June 2011. Further details about these workshops are provided in **ANNEX 1**.

not diagnosed at all, was documented. Reliance on expert opinion is one of the reasons for uncertainty in estimates (**Box 2.1**); strengthening of surveillance and better quantification of under-reporting (i.e. the number of cases that are missed by surveillance systems) are needed to reduce this uncertainty (efforts to do this are discussed in **section 2.5**).

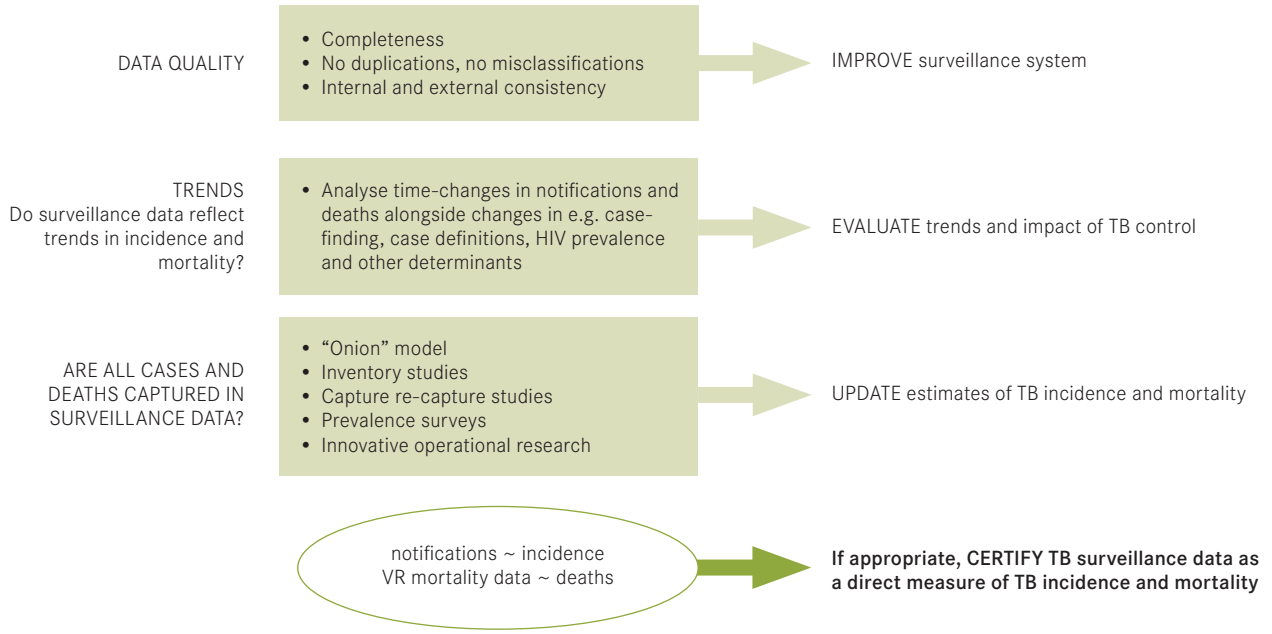
When the 2010 global report was published, 78 countries had been covered by regional or country workshops. Between November 2010 and July 2011, a further 17 countries in the African Region as well as India were covered, and a national-level workshop was held in China as follow-up to a regional workshop held in June 2010. Major revisions were made for most African countries (**Box 2.2**); these explain why the global estimates of cases (as well as deaths) that appear in this report – not only for 2010 compared with 2009, but also for the time-series dating back to 1990 – are lower than those published in previous reports. For countries not covered in workshops, estimates are based on extending previous time-series (see **Annex 1** for details).

In 2010, there were an estimated 8.8 million incident cases of TB (range, 8.5 million–9.2 million) globally, equivalent to 128 cases per 100 000 population (**Table 2.1**, **Table 2.2**, **Figure 2.3**). Most of the estimated number of cases in 2010 occurred in Asia (59%) and Africa (26%);[1] smaller proportions of cases occurred in the Eastern Mediterranean Region (7%), the European Region (5%) and the Region of the Americas (3%). The 22 HBCs that have been given highest priority at the global level since 2000 (listed in **Table 2.1** and **Table 2.2**) accounted for 81%

[1] Asia refers to the WHO regions of South-East Asia and the Western Pacific. Africa means the WHO African Region.

FIGURE 2.2

Framework for assessment of TB surveillance data (notification and vital registration data)



BOX 2.2

Revision of estimates of the burden of disease caused by TB in African countries

This report includes improved estimates of TB incidence, prevalence and mortality for countries in the African Region, following consultations with representatives from 17 countries during a five-day workshop held in Zimbabwe in December 2010. It was the first such workshop held in the African region for more than 10 years. In the interim, country missions were used to review and update estimates for Kenya (in 2006) and the United Republic of Tanzania (in 2009). Participants at the workshop represented the following countries: Botswana, Burkina Faso, Burundi, Côte d'Ivoire, the Democratic Republic of the Congo, Ethiopia, Ghana, Kenya, Malawi, Mali, Mozambique, Namibia, Nigeria, Rwanda, Uganda, Zambia and Zimbabwe.

Before the workshop, estimates of TB incidence were mostly based on assessments of the fraction of incident cases captured in notification data in the late 1990s. With the analysis of detailed national and sub-national surveillance data undertaken in the workshop, previous assumptions were found to be overestimating cases (and in turn, prevalence and mortality). Estimates of the proportion of cases being diagnosed and reported to national TB control programmes (NTPs) were heavily revised, mostly upwards; that is, fewer incident cases were assessed as being missed by NTPs. Following the workshop, the number of incident cases in the African Region was estimated at 2.3 million in 2010 (range, 2.1 million–2.5 million) and the number of deaths caused by TB (including those among HIV-positive people) was estimated at 254 000 (range, 227 000–282 000).

As with previous workshops in other regions, considerable attention was also given to assessments of surveillance systems. Recommendations for strengthening surveillance to move towards the ultimate goal of directly measuring cases and deaths from notification and VR data were defined.

A full report of the workshop in Zimbabwe can be found at:
www.who.int/tb/advisory_bodies/impact_measurement_taskforce/meetings

of all estimated cases worldwide. The five countries with the largest number of incident cases in 2010 were India (2.0 million–2.5 million), China (0.9 million–1.2 million), South Africa (0.40 million–0.59 million), Indonesia (0.37 million–0.54 million) and Pakistan (0.33 million–0.48 million). India alone accounted for an estimated one quarter (26%) of all TB cases worldwide, and China and India combined accounted for 38%.

Of the 8.8 million incident cases in 2010, 1.0 million–1.2 million (12–14%) were among people living with HIV, with a best estimate of 1.1 million (13%) (**Table 2.1**). The proportion of TB cases coinfected with HIV is highest in countries in the African Region (**Figure 2.4**); overall, the African Region accounted for 82% of TB cases among people living with HIV.

Globally, incidence rates fell slowly from 1990 to around 1997, and then increased up to around 2001 as the number of TB cases in Africa was driven upwards by

TABLE 2.1

Estimated epidemiological burden of TB, 2010. Numbers in thousands[a]

	POPULATION	MORTALITY[b]			PREVALENCE			INCIDENCE			HIV-POSITIVE INCIDENT TB CASES		
		BEST[c]	LOW	HIGH	BEST	LOW	HIGH	BEST	LOW	HIGH	BEST	LOW	HIGH
Afghanistan	31 412	12	8.6	16	110	51	180	59	49	71	–	–	–
Bangladesh	148 692	64	47	85	610	280	1 000	330	270	400	0.7	0.3	1.1
Brazil	194 946	5.0	3.1	8.3	92	34	160	85	70	100	18	15	22
Cambodia	14 138	8.6	6.2	12	93	42	150	62	53	72	4.0	3.4	4.7
China	1 341 335	54	52	56	1 500	1 300	1 700	1 000	910	1 200	18	10	28
DR Congo	65 966	36	27	45	350	160	560	220	190	250	18	13	24
Ethiopia	82 950	29	23	35	330	140	520	220	200	230	–	–	–
India[d]	1 224 614	320	210	470	3 100	2 000	4 600	2 300	2 000	2 500	110	75	160
Indonesia	239 871	64	42	91	690	300	1 200	450	370	540	18	9.9	29
Kenya	40 513	6.9	4.9	9.4	110	49	180	120	120	130	50	45	55
Mozambique	23 391	11	7.0	17	110	54	200	130	87	170	77	53	110
Myanmar	47 963	20	12	31	250	180	310	180	160	210	37	21	57
Nigeria	158 423	33	11	68	320	110	690	210	99	360	51	25	87
Pakistan	173 593	58	39	84	630	270	1 100	400	330	480	1.2	0.7	1.9
Philippines	93 261	31	21	43	470	410	530	260	210	310	1.0	0.5	1.8
Russian Federation	142 958	26	16	42	190	70	330	150	130	180	8.1	6.8	9.4
South Africa	50 133	25	16	38	400	180	630	490	400	590	300	240	350
Thailand	69 122	11	7.0	16	130	55	210	94	78	110	15	13	18
Uganda	33 425	5.1	3.3	7.3	64	32	100	70	56	85	38	30	46
UR Tanzania	44 841	5.8	4.7	6.9	82	39	130	79	75	85	30	28	32
Viet Nam	87 848	29	19	43	290	130	510	180	130	220	7.6	4.6	11
Zimbabwe	12 571	3.4	2.1	5.1	51	23	80	80	61	100	60	47	76
High-burden countries	**4 321 967**	**860**	**730**	**1 000**	**10 000**	**8 500**	**12 000**	**7 200**	**6 800**	**7 500**	**860**	**780**	**950**
AFR	836 970	250	220	280	2 800	2 300	3 300	2 300	2 100	2 500	900	820	980
AMR	933 447	20	17	23	330	260	410	270	250	280	35	31	38
EMR	596 747	95	74	120	1 000	670	1 500	650	580	730	12	9.8	15
EUR	896 480	61	48	75	560	430	720	420	390	450	20	19	22
SEAR	1 807 594	500	370	640	5 000	3 700	6 500	3 500	3 200	3 700	190	140	230
WPR	1 798 335	130	120	150	2 500	2 200	2 800	1 700	1 500	1 800	35	26	45
Global	**6 869 573**	**1 100**	**920**	**1 200**	**12 000**	**11 000**	**14 000**	**8 800**	**8 500**	**9 200**	**1 100**	**1 000**	**1 200**

– indicates no estimate available.

[a] Numbers for mortality, prevalence and incidence shown to two significant figures.

[b] Mortality excludes deaths among HIV-positive TB cases. Deaths among HIV-positive TB cases are classified as HIV deaths according to ICD-10.

[c] Best, low and high indicate the point estimate and lower and upper bounds of the 95% uncertainty interval.

[d] Estimates for India have not yet been officially approved by the Ministry of Health & Family Welfare, Government of India and should therefore be considered provisional.

the HIV epidemic (**Figure 2.5**). Since 2002, the incidence rate has fallen at around 1.3% per year and if this trend is sustained, MDG Target 6.c will be achieved. It should be highlighted that in previous reports in this series, incidence rates were estimated to have peaked in 2004; this has been revised following the major review of estimates of TB cases and deaths in African countries in December 2010 (**Box 2.2**). The absolute number of incident cases has also started to fall very slowly since 2006, when the decline in the incidence rate (per 100 000 population) started to exceed the rate of growth in the world's population.

Incidence rates are declining in all of WHO's six regions (**Figure 2.6**). The rate of decline varies from less than 1% per year in the Eastern Mediterranean Region to 1.8% per year in the African Region and 3.7% per year in the Region of the Americas. Incidence rates peaked around the mid-1990s in the Eastern Mediterranean Region, around 2000 in the European and South-East Asia regions and around 2004 in the African Region. The incidence rate has been declining since 1990 in the Region of the Americas and the Western Pacific Region.

The latest assessment for the 22 HBCs suggests that incidence rates are falling in 10 countries, approximately stable in 11 countries and increasing slowly in South Africa (**Figure 2.7**). Estimates of TB incidence have wide uncertainty intervals in Mozambique, Nigeria and Uganda; the prevalence surveys planned in these countries

TABLE 2.2

Estimated epidemiological burden of TB, 2010. Rates per 100 000 population except where indicated

	POPULATION (THOUSANDS)	MORTALITY[a]			PREVALENCE			INCIDENCE			HIV PREVALENCE IN INCIDENT TB CASES (%)		
		BEST[b]	LOW	HIGH	BEST	LOW	HIGH	BEST	LOW	HIGH	BEST	LOW	HIGH
Afghanistan	31 412	38	27	50	352	161	578	189	155	226	–	–	–
Bangladesh	148 692	43	32	57	411	188	671	225	184	269	0.2	0.1	0.3
Brazil	194 946	2.6	1.6	4.3	47	17	80	43	36	51	23	23	23
Cambodia	14 138	61	44	82	660	296	1 070	437	373	506	6.6	6.3	6.8
China	1 341 335	4.1	3.9	4.2	108	93	123	78	68	88	1.7	1.0	2.8
DR Congo	65 966	54	41	69	535	250	850	327	281	376	8.2	6.0	11
Ethiopia	82 950	35	28	42	394	173	623	261	240	282	–	–	–
India[c]	1 224 614	26	17	39	256	161	373	185	167	205	5.0	3.3	7.1
Indonesia	239 871	27	18	38	289	123	484	189	155	226	4.0	2.3	6.4
Kenya	40 513	17	12	23	283	122	448	298	286	311	41	37	45
Mozambique	23 391	49	30	74	491	233	844	544	374	746	61	60	61
Myanmar	47 963	41	24	65	525	381	643	384	328	445	20	10	30
Nigeria	158 423	21	7.2	43	199	70	438	133	63	228	25	24	25
Pakistan	173 593	34	22	49	364	154	611	231	189	277	0.3	0.2	0.5
Philippines	93 261	33	22	46	502	438	566	275	226	329	0.4	0.2	0.7
Russian Federation	142 958	18	11	29	136	49	233	106	90	124	5.3	5.2	5.4
South Africa	50 133	50	31	75	795	364	1 260	981	806	1 170	60	60	61
Thailand	69 122	16	10	23	182	80	300	137	112	163	16	16	17
Uganda	33 425	15	10	22	193	95	306	209	168	254	54	53	55
UR Tanzania	44 841	13	11	15	183	87	281	177	166	189	38	38	39
Viet Nam	87 848	34	21	49	334	147	576	199	152	253	4.3	2.9	6.2
Zimbabwe	12 571	27	17	40	402	185	639	633	486	799	75	75	76
High-burden countries	**4 321 967**	**20**	**17**	**23**	**231**	**196**	**268**	**166**	**158**	**174**	**12**	**11**	**14**
AFR	836 970	30	26	34	332	277	392	276	256	296	39	35	44
AMR	933 447	2.2	1.9	2.5	36	28	44	29	27	30	13	12	15
EMR	596 747	16	12	20	173	112	246	109	97	122	2.2	1.7	2.8
EUR	896 480	6.8	5.4	8.3	63	47	80	47	44	50	5.0	4.4	5.5
SEAR	1 807 594	27	21	35	278	206	360	193	179	207	5.4	4.1	6.9
WPR	1 798 335	7.5	6.6	8.5	139	124	156	93	85	102	2.1	1.5	2.7
Global	**6 869 573**	**15**	**13**	**18**	**178**	**156**	**201**	**128**	**123**	**133**	**13**	**12**	**14**

– indicates no estimate available.

[a] Mortality excludes deaths among HIV-positive TB cases. Deaths among HIV-positive TB cases are classified as HIV deaths according to ICD-10.

[b] Best, low and high indicate the point estimate and lower and upper bounds of the 95% uncertainty interval.

[c] Estimates for India have not yet been officially approved by the Ministry of Health & Family Welfare, Government of India and should therefore be considered provisional.

should help to improve estimates of disease burden (see **section 2.5**).

Estimates of the number of cases broken down by age and sex have been prepared by an expert group as part of an update to the Global Burden of Disease (GBD) study.[1] These indicate that women[2] account for an estimated 3.2 million incident cases (range, 3.0 million–3.5 million), equivalent to 36% of all cases. Estimates of the numbers of TB cases among women and children need to be improved through more reporting and more analysis of notification data disaggregated by age and sex.

2.2 Estimates of the prevalence of TB

The prevalence of TB can be directly measured in nationwide population-based surveys; WHO has recently published comprehensive theoretical and practical guidance on how to design, implement, analyse and report such surveys.[3] When repeat surveys are conducted, trends in TB prevalence can be directly measured as well. If sur-

[1] The expert group is convened by the WHO Global Task Force on TB Impact Measurement. The GBD study is an update to Lopez AD et al. *Global burden of disease and risk factors*. New York, Oxford University Press and The World Bank, 2006.

[2] Defined as females aged ≥15 years old.

[3] *TB prevalence surveys: a handbook*. Geneva, World Health Organization, 2011 (WHO/HTM/TB/2010.17).

FIGURE 2.3

Estimated TB incidence rates, 2010

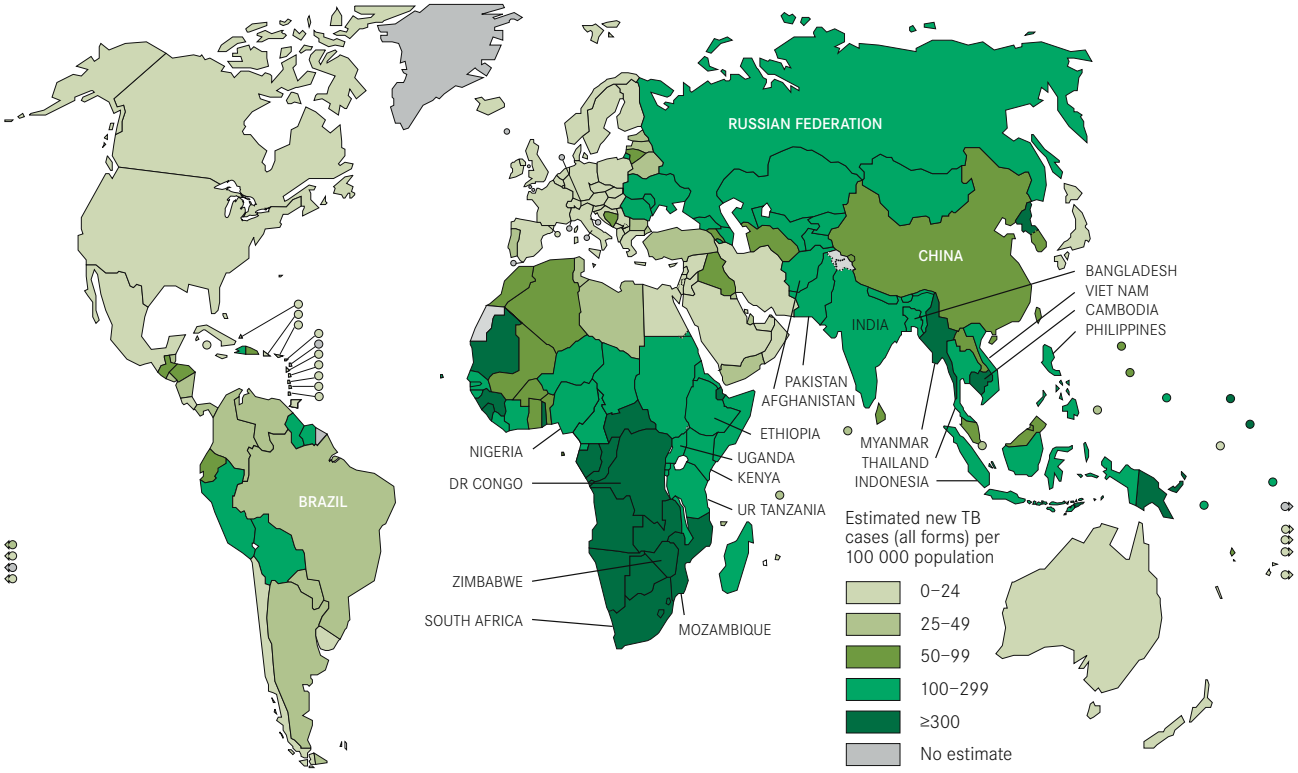


FIGURE 2.4

Estimated HIV prevalence in new TB cases, 2010

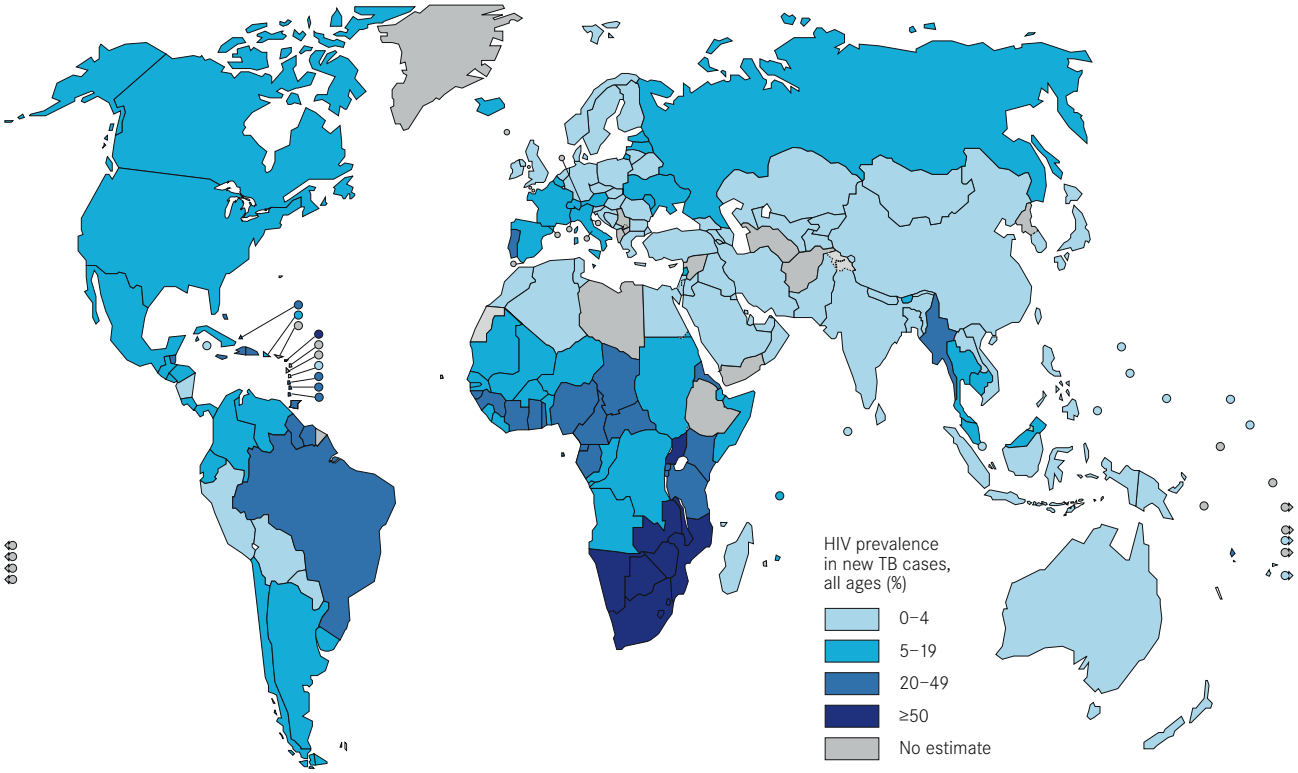


FIGURE 2.5

Global trends in estimated rates of TB incidence, prevalence and mortality. Left: Global trends in estimated incidence rate including HIV-positive TB (green) and estimated incidence rate of HIV-positive TB (red). Centre and right: Trends in estimated TB prevalence and mortality rates 1990–2010 and forecast TB prevalence and mortality rates 2011–2015. The horizontal dashed lines represent the Stop TB Partnership targets of a 50% reduction in prevalence and mortality rates by 2015 compared with 1990. Shaded areas represent uncertainty bands. Mortality excludes TB deaths among HIV-positive people.

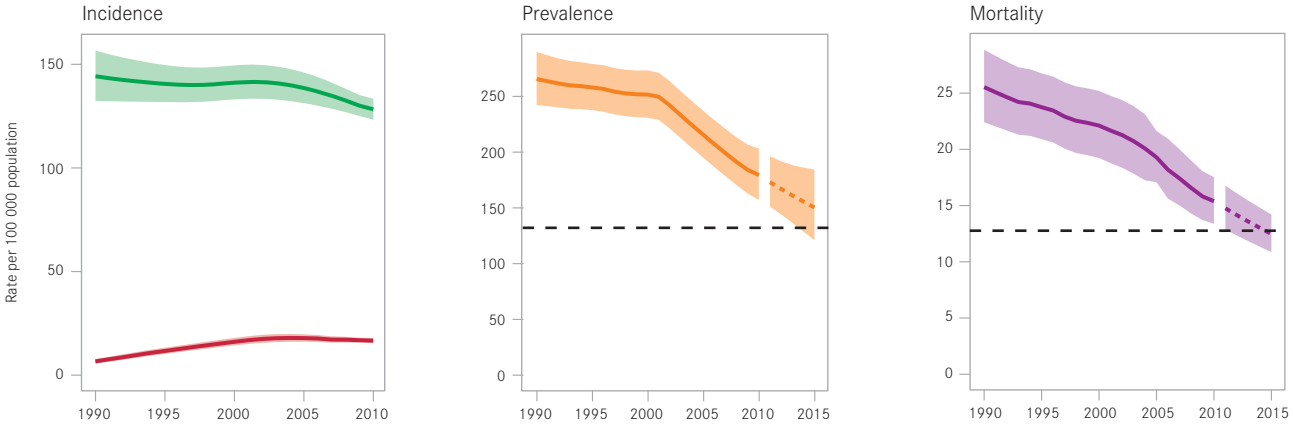


FIGURE 2.6

Estimated TB incidence rates by WHO region, 1990–2010. Regional trends in estimated TB incidence rates (green) and estimated incidence rates of HIV-positive TB (red). Shaded areas represent uncertainty bands.

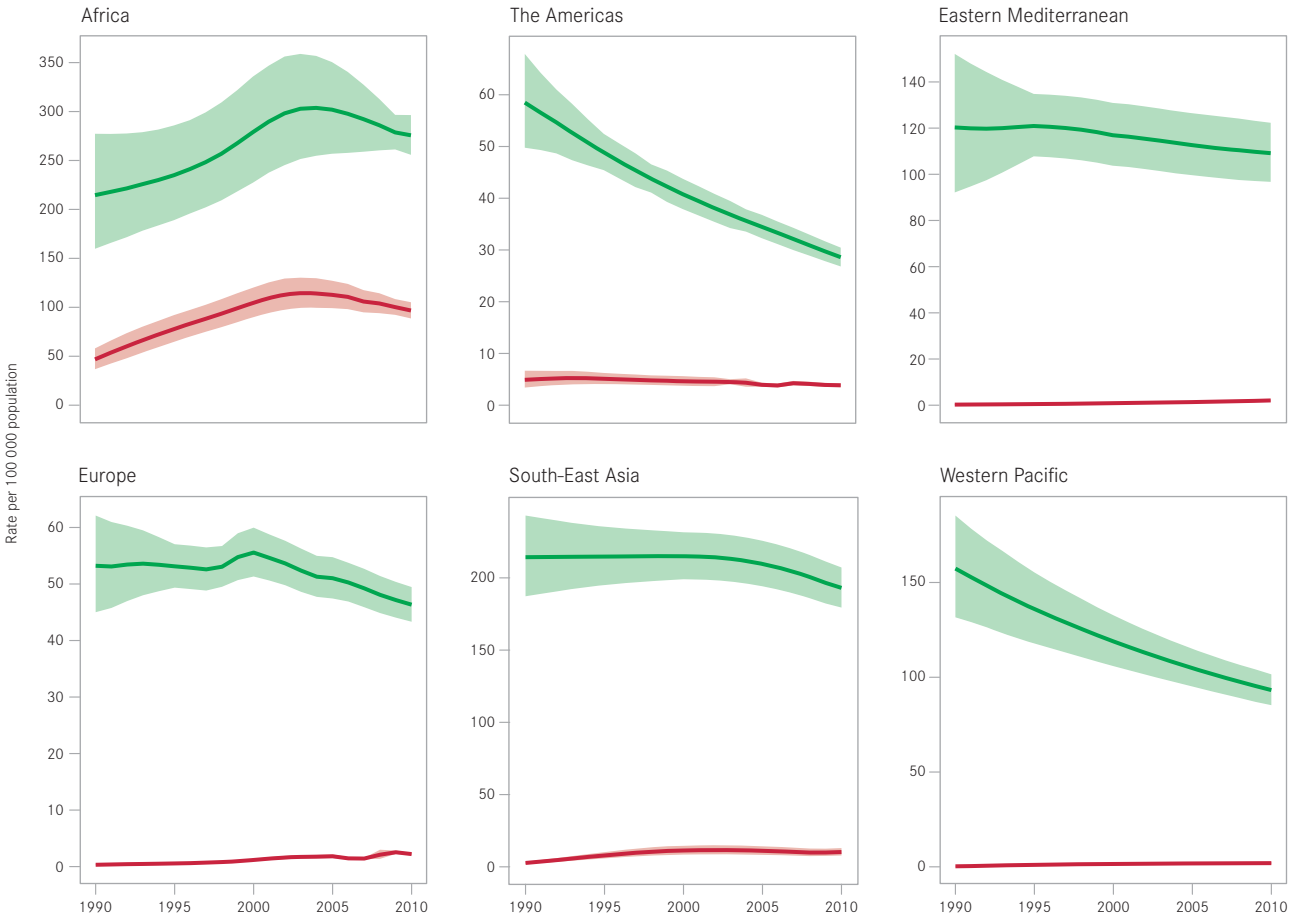
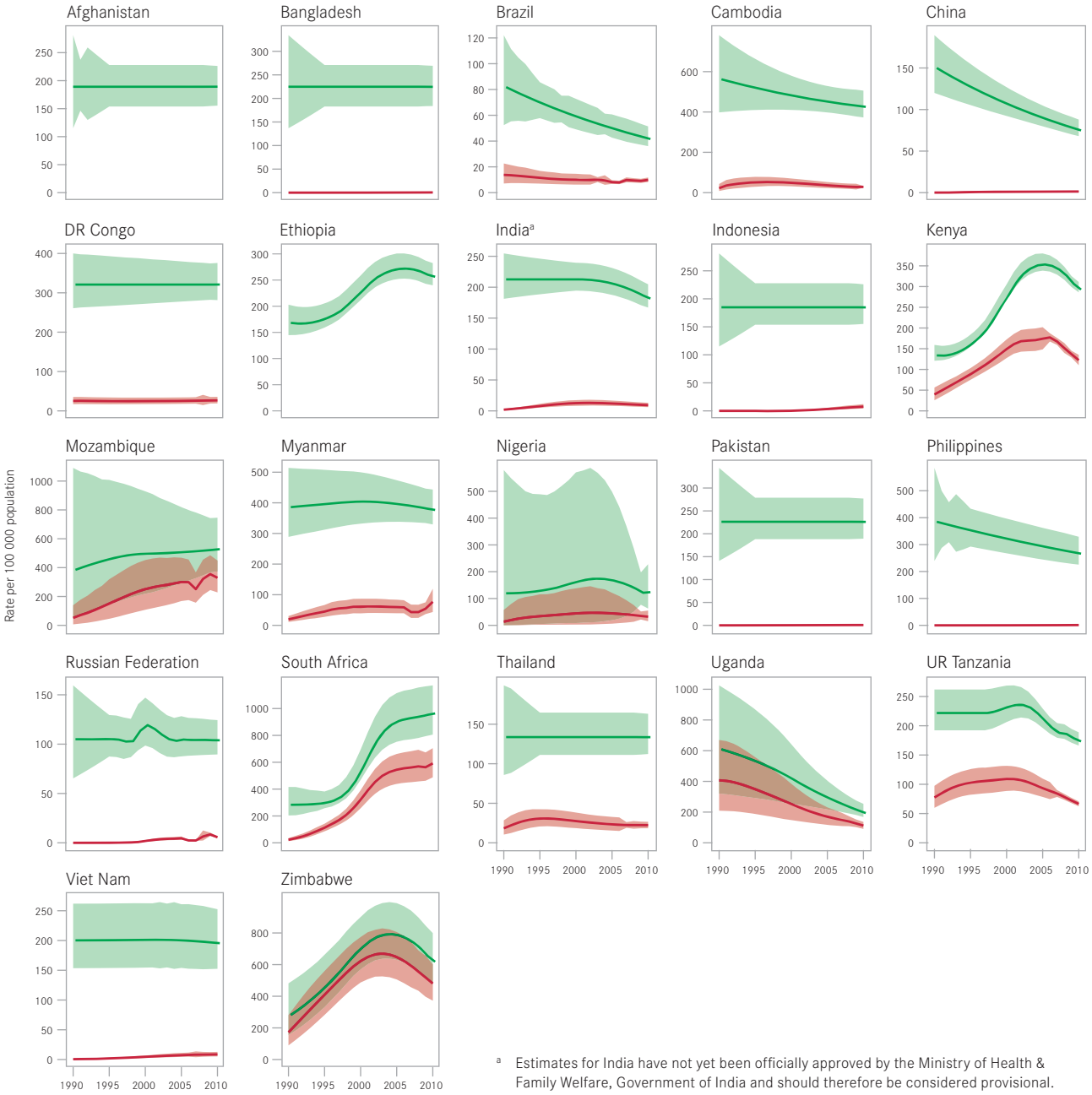


FIGURE 2.7

Estimated TB incidence rates, 22 high-burden countries, 1990–2010. Trends in estimated TB incidence rates (green) and estimated incidence rates of HIV-positive TB (red). Shaded areas represent uncertainty bands.



[a] Estimates for India have not yet been officially approved by the Ministry of Health & Family Welfare, Government of India and should therefore be considered provisional.

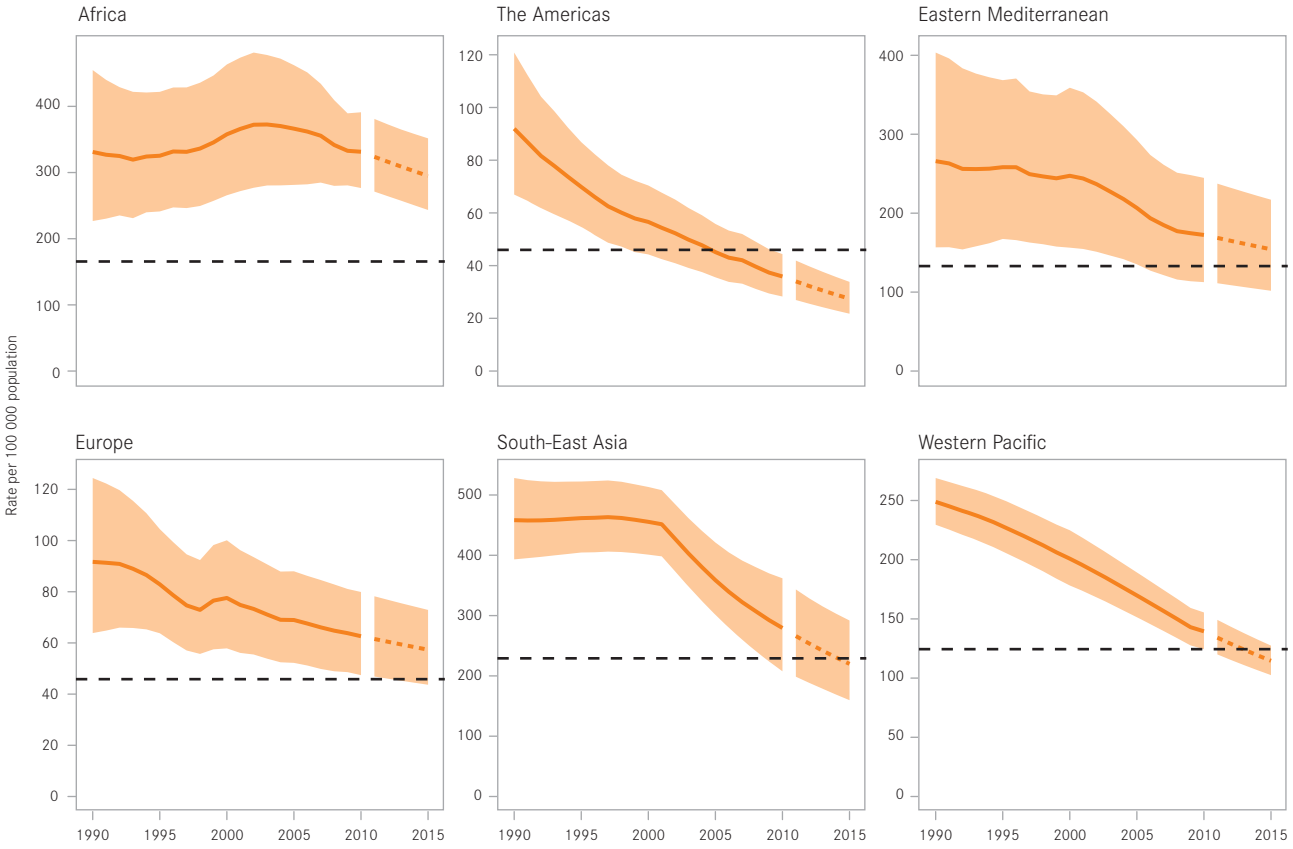
vey data are not available, prevalence can be indirectly estimated as the product of incidence and the average duration of disease, but with considerable uncertainty (**Annex 1**). Although the data available from prevalence surveys allow for a robust assessment of trends in the Western Pacific Region (especially in China and the Philippines) and are becoming more widely available for countries with a high burden of TB (see **section 2.5**), TB prevalence can be estimated only indirectly in most countries.

There were an estimated 12.0 million prevalent cases (range, 11.0 million–14.0 million) of TB in 2010 (**Table 2.1**). This is equivalent to 178 cases per 100 000 population (**Table 2.2**). Globally, prevalence rates have been falling since 1990, with a faster decline after 1997. However, current forecasts suggest that the Stop TB Partnership's target of halving TB prevalence by 2015 compared with a baseline of 1990 will not be met (**Figure 2.5**). Regionally, prevalence rates are declining in all of WHO's six regions (**Figure 2.8**). The Region of the Americas has halved the 1990 level of TB prevalence already, well in advance of the target year of 2015, and the Western Pacific Region is close to doing so. Reductions in TB prevalence in the Eastern Mediterranean, European and South-East Asia

FIGURE 2.8

Trends in estimated TB prevalence rates 1990–2010 and forecast TB prevalence rates 2011–2015, by WHO region

Shaded areas represent uncertainty bands. The horizontal dashed lines represent the Stop TB Partnership target of a 50% reduction in the prevalence rate by 2015 compared with 1990. The other dashed lines show projections up to 2015.



regions have been considerable since 1990, and appear to have accelerated since 2000. Nonetheless, current forecasts suggest that the 2015 target will not be reached. In the African Region, estimates of TB prevalence rates are far from the target level, and halving the 1990 rate by 2015 appears unlikely.

2.3 Estimates of deaths caused by TB

Mortality caused by TB can be directly measured if a national VR system of high coverage with accurate coding of causes of death according to the latest revision of the international classification of diseases (ICD-10) is in place. Sample VR systems can provide an interim solution, and mortality surveys can sometimes be used to obtain direct measurements of TB deaths in countries with no VR system. In the absence of VR systems or mortality surveys, TB mortality can be estimated as the product of TB incidence and the case fatality rate.

Until 2008, WHO estimates of TB mortality used VR data for only three countries. This was dramatically improved to 89 countries in 2009, although most of these countries were in the European Region and the Region of the Americas, which account for only 8% of the world's TB cases. The use of sample VR data from China and survey data from India for the first time in 2011 has enabled a further major improvement to estimates of TB mortality in this report (**Box 2.3**). The total of 91 countries for which estimates of TB deaths are now based on direct measurements represent 46% of the deaths caused by TB in 2010.

In 2010, an estimated 1.1 million deaths (range, 0.9 million–1.2 million) occurred among HIV-negative cases of TB (**Table 2.1**), including 0.32 million deaths (range, 0.20 million–0.44 million) among women. This was equivalent to 15 deaths per 100 000 population. In addition, there were an estimated 0.35 million deaths (range, 0.32 million–0.39 million) among incident TB cases that were HIV-positive (data not shown); these deaths are classified as HIV deaths in ICD-10.[1] Thus in total, approximately 1.4 million people (range, 1.2 million–1.5 million) died of TB in 2010. This estimate is considerably lower than the estimates of 1.3 million TB deaths among HIV-negative people and 0.4 million deaths from TB among HIV-positive people that were published in 2010,[2] following a major revision of esti-

[1] *International statistical classification of diseases and related health problems, 10th revision (ICD-10)*, 2nd ed. Geneva, World Health Organization, 2007.

[2] *Global tuberculosis control 2010*. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.7).

BOX 2.3

Estimates of TB mortality are increasingly based on direct measurements

Estimates of TB mortality published in this report are much improved compared with those of previous years, following a major increase in the availability and use of direct measurements from national or sample vital registration (VR) systems as well as mortality surveys. In the 2010 global report, 602 country-year data points from 89 countries (including 3 high-burden countries – Brazil, the Russian Federation and the Philippines) were used. In this 2011 report, direct measurements from China and India have been used for the first time. In China, the data come from a sample VR system covering all 31 provinces. In India, data from 6 mortality surveys were pooled to obtain a national estimate for 2005, and to derive a complete time-series for 1990–2010. As a result, direct measurements of mortality from 91 countries with 720 country-year VR data points and 2 mortality survey data points were used; the proportion of global mortality due to TB that is measured directly has increased from 8% to 46%. Estimates for 2010 and trends since 1990 are now more robust, with narrower uncertainty intervals.

Deaths caused by TB in India were estimated at 408 000 in 2005 (range, 290 000–546 000), higher than the previous indirect estimate of 291 000 (range, 177 000–437 000). In China, TB deaths were previously estimated at 155 000 (99 000–226 000) in 2009; the updated estimate is 55 000 (53 000–57 000).

Measurements of TB mortality among HIV-positive people from VR data remain scarce and are often unreliable. HIV deaths may be miscoded as TB deaths, and TB deaths among HIV-positive people may be impossible to quantify because TB is only recorded as a contributory cause of death. About one third of countries submitting aggregated VR data on causes of death to WHO do not report data on contributory causes. Estimates of TB mortality in HIV-infected individuals thus remain highly uncertain.

Further efforts to implement national or sample VR systems are essential to strengthen TB surveillance and improve assessment of progress towards the 2015 global target for reductions in TB mortality.

BOX 2.4

Parental deaths caused by TB have created large numbers of orphans

Globally in 2009, there were an estimated 14 million (range, 13–15 million) children aged <15 years who were orphans as a consequence of a parental death caused by HIV/AIDS.[1] Of these children, an estimated 3.1 million (range, 2.7–3.5 million) had been orphaned as a result of a parental death from HIV-associated TB. There were also an estimated 6.5 million (range, 5.5–7.7 million) children who were orphans as a result of a parental death caused by TB among people who were HIV-negative.

In total in 2009, there were an estimated 9.7 million (range, 8.5–11 million) children who were orphans as a result of losing at least one of their parents to TB (including HIV-associated TB).

[1] UNAIDS. **www.unaids.org/en/dataanalysis/epidemiology**, accessed 27 June 2011.

mates of the numbers of TB cases and deaths in African countries (**Box 2.2**).

The number of TB deaths per 100 000 population among HIV-negative people plus the estimated number of TB deaths among HIV-positive people equates to a best estimate of 20 deaths per 100 000 population.

Globally, mortality rates (excluding deaths among HIV-positive people)[1] have fallen by more than one-third since 1990, and the current forecast suggests that the Stop TB Partnership's target of a 50% reduction by 2015 compared with a baseline of 1990 will be achieved (**Figure 2.5**). Mortality rates are also declining in all of WHO's six regions (**Figure 2.9**). The Region of the Americas and the Western Pacific Region halved the 1990 level of mortality by 2000 and 2003 respectively, well in advance of the target year of 2015. The Eastern Mediterranean and European regions appear to have halved the 1990 level of mortality by 2010, and the South-East Asia Region is on track to reach the target by 2015. It is only in the African Region that the target of halving mortality rates by 2015 looks out of reach.

Among the 22 HBCs, mortality rates appear to be falling with the possible exception of Afghanistan (**Figure 2.10**). Even allowing for uncertainty in the estimates, five countries have reached the target of halving the 1990 mortality rate by 2010 (Brazil, Cambodia, China, Uganda and the United Republic of Tanzania), and several other countries have a good chance of achieving the target by 2015.

[1] Trends in TB mortality rates are restricted to TB deaths among HIV-negative people, given that TB deaths among HIV-positive people are classified as HIV deaths in ICD-10.

BOX 2.5

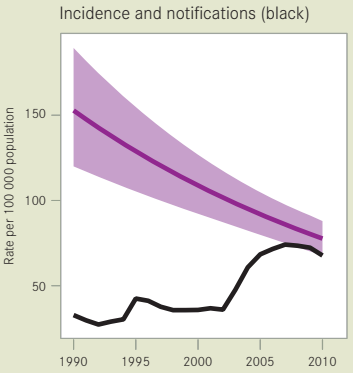
China has dramatically reduced the burden of disease caused by TB

The past 20 years have seen major efforts to reduce the burden of TB in China and to measure trends to demonstrate impact. In the 1990s, a World Bank loan was used to fund the introduction and expansion of DOTS in 13 provinces of the country; this was followed by nationwide coverage. After the SARS [severe acute respiratory syndrome] epidemic in 2003, surveillance of TB cases was strengthened as part of wider improvements to surveillance of all infectious diseases, and reporting of cases and treatment outcomes from all providers – notably TB dispensaries – improved dramatically. National prevalence surveys were undertaken in 1990, 2000 and 2010. Following discussions with WHO during an epidemiology workshop for countries in the Western Pacific Region in June 2010, data on TB deaths recorded in a sample vital registration (VR) system covering all 31 provinces were analysed for the first time.

In June 2011, a workshop to review and update estimates of TB cases and deaths based on the new data was hosted by the Chinese Centers for Disease Control in Beijing. A team from WHO participated in this workshop. The main conclusions were that prevalence was halved between 1990 and 2010, mortality rates fell by almost 80% between 1990 and 2010 and that incidence rates have fallen by 3.4% per year since 1990. Further details are provided below.

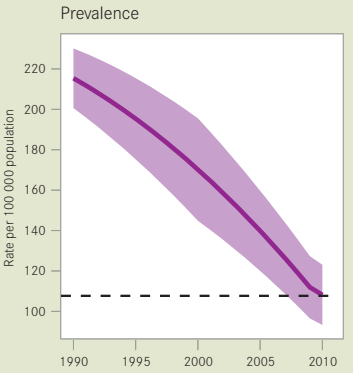
TB prevalence

National surveys found a prevalence rate of bacteriologically-confirmed pulmonary TB of 177 (165–189) per 100 000 population (all ages) in 1990, 160 (142–177) per 100 000 population (all ages) in 2000 and 119 (113–135) per 100 000 population aged ≥15 years in 2010. Adjusting for age and accounting for extrapulmonary TB, the estimated overall prevalence rate per 100 000 population fell from 215 (200–230) per 100 000 population in 1990 to 108 (93–123) per 100 000 population in 2010.[1] The rate of decline was 2.2% per year between 1990 and 2000, and 4.7% per year between 2000 and 2010. These estimated reductions in TB prevalence are likely to be conservative, because screening methods were improved over time (for example, full chest X-rays were taken in 2010 compared with the use of less sensitive fluoroscopy in 2000) and thus cases were more likely to be detected in successive surveys.



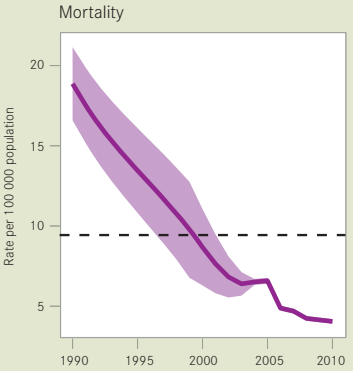
TB mortality

Data on TB mortality are available from two sources. The first is a series of two national mortality surveys conducted in 1989 and 1999. The second is a sample VR system in which mortality data are recorded for 161 counties with a population of about 76 million representing all 31 provinces of China. Standardized coding of causes of deaths has been in place since 2004, using a national coding scheme derived from ICD-10. The data from the surveys and the sample VR system are remarkably consistent. The ratio of TB deaths (excluding HIV) to TB notifications fell from 24% in 2000 to 6% in 2010, as a result of (i) a likely decline in case fatality rates associated with improvements in the quality of TB care and (ii) improved reporting of TB cases at the time of diagnosis, particularly after 2005 (see below). Overall, TB mortality has declined rapidly, at an average rate of 8.6% per year between 1990 and 2010.



TB incidence

If TB surveillance performs to very high standards, TB incidence is best measured from routine notification data. Since 2005, a web-based and mandatory TB reporting system has been fully operational and directly covers almost all health facilities in the country. In some remote areas where facilities are not linked directly to the system, reports are provided to the nearest facility that is linked to the system. In 2009, the TB surveillance system was assessed to capture close to 100% of all detected TB cases. When combined with measured trends in prevalence and mortality, incidence rates were estimated to have declined by 3.4% per year since 1990.



MDR-TB

Two sources of drug resistance surveillance (DRS) data are available: (i) data from surveys designed to measure the magnitude of drug resistance that were conducted among samples of notified TB cases in 10 provinces between 1995 and 2005 and at national level in 2007; and (ii) data from the TB prevalence surveys conducted in 2000 and 2010 in which all diagnosed culture-positive cases were tested for drug susceptibility. In the 2000 prevalence survey, 7.6% of culture-positive TB cases were found to have MDR strains (standard deviation (SD), 1.6%), compared with 5.4% (SD, 1.6%) in the 2010 prevalence survey. The difference is not statistically significant. However, the estimated number of prevalent MDR-TB cases in the general population, obtained from taking the product of TB prevalence and the observed proportion of prevalent cases with MDR-TB, fell from 164 000 (99 000–250 000) in 2000 to 78 000 (41 000–126 000) in 2010.

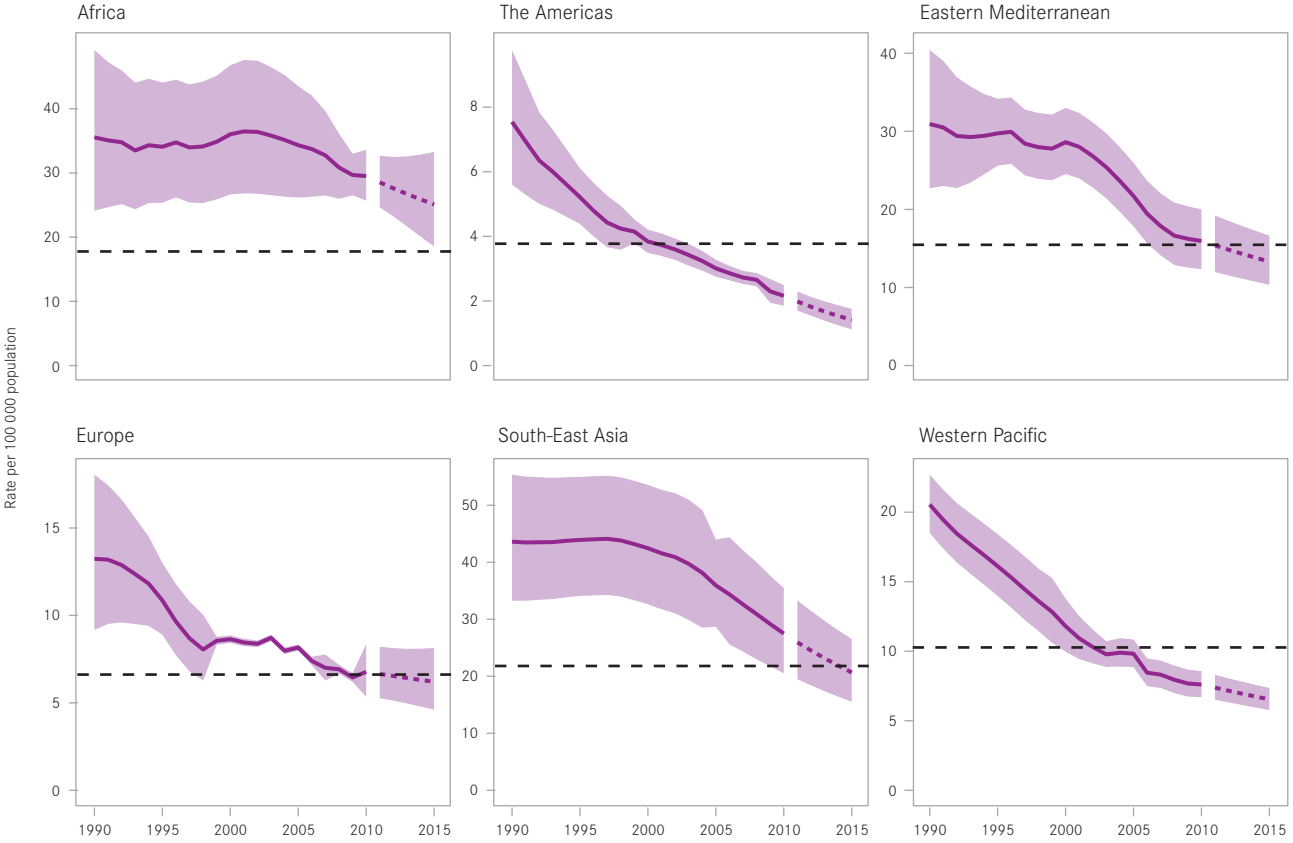
Trends in the proportion of notified cases that have MDR-TB in China cannot be established with confidence due to the highly heterogeneous trends across provinces in which surveys of drug resistance have been carried out. A second national drug resistance survey will provide a robust assessment of trends in the proportion of MDR-TB among notified cases.

[1] This is despite rapid aging of the population which, other things being equal, increases the burden of TB because TB is more common among adults. The proportion of children in the population fell from 28% in 1990 to 26% in 2000 and 20% in 2010.

FIGURE 2.9

Trends in estimated TB mortality rates 1990–2010 and forecast TB mortality rates 2011–2015, by WHO region

Estimated TB mortality excludes TB deaths among HIV-positive people. Shaded areas represent uncertainty bands.[a] The horizontal dashed lines represent the Stop TB Partnership target of a 50% reduction in the mortality rate by 2015 compared with 1990. The other dashed lines show projections up to 2015.



[a] The width of uncertainty bands narrows as the proportion of regional mortality estimated using vital registration data increases.

2.4 Estimates of the number of cases of MDR-TB

In previous reports in this series as well as WHO reports on drug-resistant TB specifically, estimates of the number of incident cases of MDR-TB have been presented.[1] For the first time in this report, estimates of the number of prevalent cases of MDR-TB are presented instead. The reasons are that MDR-TB is a chronic disease and without appropriate diagnosis and treatment for most of these cases (see **Chapter 3**), there are many more prevalent cases than incident cases; calculations of the number of prevalent cases of MDR-TB are more readily understood compared with the complex calculations needed to estimate the incidence of MDR-TB; and the number of prevalent cases of MDR-TB directly influences the active transmission of strains of MDR-TB.

The estimated number of prevalent cases of MDR-TB can be estimated at global level as the product of the estimated number of prevalent cases of TB and the best estimate of the proportion of notified TB patients[2] with MDR-TB at global level. In 2010, there were an estimated 650 000 cases of MDR-TB among the world's 12.0 million prevalent cases of TB. Estimates at country level are not presented for reasons explained in **Annex 1**. However, estimates of the proportion of new and retreatment cases that have MDR-TB are summarized in **Table 2.3**.

A recurring and important question is whether the number of MDR-TB cases is increasing, decreasing or stable. A reliable assessment of trends in MDR-TB requires data from Class A continuous surveillance[3] or data from periodic surveys of drug resistance that are designed, implemented and analysed according to WHO guidelines.[4] There has been substantial progress in the coverage of continuous surveillance and surveys of drug resistance (**Figure 2.11**). Unfortunately, progress is not yet sufficient to provide a definitive assessment of trends in MDR-TB globally or regionally (**Box 2.6**).

[1] In the 2010 WHO report on global TB control, it was estimated that there were 440 000 incident cases of MDR-TB in 2008.

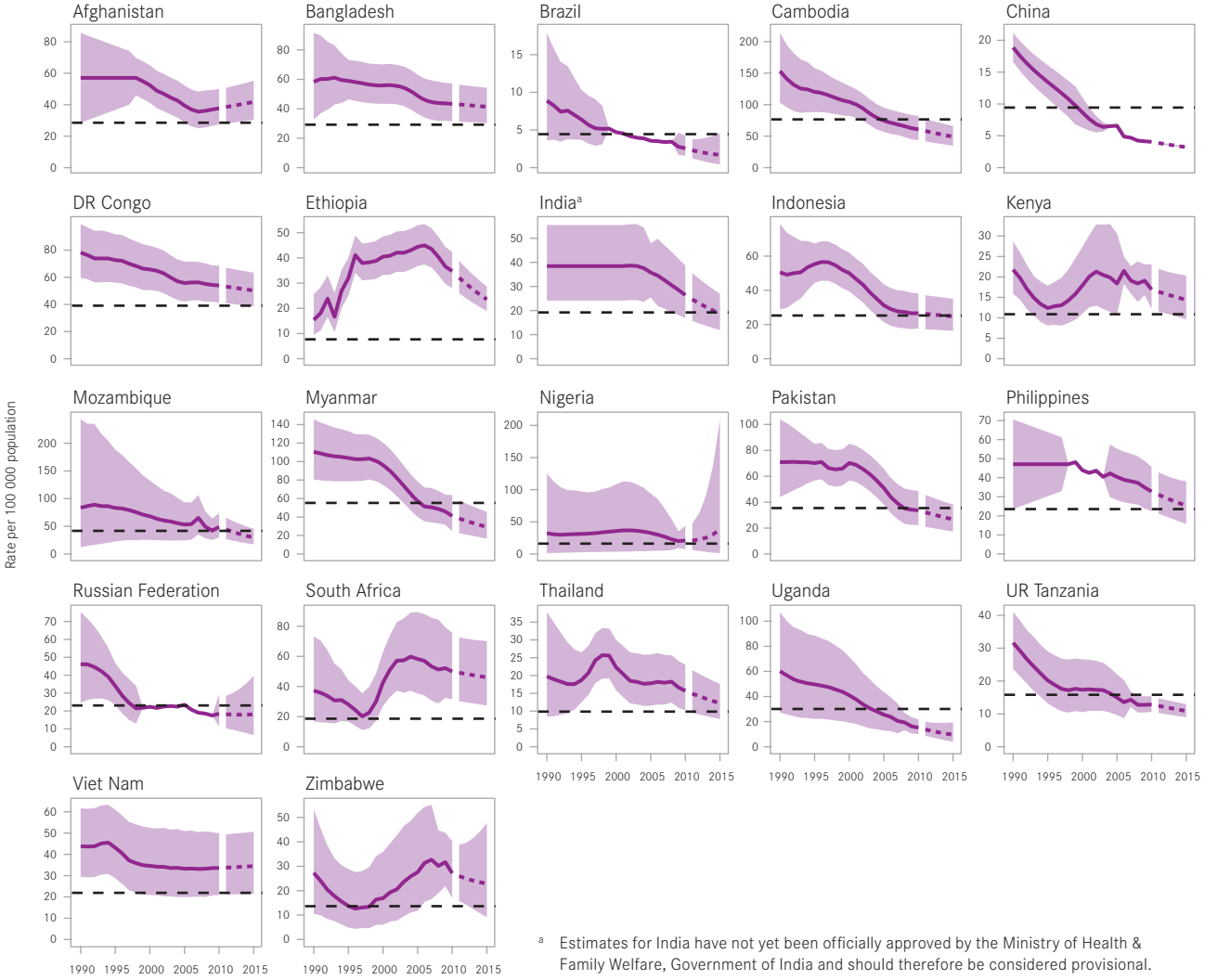
[2] This includes new and retreatment cases (see **Chapter 3** for definitions).

[3] Class A continuous surveillance refers to data from ongoing surveillance of drug resistance that are representative of the caseload of patients.

[4] *Guidelines for the surveillance of drug resistance in tuberculosis – 4th ed*. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2009.422).

FIGURE 2.10

Trends in estimated TB mortality rates 1990–2010 and forecast TB mortality rates 2011–2015, 22 high-burden countries
Estimated TB mortality excludes TB deaths among HIV-positive people. Shaded areas represent uncertainty bands. The horizontal dashed lines represent the Stop TB Partnership target of a 50% reduction in the mortality rate by 2015 compared with 1990. The other dashed lines show projections up to 2015.



[a] Estimates for India have not yet been officially approved by the Ministry of Health & Family Welfare, Government of India and should therefore be considered provisional.

2.5 Strengthening measurement of the burden of disease caused by TB: the WHO Global Task Force on TB Impact Measurement

The estimates of TB incidence, prevalence and mortality and their trend presented in sections 2.1–2.4 are based on the best available data and analytical methods. In 2009, methods were fully reviewed and updated, and between April 2009 and July 2011 consultations were held with 96 countries accounting for 89% of the world's TB cases. Nonetheless, there is considerable scope for further improvement. In this final section of the chapter the latest status of efforts to improve measurement of the burden of disease caused by TB, under the umbrella of the WHO Global Task Force on TB Impact Measurement, are described.

Established in mid-2006, the mandate of the WHO Global Task Force on TB Impact Measurement is to ensure the best possible assessment of progress towards achieving the 2015 global targets for reductions in the burden of disease caused by TB, to report on progress in the interim and to strengthen capacity for monitoring and evaluation at the country level. The Task Force includes representatives from leading technical and financial partners and countries with a high burden of TB.[1]

[1] Partners that are actively participating in the work of the Task Force include the Centers for Diseases Control (United States of America), the European Centre for Disease Prevention and Control, the Global Fund, the Health Protection Agency in the UK, the KNCV Tuberculosis Foundation, the London School of Hygiene and Tropical Medicine in the UK, the Research Institute for Tuberculosis in Japan, the Union and USAID. Many countries with a high burden of TB are engaged in the work of the Task Force.

TABLE 2.3

Estimated proportion of TB cases that have MDR-TB, 27 high MDR-TB burden countries and WHO regions

	ESTIMATED % OF NEW TB CASES WITH MDR-TB[a]	CONFIDENCE INTERVAL	ESTIMATED % OF RETREATMENT TB CASES WITH MDR-TB[a]	CONFIDENCE INTERVAL
Armenia	9.4	7.0–12	43	38–49
Azerbaijan	22	19–27	56	50–62
Bangladesh	*2.1*	*1.7–2.5*	28	25–32
Belarus	26	24–28	60	58–63
Bulgaria	2.0	1.1–3.2	24	18–32
China	5.7	4.6–7.1	26	22–30
DR Congo	*2.2*	*0.1–5.3*	*9.4*	*1.9–17*
Estonia	18	13–24	44	32–58
Ethiopia	1.6	0.9–2.8	12	5.6–21
Georgia	9.5	8.2–11	31	27–35
India	2.1	1.5–2.7	15	13–17
Indonesia	1.8	1.1–2.7	17	8.1–26
Kazakhstan	14	11–18	45	44–47
Kyrgyzstan	*14*	*12–17*	*39*	*35–43*
Latvia	10	8.0–13	24	16–33
Lithuania	11	8.8–13	52	47–57
Myanmar	4.2	3.1–5.6	10	6.9–14
Nigeria	*2.2*	*0.1–5.3*	*9.4*	*1.9–17*
Pakistan	*3.4*	*0.8–6.0*	*21*	*7.3–34*
Philippines	4.0	2.9–5.5	21	14–29
Republic of Moldova	19	17–22	65	62–68
Russian Federation	18	16–19	46	41–52
South Africa	1.8	1.4–2.3	6.7	5.4–8.2
Tajikistan	17	11–24	62	53–70
Ukraine	16	14–19	44	40–49
Uzbekistan	14	11–19	49	42–56
Viet Nam	2.7	2.0–3.7	19	14–25
High MDR-TB burden countries	**3.8**	**2.0–5.7**	**21**	**14–28**
AFR	1.9	0.6–3.3	9.4	3.0–16
AMR	2.1	0.7–3.4	12	3.8–19
EMR	3.4	0.9–5.9	21	7.5–34
EUR	12	8.6–16	37	33–41
SEAR	2.1	1.7–2.5	17	17–18
WPR	4.9	3.6–6.1	23	20–27
Global	**3.4**	**1.9–5.0**	**20**	**14–25**

[a] Best estimates are for the latest available year. Estimates in italics are based on regional data.

At its second meeting in December 2007, the Task Force defined three strategic areas of work:[1]

- strengthening surveillance towards the ultimate goal of direct measurement of incidence and mortality from notification and VR systems;
- conducting surveys of the prevalence of TB disease in a set of global focus countries that met epidemiological and other relevant criteria; and
- periodic review and updating of the methods used to translate surveillance and survey data into estimates of TB incidence, prevalence and mortality.

The third area of work is discussed in more detail in **Annex 1**. The following sections focus on the first two strategic areas of work. Full details of the Task Force's work are available on its web site.[2]

2.5.1 Strengthening surveillance

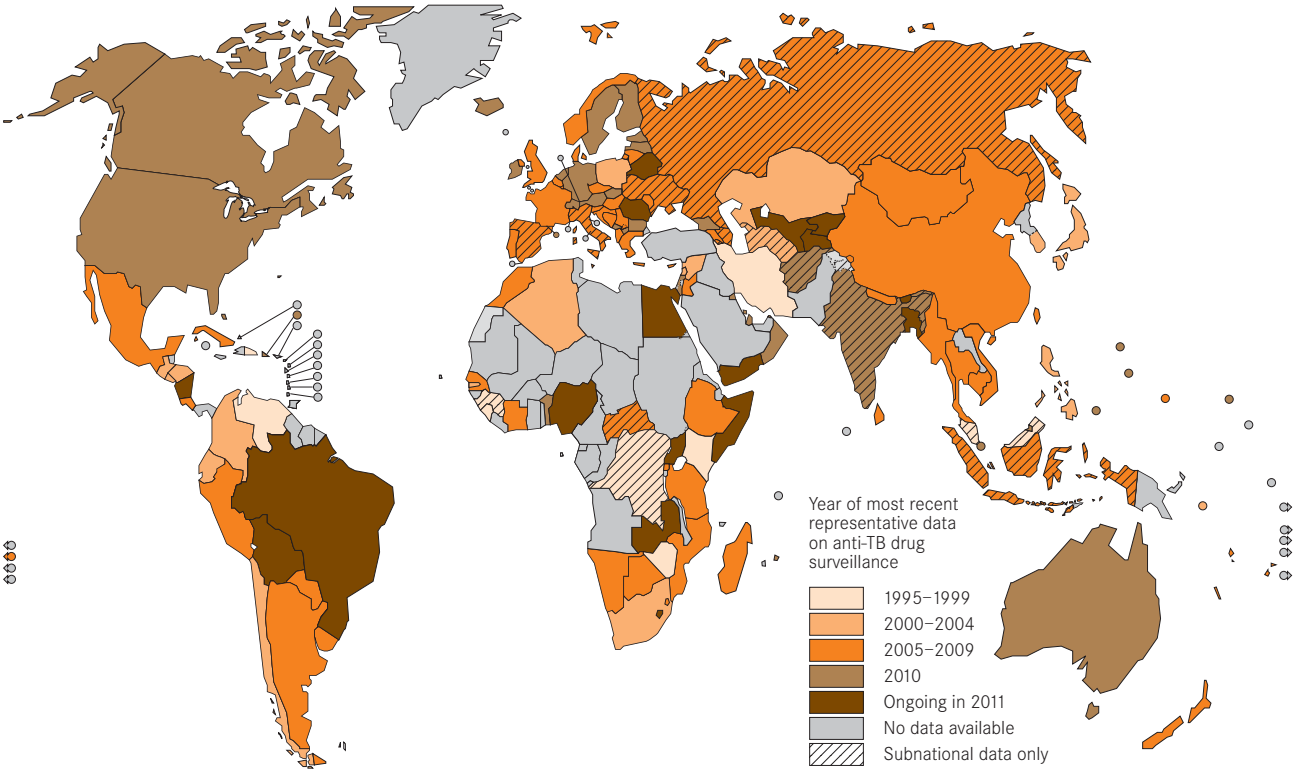
In 2008, the Task Force defined a conceptual framework for assessment of surveillance data, as a basis for updating estimates of the burden of disease caused by TB and for defining recommendations for how surveillance needs to

[1] *TB impact measurement: policy and recommendations for how to assess the epidemiological burden of TB and the impact of TB control*. Geneva, World Health Organization, 2009 (Stop TB policy paper no. 2; WHO/HTM/TB/2009.416).

[2] **www.who.int/tb/advisory_bodies/impact_measurement_taskforce**

FIGURE 2.11

Progress in global coverage of data on drug resistance, 1994–2010



be improved to reach the ultimate goal of direct measurement of TB cases and deaths from notification and VR data (**Figure 2.2**). Tools to implement it in practice were also developed, and used in the 96 country consultations illustrated in **Figure 2.1**.

Building on progress and lessons learnt in the past two years, the Task Force's four priorities in 2011 and 2012 are:

- defining standards and related benchmarks that must be met for notification and VR data to be considered a direct measurement of TB cases and deaths;
- development of guidance on inventory studies;
- development of guidance on patient or case-based electronic recording and reporting (ERR);
- institutionalizing assessments of trends in disease burden and related efforts to strengthen surveillance within the grant cycle of the Global Fund.

The mid-2011 version of the Task Force's framework for assessing surveillance data implicitly defines some of the standards required for notification and VR data to be considered a direct measurement of cases and deaths, respectively. For instance, notification data should be complete and without duplications or misclassifications. However, for some of the elements that are assessed, standards and benchmarks have not been explicitly defined. For example:

- the framework states that data should be internally and externally consistent, but it does not define what this means in practice;
- the framework states that no diagnosed cases should be missed by notification systems, but it does not specify how this should be demonstrated or at what level "under-reporting" would be considered acceptable (understanding that even the best surveillance systems do not capture all diagnosed cases);
- the framework states that TB deaths should be recorded in VR systems, but it does not specify the standards of coverage and accuracy in coding that must be met for VR data to be considered a direct measure of TB mortality.

In 2011, the Task Force convened an expert group to develop draft standards and benchmarks, and to field-test these in a variety of countries (including those with both strong and weaker surveillance systems). The aim is to reach agreement on a set of standards and benchmarks (and associated surveillance checklist) that can be used as a basis for efforts to strengthen surveillance in many countries (including all those with Global Fund grants – see below) as well as to determine the countries for which national surveillance data can already be used as a direct proxy for TB cases and deaths. By July 2011, field-testing was planned or underway in Brazil, China, Egypt, Kenya, Thailand, the UK and the United States of America.

BOX 2.6

Global and regional trends in MDR-TB

The Global Project on anti-tuberculosis drug resistance surveillance was launched in 1994 with two key objectives: (i) to estimate the magnitude of drug resistance; and (ii) to monitor trends in drug resistance. Since 1994, significant efforts to promote the monitoring of drug resistance through national surveys and continuous surveillance based on diagnostic testing have been made, with coordination at the global level by WHO. A total of six global reports on drug resistance and four editions of guidelines on the conduct of drug resistance surveys have been published. The coverage of data has improved considerably (**Figure 2.11**), and about 60% of countries now have at least one direct and representative measurement of the level of drug resistance among their TB patients. For some of these countries, data reported for successive years have allowed the analysis of trends.

The latest available data were used to conduct an analysis of trends in MDR-TB among new (previously untreated) TB patients for WHO regions and the world as a whole.[1] Data from 74 countries and territories with measurements for at least two years were used. There were on average 7 measurements for each of these 74 countries (range, 2–17 per country or territory). Missing country data were imputed from a pooled estimate for countries with similar epidemiological characteristics (these groups of countries are different from the WHO regions shown in the table), assuming that levels of MDR-TB as well as efforts to control MDR-TB were comparable among these countries. The annual change in the percentage of new TB patients with MDR-TB was calculated for each country or territory and then combined (with weighting according to the total number of new TB cases in the country) to produce regional and global estimates along with their uncertainty bounds. Results are presented in the table.

WHO REGION	ANNUAL CHANGE	ANNUAL CHANGE LOW ESTIMATE	ANNUAL CHANGE HIGH ESTIMATE
African	5.6%	−7.5%	18.7%
Americas	0.2%	−17.1%	17.5%
Eastern Mediterranean	−0.7%	−23.5%	22.0%
Europe	3.5%	−4.8%	11.9%
South-East Asia	−1.3%	−31.4%	28.8%
Western Pacific	−4.5%	−12.7%	3.8%
GLOBAL	**−0.3%**	**−14.7%**	**14.1%**

The best estimates suggest that levels of MDR-TB among new TB patients are relatively stable at global level and the Region of the Americas, falling in the Eastern Mediterranean, South-East Asia and Western Pacific regions, and increasing in the African and European Regions. However, there is considerable uncertainty as illustrated by the low and high estimates of rates of change. Despite rapid increases in the coverage of data on drug resistance, this means that a definitive answer to the question of whether the proportion of TB cases with MDR-TB is increasing, decreasing or stable at the global level cannot yet be provided.

Coverage of surveillance of anti-tuberculosis drug resistance must improve further and be considered an essential and fundamental element of TB surveillance. Recent technological advances now make the diagnosis of drug-resistant TB easier, quicker and more accessible (**Chapter 5**), and offer opportunities for rapid gains in global surveillance of drug-resistant TB. For this potential to be realized, anti-tuberculosis drug resistance surveillance must be prioritized by national TB control programmes and funding agencies.

[1] Data on the prevalence of MDR-TB among previously treated TB patients were too limited to allow assessment of trends.

Inventory studies with record-linkage are used to quantify the number of TB cases that are diagnosed but not recorded in notification data. They allow a much better estimation of TB incidence because they provide concrete evidence of the gap between notified cases and diagnosed cases (which may be especially big in countries with a large private sector), and under some circumstances allow estimation of the number of undiagnosed cases as well. They are also an essential part of the evidence needed to demonstrate that surveillance meets the standards required for notification data to be considered a direct measure of TB incidence. Unfortunately, inventory studies have been implemented in very few countries to date, and the lack of such studies is a major reason for uncertainty in estimates of TB incidence (**section 2.1**). Examples of countries where inventory studies have been implemented include the UK, the Netherlands and several countries in the Eastern Mediterranean Region (for example, Egypt, the Syrian Arab Republic and Yemen). To facilitate and encourage much wider implementation, WHO and its partners (notably the Centers for Disease Control, United States of America, and the Health Protection Agency in the UK) are developing a guide on how to design, implement, analyse and report on inventory studies. As this report went to press, the guide was due to be published by the end of 2011.

Assessment of various aspects of data quality is the first and most basic of the three major components of the Task Force's framework for assessing surveillance data (**Figure 2.2**). It was clear in all regional and country workshops that many aspects of data quality could not be assessed because of the absence of patient or case-based ERR systems. For example, it was not possible to assess whether notification data included duplicate entries or misclassified cases. Electronic datasets are also needed to facilitate analysis of data; for example, to check for

internal and external consistency. In 2011, WHO and its partners are developing a guide on ERR (**Box 2.7**).

The Global Fund is the major source of international funding for national TB control programmes (NTPs), amounting to US$ 0.5 billion in 2012 (**Chapter 4**). More than 100 low-income and middle-income countries receive grants for TB control from the Global Fund. In 2010, the Global Fund took steps to streamline several aspects of the grant cycle. These include transitioning from multiple grants within the same country to one consolidated grant, and periodically reviewing the performance of grants, including in-depth assessments of trends in the disease burden caused by TB using surveillance and survey data. These assessments of trends will in turn be linked to recommendations for strengthening surveillance; their implementation can be followed through the Global Fund's standard monitoring and evaluation processes. This new "grant architecture" offers an excellent opportunity to institutionalize assessments of surveillance systems and related efforts to strengthen surveillance in many countries (**Box 2.8**). The secretariat of WHO's Global Task Force on TB Impact Measurement is working closely with the Global Fund to make this opportunity a reality.

2.5.2 Surveys of the prevalence of TB disease

Nationwide population-based surveys of the prevalence of TB disease provide a direct measurement of the number of TB cases; repeat surveys conducted several years apart can allow direct measurement of trends in disease burden. Surveys are most relevant in countries where the burden of TB is high (otherwise sample sizes and associated costs and logistics become prohibitive) and surveillance systems are thought (or known) to miss a large fraction of cases. A good illustration of the value of prevalence surveys is provided by the results from three surveys in China (**Box 2.5**). Before 2007, however, few countries had implemented prevalence surveys (**Figure 2.12**). From 2002 to 2008, there was typically one survey per year. In the 1990s, national surveys were confined

BOX 2.7

New guidance on electronic recording and reporting

Surveillance systems depend on countries keeping good records of all TB cases notified to national TB control programmes (NTPs) and of TB treatment outcomes. This is a data-intensive activity that is increasingly moving away from paper-based to electronic recording and reporting (ERR).

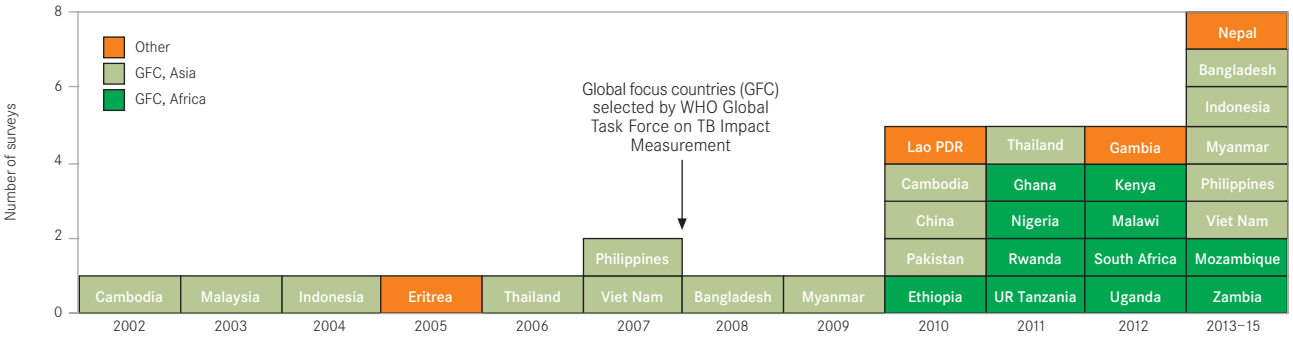
Advantages of ERR include:

- Better management of individual patients, for example by providing fast access to laboratory results;
- Better programme and resource management, by encouraging staff to use and act upon live data. This may help to prevent defaulting from treatment and assist with management of drug supplies (including avoidance of stockouts);
- Improved surveillance by making it easier for facilities not traditionally linked to the NTP, such as hospitals, prisons and the private sector, to report TB cases, and by reducing the burden of compiling and submitting data through paper-based quarterly reports;
- Greater analysis and use of data, since data can be readily imported into statistical packages, results are available to decision-makers more quickly and it is possible to detect outbreaks promptly;
- Higher quality data, since automated data quality checks can be used and duplicate or misclassified notifications can be identified and removed (which is very difficult or impossible to do nationally with paper-based systems). It is also easier to introduce new data items.

WHO is coordinating the development of a guide on how to design and implement ERR according to best-practice standards. It is due to be published in 2011.

FIGURE 2.12

Global progress in implementing national surveys of the prevalence of TB disease, actual (2002–2010) and planned (2011–2015)



BOX 2.8

Periodic reviews of Global Fund grants – an opportunity to improve measurement of trends in disease burden and strengthen surveillance worldwide

In November 2009, the Board of the Global Fund approved a new grant architecture.[1] This includes the introduction of a single grant agreement per disease (HIV, TB or malaria), in contrast to the old model in which each newly-approved proposal generated a separate grant agreement with its own budget and performance framework (such that some countries had multiple grants and multiple performance frameworks for multiple time-periods). The new grant architecture also introduces periodic reviews. These will be conducted at least once every three years and include an in-depth evaluation of how funds have been used, programmatic performance and progress towards the proposal targets, including targets for reductions in disease burden.[2] Results will determine funding levels in future years.

Periodic reviews replace the previous model of reviewing each grant agreement after two years, prior to the approval of Phase 2 (years 3–5 of the standard five-year grant). Existing country-led review processes (such as National Programme Reviews and Joint External Programme Evaluations) will be encouraged as inputs to the periodic review process.

With the introduction of periodic reviews, evaluations of progress in reducing the burden of TB disease will be closely linked to decisions about future funding commitments. The indicators that will be used to evaluate progress have been defined in consultation with partners including WHO. For all countries, assessments for TB will include analysis of trends in the case notification rate, after careful assessment of its suitability as a proxy for trends in TB incidence. Assessment of trends in notifications will require analysis of trends in case-finding efforts, the quality and coverage of surveillance and risk factors for TB. If data from national or sample vital registration systems are available, trends in mortality will be assessed and used to inform the periodic review. In countries that have conducted at least two surveys of the prevalence of TB disease, trends in TB prevalence will be assessed and used to inform the periodic review. In addition to case notification rates, the treatment success rate for new smear-positive TB cases will also be assessed. It is anticipated that analysis of trends in disease burden will be undertaken prior to the periodic review; to facilitate this work, the Global Fund will allocate the necessary resources within the monitoring and evaluation budget of grant agreements. An indicative budget of up to US$ 100 000 may be allocated.[3]

Periodic reviews provide an unprecedented opportunity for regular and systematic assessment of trends in the burden of disease caused by TB in more than 100 countries, using the framework and associated tools developed by the WHO Global Task Force on TB Impact Measurement.[4] If this opportunity is taken, periodic reviews will substantially improve estimates of trends in the burden of disease caused by TB and provide a foundation for strengthening surveillance of the disease worldwide.

[1] *New grant architecture*. Geneva, The Global Fund to Fight AIDS, Tuberculosis and Malaria, 2011 (also available at: **www.theglobalfund.org/en/grantarchitecture**).
[2] *Operational policy note on periodic reviews*. Geneva, The Global Fund to Fight AIDS, Tuberculosis and Malaria, 2011 (also available at: **www.theglobalfund.org/documents/core/manuals/Core_OperationalPolicy_Manual_en.pdf**)
[3] This is separate from the dedicated budgets required to undertake TB prevalence surveys (cumulative investments amount to US$ 25 million) or other studies that will feed into the assessment.
[4] The tool used to date is available at: **www.who.int/tb/advisory_bodies/impact_measurement_taskforce**. Additional tools including a surveillance checklist and associated standards and benchmarks (see section 2.5.1) will be made available on the same site as they become available.

to China, Myanmar, the Philippines and the Republic of Korea. Before 2009 and with the exception of Eritrea in 2005, the last national surveys in the African Region were undertaken between 1957 and 1961.

In 2007, WHO's Global Task Force on TB Impact Measurement identified 53 countries that met epidemiological and other criteria for implementing a survey. A set of 22 global focus countries were selected to receive particular support in the years leading up to 2015. Many of the global focus countries had already developed plans to implement surveys and had sought funding from the Global Fund at this time, but in most countries experience and expertise in such surveys were limited.

Since early 2008, the Task Force has made substantial efforts to support countries to design, implement, analyse and report on surveys. These efforts include close collaboration with the Global Fund to help secure full funding for surveys through reprogramming of grants (several surveys were initially under-budgeted); workshops to develop protocols; expert reviews of protocols; training courses for survey coordinators without prior experience of survey implementation, including an opportunity to observe field operations in Cambodia; training courses to build a group of junior international consultants who can provide technical assistance to countries; country missions by experts from the Task Force; and the facilitation of Asia–Africa collaboration in which survey coordinators from Asian countries provide guidance and support to those leading surveys in African countries where no recent experience exists (which should later develop into Africa–Africa collaboration). Besides WHO, those actively engaged in these efforts include the staff who have led and managed surveys in Cambodia, China, Myanmar and Viet Nam; the Centers for Disease Control, United States of America; the Global Fund; the KNCV Tuberculosis Foundation in the Netherlands; the

London School of Hygiene and Tropical Medicine, UK; and the Research Institute for Tuberculosis, Japan. All of this support is underpinned by a new handbook on TB prevalence surveys (also known as "the lime book"), which provides comprehensive theoretical and practical guidance on all aspects of surveys.[1] The book was produced as a major collaborative effort involving 15 agencies and institutions and 50 authors in 2010, and was widely disseminated in 2011.

As a result of these collaborative efforts, there is now major global and national momentum behind prevalence surveys. If surveys are implemented according to schedule, between five and eight surveys per year will be implemented during the period 2010–2015. These include surveys in 20 global focus countries – 9 in Asia and 11 in Africa (**Figure 2.12**).

A landmark achievement in 2011 was the successful completion of the first national prevalence survey in Ethiopia. This is the first such survey in Africa following WHO guidelines in more than 50 years. Results will be featured in the 2012 global report, alongside results from surveys undertaken in Cambodia and Pakistan.

[1] *TB prevalence surveys: a handbook*. Geneva, World Health Organization, 2011 (WHO/HTM/TB/2010.17).

CHAPTER 3

Case notifications and treatment outcomes

KEY MESSAGES

- In 2010, 6.2 million people were diagnosed with TB and notified to national TB control programmes. Of these, 5.4 million had TB for the first time and 0.3 million had a recurrent episode of TB after being cured of TB in the past. Besides a small number of cases whose history of treatment was not recorded, the remaining 0.4 million had already been diagnosed with TB but had their treatment changed to a retreatment regimen after treatment failed or was interrupted.
- India and China accounted for 40% of the world's notified cases of TB in 2010; Africa accounted for a further 24%, of which one quarter were in South Africa. The 22 high-TB burden countries accounted for 82%.
- Public-private and public-public mix (PPM) initiatives to engage the full range of care providers can help to increase case notifications. In 20 countries for which data were available, PPM contributed between about one fifth to around 40% of total notifications in 2010, in the geographical areas in which PPM was implemented.
- Treatment outcomes are most closely monitored among new cases with smear-positive pulmonary TB. Among cases treated in 2009, 87% were successfully treated – the highest level reported to date. Treatment success rates remained low in the European Region, at 67%, with high death and failure rates.
- There has been an increase in the number of TB patients diagnosed with MDR-TB in the last five years. However, patients enrolled on treatment for MDR-TB in 2010 only represented 16% of the MDR-TB cases estimated to exist among reported TB cases. Outcomes of treatment for MDR-TB are available for a small number of patients. The numbers of TB cases tested for MDR-TB, diagnosed with MDR-TB and successfully treated for MDR-TB lag far behind the targets set in the Global Plan.
- In most parts of the world, less than 5% of TB patients are tested for MDR-TB. Laboratory strengthening and new diagnostics are urgently needed to improve the coverage of diagnostic testing for MDR-TB.
- Between 1995 and 2010, 55 million TB patients were treated for TB in programmes that had adopted the DOTS/Stop TB Strategy; 46 million of these people were successfully treated. These treatments saved an estimated 6.8 million lives compared with the pre-DOTS standard of care.

The total number of TB cases that occur each year can be estimated for the world as a whole and for regions and individual countries, but with uncertainty (as explained in **Chapter 2**). This uncertainty reflects the fact that in most countries – especially countries that have the largest number of reported cases of TB – surveillance systems do not capture all TB cases. Cases may be missed by routine notification systems because people with TB do not seek care, seek care but remain undiagnosed, or are diagnosed by public and private providers that do not report cases to local or national authorities.

Routine recording and reporting of the numbers of TB cases diagnosed and treated by national TB control programmes (NTPs) and monitoring of the outcomes of treatment was one of the five elements of TB control emphasized in the DOTS strategy, and remains one of the core elements of the Stop TB Strategy (**Chapter 1**). Following the introduction and roll-out of the DOTS/Stop TB Strategy in most countries since the mid-1990s, data on the number of people diagnosed and treated for TB and associated treatment outcomes are routinely reported by NTPs in almost all countries, and in turn these data are reported to WHO in annual rounds of global TB data collection. With increasing engagement by NTPs of the full range of care providers, including those in the private sector and those in the public sector not previously linked to NTP reporting systems, data are also better reflecting the total number of diagnosed cases. The number of TB cases that are not diagnosed is expected to be low in countries where health care is of high quality and readily accessible. In other countries, the numbers of undiagnosed cases can only be estimated with considerable uncertainty, using relevant data sources such as population-based surveys of the prevalence of TB disease, inventory studies including record-linkage and capture re-capture modelling, and indicators on the coverage and cost of health services (for further details, see **Chapter 2**).

This chapter summarizes the total number of people who were diagnosed with TB and notified by NTPs in 2010 as well as trends in notifications of TB cases since 1990. It is assumed that notified cases were treated for TB. Data from 20 countries illustrating the contribution to total notifications of efforts to engage public and private providers not traditionally linked to the NTP are also presented. The chapter then summarizes information

BOX 3.1

Definitions of TB cases[1]

Definite case of TB A patient with *Mycobacterium tuberculosis* complex identified from a clinical specimen, either by culture or by a newer method such as molecular line probe assay. In countries that lack laboratory capacity to routinely identify *Mycobacterium tuberculosis*, a pulmonary case with one or more initial sputum specimens positive for acid-fast bacilli (AFB) is also considered to be a "definite" case, provided that there is functional external quality assurance (EQA) with blind rechecking.

Case of TB A definite case of TB (defined above) or one in which a health worker (clinician or other medical practitioner) has diagnosed TB and decided to treat the patient with a full course of TB treatment.

Case of pulmonary TB A patient with TB disease involving the lung parenchyma.

Smear-positive pulmonary case of TB A patient with one or more initial sputum smear examinations (direct smear microscopy) AFB-positive; or one sputum examination AFB+ and radiographic abnormalities consistent with active pulmonary TB as determined by a clinician. Smear-positive cases are the most infectious and thus of the highest priority from a public health perspective.

Smear-negative pulmonary case of TB A patient with pulmonary TB not meeting the above criteria for smear-positive disease. Diagnostic criteria should include: at least two sputum smear examinations negative for AFB; radiographic abnormalities consistent with active pulmonary TB; no response to a course of broad-spectrum antibiotics (except in a patient for whom there is laboratory confirmation or strong clinical evidence of HIV infection); and a decision by a clinician to treat with a full course of anti-TB chemotherapy. A patient with positive culture but negative AFB sputum examinations is also a smear-negative case of pulmonary TB.

Extrapulmonary case of TB A patient with TB of organs other than the lungs (e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges). Diagnosis should be based on one culture-positive specimen, or histological or strong clinical evidence consistent with active extrapulmonary disease, followed by a decision by a clinician to treat with a full course of anti-TB chemotherapy. A patient in whom both pulmonary and extrapulmonary TB has been diagnosed should be classified as a pulmonary case.

New case of TB A patient who has never had treatment for TB or who has taken anti-TB drugs for less than one month.

Retreatment case of TB There are three types of retreatment case: (i) a patient previously treated for TB, who is started on a retreatment regimen after previous treatment has failed (treatment after failure); (ii) a patient previously treated for TB who returns to treatment having previously defaulted; and (iii) a patient who was previously declared cured or treatment completed and is diagnosed with bacteriologically-positive (sputum smear or culture) TB (relapse).

Case of multidrug-resistant TB (MDR-TB) TB that is resistant to two first-line drugs: isoniazid and rifampicin. For patients diagnosed with MDR-TB, WHO recommends treatment of at least 20 months with a regimen that includes second-line anti-TB drugs.

Note: New and relapse cases of TB are incident cases. Cases of TB started on a retreatment regimen following treatment failure or treatment interruption are prevalent cases.

[1] See *Treatment of tuberculosis guidelines*, 4th ed. Geneva, World Health Organization, 2010 (WHO/HTM/STB/2009.420).

on the diagnosis and treatment of multidrug-resistant TB (MDR-TB)[1] specifically, and compares the numbers of cases tested for MDR-TB and the numbers of cases diagnosed and started on treatment with the targets set out in the Global Plan to Stop TB 2011–2015 (**Chapter 1**). Finally, the chapter summarizes data on treatment outcomes among new sputum smear-positive cases of pulmonary TB, which have traditionally been the focus of efforts to monitor treatment outcomes, and the available data on treatment outcomes among TB patients diagnosed with MDR-TB who were treated with second-line anti-TB drugs.

3.1 Number of diagnosed and notified cases of TB

In 2010, 6.2 million people were diagnosed with TB and notified to NTPs. Of these, 5.4 million had TB for the first time and 0.3 million had a recurrent episode of TB after being previously cured of TB. Besides a small number of cases whose history of treatment was not recorded, the remaining 0.4 million had already been diagnosed with TB but had their treatment changed to a retreatment regimen after treatment failed or was interrupted (for definitions of each type of case, see **Box 3.1**).

Among people who were diagnosed with TB for the first time (new cases), there were 2.6 million cases of sputum smear-positive pulmonary TB, 2.0 million cases of sputum smear-negative pulmonary TB (including cases for which smear status was unknown) and 0.8 million cases of extrapulmonary TB (**Table 3.1**).[2] Of the new cases of pulmonary TB, 57% were sputum smear-positive.

[1] For definitions, see **Box 3.1**.

[2] No distinction is made between DOTS and non-DOTS programmes. This is because by 2007, virtually all (more than 99%) notified cases were reported to WHO as treated in DOTS programmes.

TABLE 3.1

Case notifications, 2010

	TOTAL NOTIFIED	NEW				RETREATMENT		NEW AND RELAPSE	HISTORY UNKNOWN	PERCENT NEW PULMONARY CASES SMEAR-POSITIVE
		SMEAR-POSITIVE	SMEAR-NEGATIVE/ UNKNOWN	EXTRA-PULMONARY	CASE TYPE UNKNOWN	RELAPSE	RETREATMENT EXCL. RELAPSE			
Afghanistan	28 238	12 947	7 085	6 248	633	1116	209	28 029		65
Bangladesh	158 252	105 624	21 420	23 438	3 231	2 989	1 550	156 702	0	83
Brazil	81 946	37 932	23 030	10 017	18	3 398	7 551	74 395	0	62
Cambodia	41 628	17 454	8 301	14 239	0	466	1 168	40 460	0	68
China	923 308	429 899	432 868	6 325	0	39 307	14 909	908 399	0	50
DR Congo	118 636	73 653	14 039	22 340	0	4 138	4 466	114 170	0	84
Ethiopia	156 928	46 634	54 979	50 417	0	2 664	2 234	154 694	–	46
India	1 522 147	630 165	366 381	231 121	1 508	110 691	182 281	1 339 866	–	63
Indonesia	302 861	183 366	101 247	11 659	0	4 387	2 202	300 659	0	64
Kenya	106 083	36 260	41 962	17 382	0	3 668	6 811	99 272	0	46
Mozambique	46 174	20 097	16 408	5 621	0	1 432	2 616	43 558	0	55
Myanmar	137 403	42 318	56 840	27 976	–	4 456	5 813	131 590	–	43
Nigeria	90 447	45 416	32 616	3 422	0	2 667	6 326	84 121	0	58
Pakistan	269 290	104 263	105 623	45 443	0	5 870	5 055	261 199	3 036	50
Philippines	174 389	89 198	72 440	1 610	0	3 075	8 066	166 323	0	55
Russian Federation	170 904	31 416	67 894	3 513	0	8 737	17 741	111 560	41 603	32
South Africa	400 391	128 571	155 071	52 090	0	18 509	46 150	354 241	0	45
Thailand	68 239	33 450	20 927	10 135	0	1 885	1 111	66 397	731	62
Uganda	45 546	23 456	13 567	4 571	0	1 291	2 661	42 885	0	63
UR Tanzania	63 453	24 769	21 184	13 715	–	1 430	2 355	61 098	–	54
Viet Nam	99 022	52 145	18 237	17 651	0	6 834	1 574	94 867	2 581	74
Zimbabwe	47 557	11 654	25 157	6 061	0	1 337	3 348	44 209	0	32
High-burden countries	**5 052 842**	**2 180 687**	**1 677 276**	**584 994**	**5 390**	**230 347**	**326 197**	**4 678 694**	**47 951**	**57**
AFR	1 478 356	597 364	480 665	246 997	642	53 603	98 872	1 379 271	213	55
AMR	226 669	116 828	52 169	32 184	2 130	10 410	12 135	213 721	813	69
EMR	421 384	168 563	137 256	91 947	633	11 201	8 598	409 600	3 186	55
EUR	355 258	81 155	130 897	33 314	387	23 683	37 943	269 436	47 879	38
SEAR	2 332 333	1 046 865	615 258	328 353	4 739	130 714	205 286	2 125 929	1 118	63
WPR	1 341 391	622 211	566 146	61 042	27	54 170	32 875	1 303 596	4 920	52
Global	**6 155 391**	**2 632 986**	**1 982 391**	**793 837**	**8 558**	**283 781**	**395 709**	**5 701 553**	**58 129**	**57**

– Indicates data not available.

India and China accounted for 40% of the 5.7 million new and relapse cases of TB that were notified in 2010 (24% and 16%, respectively). African countries accounted for a further 24% (of which one quarter were from one country – South Africa). The WHO European and Eastern Mediterranean regions and the Region of the Americas accounted for 16% of new and relapse cases notified in 2010. The 22 HBCs accounted for 82%.

Among the 22 HBCs, the percentage of new cases of pulmonary TB that were sputum smear-positive was relatively low in Zimbabwe (32%), the Russian Federation (32%), Myanmar (43%), South Africa (45%), Kenya (46%) and Ethiopia (46%). A comparatively high proportion of new cases of pulmonary TB were sputum smear-positive in Bangladesh (83%), the Democratic Republic of the Congo (84%) and Viet Nam (74%).

Globally, the number of TB cases diagnosed and notified per 100 000 population has stabilized since 2008, following a marked increase between 2001 and 2007 (**Figure 3.1**). Globally and in all WHO regions, a clear gap between the numbers of notified cases and the estimated numbers of incident cases exists, although this is narrowing, particularly in the Western Pacific Region (mostly driven by trends in China) and the Region of the Americas (**Figure 3.2**). Trends in the 22 HBCs are shown in **Figure 3.3**, and for other countries are illustrated in country profiles that are available online.[1]

[1] **www.who.int/tb/data**

BOX 3.2

Achievements in TB care and control at the global level, 1995–2010

The start of WHO's efforts to systematically monitor progress in TB control on an annual basis in 1995 coincided with global promotion and expansion of the DOTS strategy. Data compiled since then allow assessment of achievements in TB control since 1995.

Between 1995 and 2010, a total of 55 million TB patients were treated in programmes that had adopted the DOTS/Stop TB Strategy; 46 million of these people were successfully treated. Conservative estimates suggest that these treatments saved around 6.8 million lives, compared with the pre-DOTS standard of care.[1]

[1] Glaziou P et al. Lives saved by tuberculosis control and prospects for achieving the 2015 global target for reducing tuberculosis mortality. *Bulletin of the World Health Organization*, 2011, 89:573–582.

FIGURE 3.1

Global trends in case notification (black) and estimated TB incidence (green) rates, 1990–2010

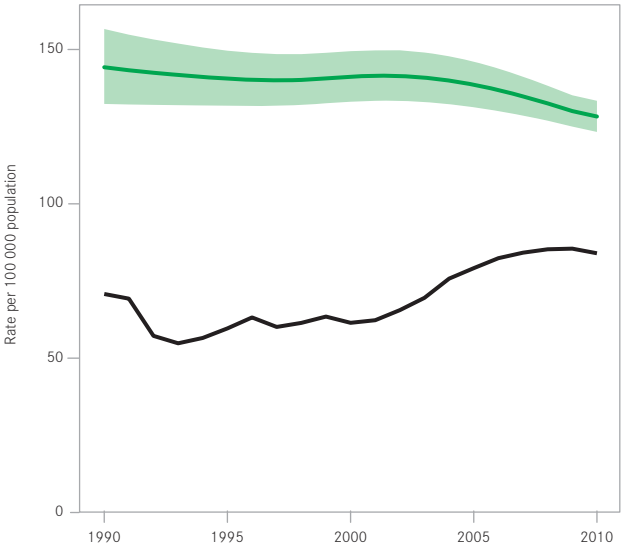


FIGURE 3.2

Case notification and estimated TB incidence rates by WHO region, 1990–2010. Regional trends in case notification rates (new and relapse cases, all forms) (black) and estimated TB incidence rate (green). Shaded areas represent uncertainty bands.

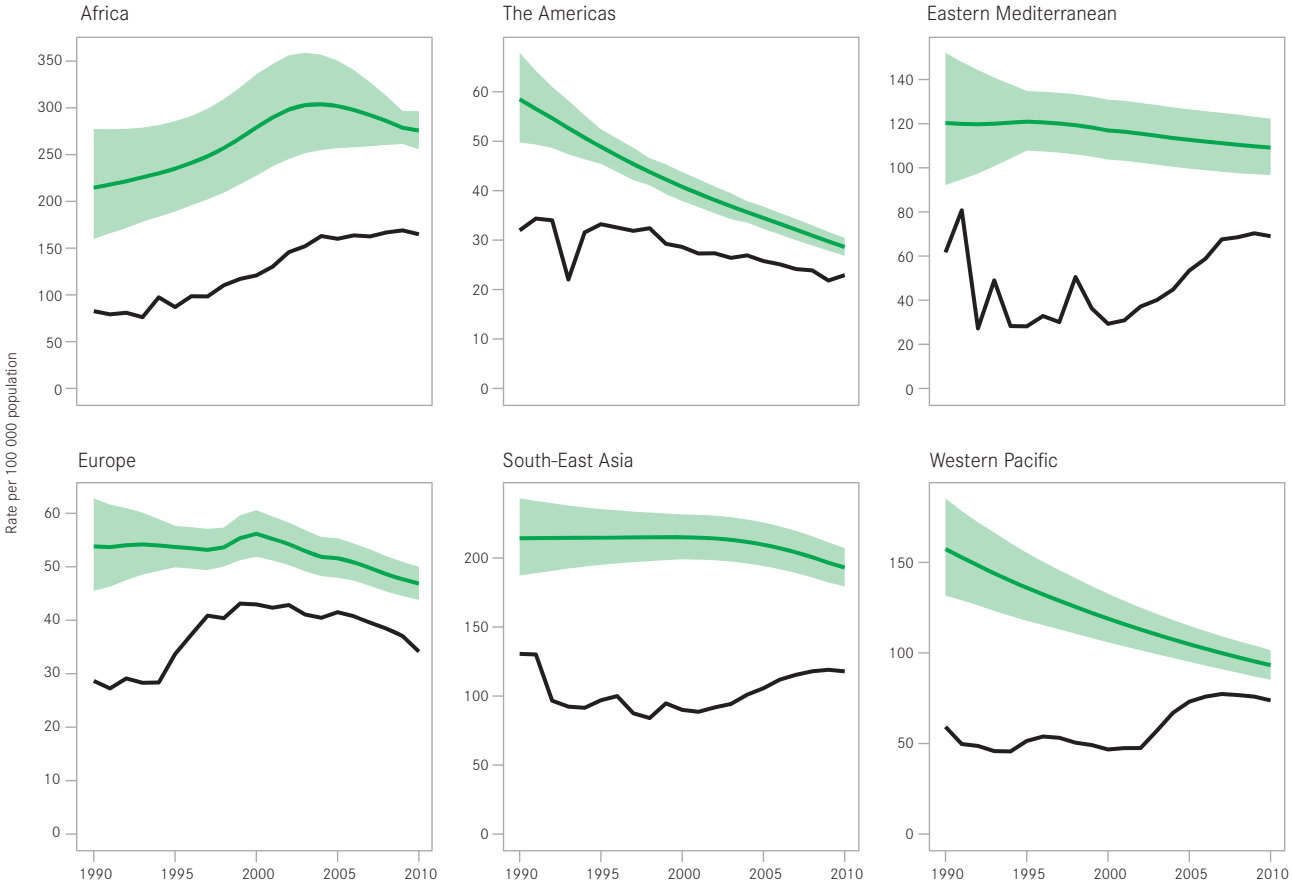
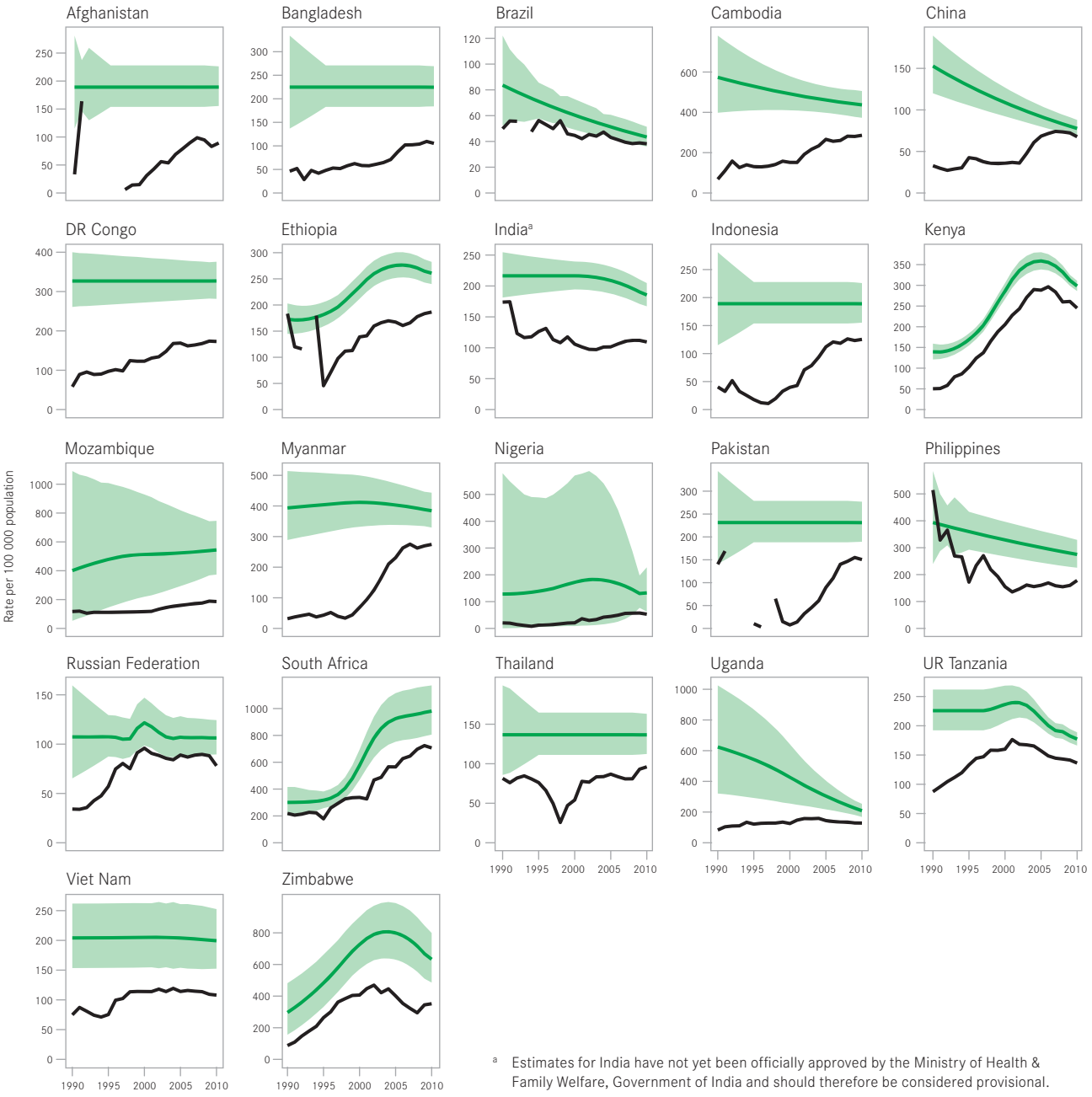


FIGURE 3.3

Case notification and estimated TB incidence rates, 22 high-burden countries, 1990–2010. Trends in case notification rates (new and relapse cases, all forms) (black) and estimated TB incidence rate (green). Shaded areas represent uncertainty bands.



[a] Estimates for India have not yet been officially approved by the Ministry of Health & Family Welfare, Government of India and should therefore be considered provisional.

3.2 Public–private and public–public mix (PPM) initiatives

In many countries, especially those with a large private sector, collaboration with the full range of health care providers is one of the best ways to ensure that all people with TB are promptly diagnosed, notified to NTPs and provided with standardized care. This is component 4 of the Stop TB Strategy (**Chapter 1**); its two subcomponents are:

- involving all public, voluntary, corporate and private providers through PPM approaches; and
- promoting the International Standards for Tuberculosis Care through PPM initiatives.

Efforts to engage all care providers through PPM initiatives, beyond those which fall under the direct responsibility of the NTP (termed "non-NTP providers" in this report), are being introduced and scaled up in many countries. Demonstrating this progress is not always possible: it requires systematic recording of the source of referral and place of TB treatment at the local level, reporting to the national level and analysis of aggregated data at the national level.[1] However, this recording and reporting is happening in a growing number of countries

[1] WHO recommends that the source of referral and the place of treatment should be routinely recorded and reported.

TABLE 3.2

Contribution of PPM[a] to notifications of TB cases in 20 countries

WHO REGION AND COUNTRY	TYPES OF NON-NTP CARE PROVIDERS ENGAGED	COVERAGE	NUMBER OF NEW TB CASES NOTIFIED IN 2010	CONTRIBUTION TO TOTAL NOTIFICATIONS OF NEW TB CASES
AFRICAN REGION				
Angola	Diverse private and public providers	Countrywide	15 676	37%
Ghana	Diverse private and public providers	Countrywide	2 032	14%
Kenya	Private clinics and hospitals, NGOs and diverse public providers	Countrywide	7 706	8.1%
Madagascar	Diverse private and public providers	Countrywide	6 749	29%
Nigeria	Private clinics and hospitals	Countrywide	31 656	39%
UR Tanzania	Private, faith-based organizations and NGO hospitals	Countrywide	11 156	19%
REGION OF THE AMERICAS				
Haiti	Private practitioners, NGOs and prison services	Countrywide	5 030	36%
Peru	Social security organizations and other public and private providers	Countrywide	5 993	21%
EASTERN MEDITERRANEAN REGION[b]				
Iran (Islamic Republic of)	Diverse private and public providers	Countrywide	4 271	43%
Pakistan	Private clinics and hospitals	Countrywide	51 563	20%
Egypt	Health insurance organizations, NGOs and other public providers	Countrywide	2 112	24%
Sudan	Diverse private and public providers	Countrywide	2389	9.4%
EUROPEAN REGION				
Ukraine	Prison and military services	Countrywide	1540	4.9%
SOUTH-EAST ASIA REGION				
Bangladesh	Hospitals, medical colleges, prison services and other public providers	Countrywide	44 732	29%
India	Diverse private, public and NGO providers	14 large cities (total population 50 million)	35 025	45% of new smear-positive cases
Indonesia	Public and private hospitals	Countrywide	48 391	16%
Myanmar	Diverse private, public and NGO providers	Countrywide	24 250	19%
WESTERN PACIFIC REGION				
China	General public hospitals	Countrywide	36 7607	42%
Philippines	Private clinics and hospitals	Countrywide	12 081	7.2%
Republic of Korea	Predominantly private providers	Countrywide	33 167	85%

NGO, non-governmental organization; FBO, Faith-based organization; NTP, national TB control programme.

[a] Private providers include private practitioners, private hospitals, private clinics, corporate services and NGOs and non-NTP public providers include hospitals, public medical colleges, prisons/detention centres and military facilities.

[b] For the Eastern Mediterranean Region, data are for the contribution of PPM to all TB cases, not just new cases.

and data for 20 countries are summarized in **Table 3.2**. In these 20 countries, the contribution of PPM initiatives typically ranges from between about one fifth to around 40% of total notifications, in the geographical areas in which PPM has been implemented.

NTPs have used a variety of approaches to engage non-NTP care providers, according to the local context. These include incentive-based schemes for individual and institutional providers (in India and Myanmar); a web-based system for mandatory reporting of TB cases by all providers (in China); and reimbursement for TB care delivered by private providers through health insurance, when care conforms with agreed-upon standards (in the Philippines). It is also noticeable that countries have prioritized different types of care providers. These include general public hospitals (in China), private clinics and hospitals (in Nigeria), social security organizations (in Peru) and private and NGO hospitals (in the United Republic of Tanzania). In general, the data illustrate the relevance of PPM in both African and Asian countries. A case study from Nigeria is provided in **Box 3.3**.

Typically, only a small proportion of targeted care providers collaborate actively with NTPs and contribute to TB case notifications in most countries. For this reason, it is not surprising that NTPs often give first priority to engaging institutional providers with whom establishing

BOX 3.3

PPM for TB care and control in Nigeria

Health services in Nigeria, including those for care of TB patients, are offered by a range of providers in the public, voluntary and private sectors. Mission hospitals run by faith-based organizations have a long history of collaboration with the National Tuberculosis and Leprosy Control Programme (NTBLCP), dating from shortly after the NTBLCP's establishment in 1989. In 1994, the NTBLCP introduced the DOTS strategy; DOTS was also implemented by mission hospitals, especially in the southern parts of the country. The private medical sector is estimated to provide health care to up to 60% of the population, although there is considerable variation within and across states. Private providers manage TB patients but rarely notify them to the NTBLCP.

To enhance access to quality-assured TB care and improve reporting of cases, the Stop TB Strategy was adopted by the NTBLCP in 2006. Efforts to engage all care providers through PPM approaches began in the same year. After a pilot project implemented in Anambra State with the support of the German Leprosy and TB Relief Association was successful, PPM was expanded systematically following WHO guidelines and with financial support from the Global Fund and the United States Agency for International Development. A comprehensive national situation assessment was conducted in 2007. Based on the findings of the assessment and lessons learnt from the pilot project, national PPM guidelines were developed. A curriculum and training modules specific to PPM were also prepared. PPM implementation was guided at the national level by a PPM Steering Committee; its counterparts at the provincial level – the State PPM Steering Committees – are operational in 12 states. In scaling up PPM and enabling productive collaboration with private providers, more than 500 medical officers, 1000 general health workers and 200 laboratory personnel have been trained. The number of private health facilities collaborating with the NTBLCP increased from about 100 in 2006 to 451 in 2010.

The expansion of PPM in Nigeria has faced several challenges. Only a proportion of private facilities tend to collaborate. Private providers have high expectations of incentives and enablers from the programme. An insufficient health work force and the high attrition rate of staff in private facilities make it difficult to maintain the quality of DOTS implementation. Under-reporting of patients managed in the private sector remains a problem. Despite these difficulties, PPM has helped to increase TB notifications and to improve TB case management in the private sector. In 2010, PPM care providers notified 31 656 cases, equivalent to 39% of the new TB cases that were notified in the country.

Further strengthening of PPM for TB care and control is planned. Current models of PPM will be evaluated and existing policies and guidelines reviewed. Advocacy to relevant stakeholders to increase the number of private facilities collaborating with the NTBLCP will be enhanced. It is anticipated that these efforts will improve access to care, save costs and ensure quality of TB services for patients seeking private care, while also increasing TB case notifications and maintaining high treatment success rates.

collaborative links may be less demanding and, for a given amount of effort, will yield a higher number of notifications. At the same time, involving front-line health workers such as community-based informal providers, private practitioners and pharmacies – who are often the first point of contact for people with symptoms of TB – can help to reduce diagnostic delays and the out-of-pocket expenditures of TB patients. The role of pharmacists is highlighted in **Box 3.4**.

3.3 Case detection rates

The case detection rate (CDR)[1] for TB is an indicator that is included within the Millennium Development Goals (**Chapter 1**). For a given country and year, the CDR is defined as the number of new and relapse TB cases (see **Box 3.1** for definitions) that were diagnosed and notified by NTPs (**Table 3.1**), divided by the estimated incident cases of TB that year. The CDR is expressed as a percentage; it gives an approximate[2] indication of the proportion of all incident TB cases that are actually diagnosed, reported to NTPs and started on treatment.

The best estimate of the CDR for all forms of TB at global level in 2010 was 65% (range, 63–68%), up from 54–60% in 2005 and 40–45% in 1995 – the year in which the DOTS strategy began to be introduced and expanded (**Table 3.3**). The highest CDRs in 2010 were estimated to be in the Western Pacific Region (best estimate 79%; range, 73–87%), the European Region (best estimate 73%; range, 68–78%) and the Region of the Americas (best estimate 80%; range, 75–85%). The other regions had estimated CDRs in the range 56–71%, with best estimates of around 60%. All regions have improved their estimated CDRs since the mid-1990s, with improvements particularly evident since 2000. Among the 22 HBCs, the highest rates of case detection in 2010 were estimated to be in Brazil, China, Kenya, the Russian Federation and the United Republic of Tanzania; the lowest rates were in Mozambique, Nigeria, Afghanistan and Bangladesh.

To close the gap between notified cases and estimated TB incidence, action is needed in three broad areas:

[1] The CDR is actually a ratio rather than a rate, but the term "rate" has become standard terminology in this context of this indicator.

[2] It is approximate because of uncertainty in the underlying incidence of TB and because notified cases are not necessarily a subset of incident cases that occurred in the same year; see **Chapter 2** for further discussion.

- **Strengthening surveillance.** This will help to ensure that all cases diagnosed with TB are reported and accounted for by routine notification systems. Establishing links with the full range of health-care providers through PPM, as well as stronger enforcement of legislation regarding notification of cases (where this is mandated by law), can help to minimize the under-reporting of TB cases. Inventory studies can be used to help quantify the extent to which diagnosed cases are unreported (the "surveillance gap"). WHO and its partners are currently developing guidance on how these studies can be done, building on pioneering work in implementing such studies in the Eastern Mediterranean Region and the UK (for further details, see **Chapter 2**).
- **Better diagnostic capacity.** This will help to ensure that people with TB who seek care are actually diagnosed. It may require better laboratory capacity as well as more knowledgeable and better trained staff, especially in peripheral-level health-care facilities.
- **Improved access to health care.** For people with TB who do not seek care, improved access (in financial and/or geographical terms) to health care as well as improved awareness of how to recognize the signs and symptoms of TB are important.

3.4 Diagnosis and treatment of MDR-TB

The diagnosis of MDR-TB (defined as resistance to isoniazid and rifampicin) requires that people with TB are tested for susceptibility to first-line anti-TB drugs. The Global Plan (**Chapter 1**) includes targets that by 2015 all new cases of TB considered at high risk of MDR-TB should be tested for drug susceptibility (estimated at about 20% of all new cases) and that 100% of retreatment cases should be tested (see **Box 3.1** for case definitions).

With the notable exception of the European Region, drug susceptibility testing (DST) for first-line drugs was done for only a small proportion of notified cases in 2010 (**Table 3.4**). Globally, less than 2% of new cases and 6% of retreatment cases were tested for MDR-TB, with particularly low levels of testing in the South-East Asia and

BOX 3.4

The role of pharmacists in TB care and control

Pharmacists can play an important role in delivering health care. Demographic and Health Surveys (DHS) carried out between 2004 and 2008 show that a high proportion of people seek care from private pharmacies: for example, in India, Nigeria, the Philippines and the United Republic of Tanzania, 11%, 27%, 24% and 75% of people in the lowest quintile of income had sought care from private pharmacies for fever, cough or diarrhoea.[1] The figures were 78%, 72%, 45% and 36% respectively for private care providers. A recent study estimating the sale of anti-TB medicines in the private sector found that in 10 high TB-burden countries (HBCs) that account for 60% of the global burden of disease caused by TB, the amount of anti-TB medicines dispensed in the private sector was sufficient to treat 66% of the estimated number of new cases of TB that occur each year in these countries. The same study estimated that the size of the private market in India was equivalent to the number of full treatment courses required to treat 1.2 times the number of patients reported and treated under the auspices of the Revised National TB Control Programme (RNTCP).[2]

To strengthen the contribution of pharmacists to TB care and control, WHO's Stop TB Department has been working with the International Pharmaceutical Federation (FIP) – a nongovernmental organization (NGO) representing more than 120 national associations of pharmacists that has an official relationship with WHO (**www.fip.org**). In September 2011, this collaboration culminated in the launch of a WHO/FIP Joint Statement on the "Role of pharmacists in TB care and control" at FIP's annual global conference in Hyderabad, India. This statement builds on WHO's mandate in public health and FIP's previous collaboration with WHO on important public health issues including HIV/AIDS, good pharmacy practice and prevention of antimicrobial resistance. The objective of publishing the statement is to stimulate national TB control programmes (NTPs) and national pharmacy associations (NPAs) to work together on effectively engaging pharmacists in TB care and control. Pharmacists can contribute in diverse ways: increasing awareness of TB among their clients, identifying people with symptoms of TB, referring them to a proper place for diagnosis, supervising and supporting TB patients to enhance treatment adherence, offering anti-TB medicines on valid prescriptions only and facilitating rational use of anti-TB medicines by prescribing physicians.

Some countries have already developed productive approaches to engaging pharmacists in TB care. In a project in Cambodia, over a period of three years, participating pharmacists referred 12 577 people with TB symptoms to health care services, among whom 6 403 attended health centres and 1418 were diagnosed with TB. Collaboration between the NTP and the NPA in Ghana helped to halt the sale of anti-TB medicines in private pharmacies.

Systematic efforts are required to enable NPAs and pharmacists to take on new tasks that could benefit TB control and potentially other health programmes. A logical first step would be to sensitize NTPs and NPAs on the benefits of working together. Country-specific models of collaboration can then be developed, tested, documented and scaled up. It is hoped that the WHO/FIP joint statement will help to catalyse such efforts in many countries.

[1] See **www.ps4h.org/globalhealthdata** (accessed 13 July 2011).
[2] Wells WA et al. Size and usage patterns of private TB drug markets in the high burden countries. *PLoS One*, 2011, 6(5): e18964.

TABLE 3.3

Estimates of the case detection rate for all cases (%), 1995–2010[a]

	1995			2000			2005			2010		
	BEST[b]	LOW	HIGH	BEST	LOW	HIGH	BEST	LOW	HIGH	BEST	LOW	HIGH
Afghanistan	–	–	–	16	14	20	42	35	51	47	39	57
Bangladesh	21	18	26	26	22	32	39	32	48	47	39	57
Brazil	79	66	97	74	61	91	84	71	100	88	74	110
Cambodia	25	20	32	31	26	37	58	50	67	65	57	77
China	33	27	40	33	28	39	74	65	86	87	77	100
DR Congo	30	25	36	38	32	45	52	45	61	53	46	61
Ethiopia	25	22	29	59	54	66	61	56	67	72	66	78
India[c]	58	51	67	49	44	54	49	44	54	59	53	65
Indonesia	9.4	7.8	12	21	17	26	59	49	73	66	55	81
Kenya	61	56	66	72	67	77	80	76	85	82	79	86
Mozambique	23	11	78	23	13	53	31	20	55	34	25	50
Myanmar	11	8.5	14	17	14	21	57	49	68	71	62	84
Nigeria	8.8	2.5	250	12	3.7	240	26	9.0	230	40	23	85
Pakistan	4.5	3.7	5.5	3.3	2.7	4.1	39	32	48	65	54	79
Philippines	48	40	59	47	39	58	53	44	66	65	54	79
Russian Federation	53	44	65	79	65	97	83	69	100	73	63	87
South Africa	56	47	69	59	49	72	61	51	75	72	60	88
Thailand	56	46	68	40	33	49	64	53	78	70	59	85
Uganda	22	14	42	29	20	49	47	36	66	61	51	76
UR Tanzania	59	51	69	68	60	78	74	69	80	77	72	82
Viet Nam	37	29	49	56	43	74	56	44	74	54	43	71
Zimbabwe	55	40	80	56	45	71	50	41	64	56	44	72
High-burden countries	**39**	**37**	**43**	**40**	**37**	**43**	**55**	**52**	**59**	**65**	**62**	**68**
AFR	37	30	46	43	36	53	53	46	62	60	56	64
AMR	68	63	73	70	65	75	75	70	80	80	75	85
EMR	23	21	26	25	22	28	47	42	54	63	56	71
EUR	63	58	67	76	71	83	80	75	87	73	68	78
SEAR	45	41	50	42	39	45	50	47	54	61	57	66
WPR	38	33	44	39	35	44	70	64	77	79	73	87
Global	**42**	**40**	**45**	**44**	**41**	**46**	**57**	**54**	**60**	**65**	**63**	**68**

– indicates data not available.

[a] Estimates for all years are recalculated as new information becomes available and techniques are refined, so they may differ from those published previously.

[b] Best, low and high indicate best estimates followed by lower and upper bounds. The lower and upper bounds are defined as the 2.5th and 97.5th centiles of outcome distributions produced in simulations.

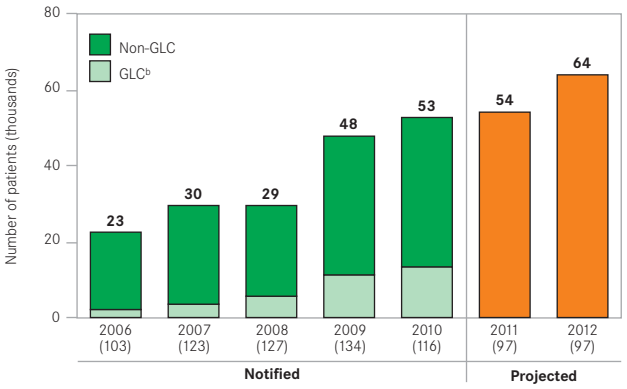
[c] Estimates for India have not yet been officially approved by the Ministry of Health & Family Welfare, Government of India and should therefore be considered provisional.

Western Pacific regions. In the European Region, 51% of retreatment cases and 30% of the new cases notified in 2010 were tested for MDR-TB. Among the 27 high MDR-TB burden countries, the proportion of notified cases that were tested was relatively high in 13 of the 15 European countries that reported data, ranging from 3% of new cases in Tajikistan to 79% of new cases in Estonia, and from 23% of retreatment cases in Tajikistan to over 90% of retreatment cases in Belarus, Latvia and Ukraine. While data on DST were not available for new and retreatment cases separately, overall more than 20% of notified cases were tested for drug resistance in South Africa (see **Annex 2**). In the other 11 countries, testing for MDR-TB among new cases was negligible or no data were reported. The proportion of retreatment cases that were tested in these 11 countries was slightly higher, but was still under 5% in countries that reported data, with the one exception of Ethiopia (10%). India and China, which collectively accounted for almost half of the global cases of MDR-TB estimated to exist among notified TB patients in 2010, did not report any data (**Table 3.5, column 2**). Improving the coverage of diagnostic DST is urgently needed to improve the diagnosis of MDR-TB, and requires strengthening laboratory capacity and introducing new rapid diagnostic tests (see **Chapter 5**).

Given low levels of testing for drug resistance in many countries, and with only 9% of TB basic management units worldwide providing curative services for MDR-TB patients, it is inevitable that the number of people who are diagnosed with MDR-TB remains low. Glob-

FIGURE 3.4

Notified cases of MDR-TB (2006–2010) and projected numbers of patients to be enrolled on treatment (2011–2012)[a]



[a] Numbers under years show the number of countries reporting data.

[b] GLC refers to project sites monitored by the Green Light Committee Initiative and known to adhere to WHO recommended norms in the care of MDR-TB patients. Non-GLC refers to all other projects that are not supported by the GLC mechanism, and include patients treated in all high-income countries.

ally, just over 50 000 cases of MDR-TB were notified to WHO in 2010, mostly by European countries and South Africa (**Table 3.5**, **Figure 3.4**). This represented 18% of the 290 000 (range, 210 000–380 000) cases of MDR-TB estimated to exist among patients with pulmonary TB who were notified in 2010. The proportion of TB patients estimated to have MDR-TB that were actually diagnosed was under 10% in all of the 27 high MDR-TB countries outside the European Region, with the notable exception of South Africa where 81% of estimated cases were diagnosed. In the 15 high MDR-TB burden countries in the European Region, the proportion of estimated cases that were diagnosed ranged from 24% (in Tajikistan) to over 90% of cases (in Belarus and Kazakhstan); no data were reported from Lithuania. In the Russian Federation, which ranks third in terms of estimated numbers of cases of MDR-TB at the global level, the proportion of estimated cases that were diagnosed was 44% in 2010. The numbers of patients diagnosed with MDR-TB and started on treatment with recommended second-line drug regimens in the high MDR-TB burden countries in 2010, at just under 40 000, was less than the number of cases notified.

Although the absolute numbers of TB cases tested for drug resistance, diagnosed with MDR-TB and started on appropriate treatment remain low, they are increasing (**Figure 3.4**). The reported number of patients enrolled on treatment for MDR-TB reached 45 553 in 2010, equivalent to 16% of the estimated 290 000 cases of MDR-TB among TB patients notified in 2010. According to country plans, further increases are expected in 2011 and 2012, although these show very small increases compared with 2010. The scale-up of diagnosis and treatment for MDR-TB falls far short of the targets set out in the Global Plan

TABLE 3.4

Diagnostic DST for rifampicin and isoniazid among new and retreatment cases of TB, 2010

	NEW CASES		RETREATMENT CASES	
	NUMBER WITH DST RESULT	% OF CASES WITH DST RESULT	NUMBER WITH DST RESULT	% OF CASES WITH DST RESULT
Armenia	471	35	220	47
Azerbaijan	493	9.6	–	–
Bangladesh	–	–	–	–
Belarus	1 972	45	1 697	152[a]
Bulgaria	801	35	165	47
China	–	–	–	–
DR Congo	–	–	100	1.2
Estonia	197	79	61	77
Ethiopia	42	<0.1	510	10
Georgia	1 987	45	558	40
India	–	–	–	–
Indonesia	0	0	324	4.9
Kazakhstan	5 214	33	4 655	51
Kyrgyzstan	–	–	–	–
Latvia	613	74	102	94
Lithuania	–	–	–	–
Myanmar	–	–	–	–
Nigeria	27	<0.1	19	0.2
Pakistan	9	<0.1	306	2.8
Philippines	3	<0.1	297	2.7
Republic of Moldova	1 234	33	1 077	64
Russian Federation	35 862	35	13 405	51
South Africa	–	–	–	–
Tajikistan	160	2.7	223	23
Ukraine	9 194	29	4 840	95
Uzbekistan	2 845	18	1 180	26
Viet Nam	–	–	–	–
High MDR-TB burden countries	**61 124**	**1.5**	**29 739**	**5.5**
AFR	2 732	0.2	4 294	2.8
AMR	10 229	5.0	4 182	19
EMR	2 323	0.6	1 250	6.3
EUR	74 820	30	31 272	51
SEAR	1 073	0.1	925	0.3
WPR	4 392	0.4	1 350	1.6
Global	**95 569**	**1.8**	**43 273**	**6.4**

– Indicates data not available.

[a] The percentage may exceed 100% if notification of TB cases is incomplete, especially in systems where reporting of TB and DST are not linked. In addition, DST may be performed repeatedly in the same patients.

TABLE 3.5

Number of cases of MDR-TB estimated, notified and expected to be treated, 27 high MDR-TB burden countries and WHO regions

	ESTIMATED CASES OF MDR-TB AMONG NOTIFIED CASES OF PULMONARY TB IN 2010[a] (A)	CONFIDENCE INTERVAL	NOTIFIED CASES OF MDR-TB IN 2010 (B)	NOTIFIED CASES OF MDR-TB AS % OF ESTIMATED CASES OF MDR-TB AMONG ALL NOTIFIED CASES OF PULMONARY TB IN 2010 (B/A)[b]	CASES ENROLLED ON TREATMENT FOR MDR-TB IN 2010	EXPECTED NUMBER OF CASES OF MDR-TB TO BE TREATED	
						2011	2012
Armenia	260	230–290	177	68	154	160	160
Azerbaijan	1 700	1 500–1 800	63	3.7	286	500	500
Bangladesh	5 900	4 400–7 400	184	3.1	339	1 558	2 597
Belarus	1 700	1 600–1 800	1 576	93	200	–	–
Bulgaria	94	71–120	56	60	56	60	65
China	63 000	56 000–70 000	2 792	4.4	1 222	6 706	7 061
DR Congo	2 700	190–5 200	87	3.2	191	220	–
Estonia	76	61–92	63	83	63	80	64
Ethiopia	2 100	1 100–3 000	140	6.7	120	836	1 218
Georgia	680	620–740	359	53	618	550	550
India	64 000	44 000–84 000	2 967	4.6	2 967	7 800	15 000
Indonesia	6 100	3 900–8 400	182	3.0	142	600	900
Kazakhstan	6 400	5 900–6 900	7 387	115	5 705	–	–
Kyrgyzstan	1 000	880–1 200	566	57	566	–	–
Latvia	100	81–120	87	87	87	125	125
Lithuania	–	–	–	–	–	280	–
Myanmar	5 100	3 800–6 300	192	3.8	192	200	400
Nigeria	2 400	170–4 700	21	0.9	23	80	100
Pakistan	9 700	4 000–15 000	444	4.6	444	750	1 000
Philippines	8 800	6 700–11 000	522	5.9	548	3 500	2 372
Republic of Moldova	1 700	1 600–1 800	1 015	60	791	–	–
Russian Federation	31 000	24 000–38 000	13 692	44	13 692	11 400	17 000
South Africa	9 100	7 700–10 000	7 386	81	5 402	6 400	–
Tajikistan	1 400	1 100–1 700	333	24	245	700	300
Ukraine	6 600	5 900–7 300	5 333	81	3 870	–	–
Uzbekistan	3 100	2 200–4 000	1 023	33	628	972	1 080
Viet Nam	3 600	2 900–4 300	101	2.8	101	700	1 500
High MDR-TB burden countries	**250 000**	**160 000–340 000**	**46 748**	**19**	**38 652**	**44 177**	**51 992**
AFR	32 000	11 000–53 000	9 504	30	7 406	10 432	8 395
AMR	6 200	1 900–10 000	2 158	35	3 186	3 337	3 322
EMR	14 000	6 200–23 000	829	5.9	1 006	1 135	1 561
EUR	53 000	39 000–68 000	32 616	62	27 844	15 593	20 714
SEAR	88 000	68 000–110 000	3 779	4.3	3 901	12 240	18 980
WPR	77 000	61 000–93 000	4 222	5.5	2 210	11 285	11 352
Global	**290 000**	**210 000–380 000**	**53 108**	**18**	**45 553**	**54 022**	**64 324**

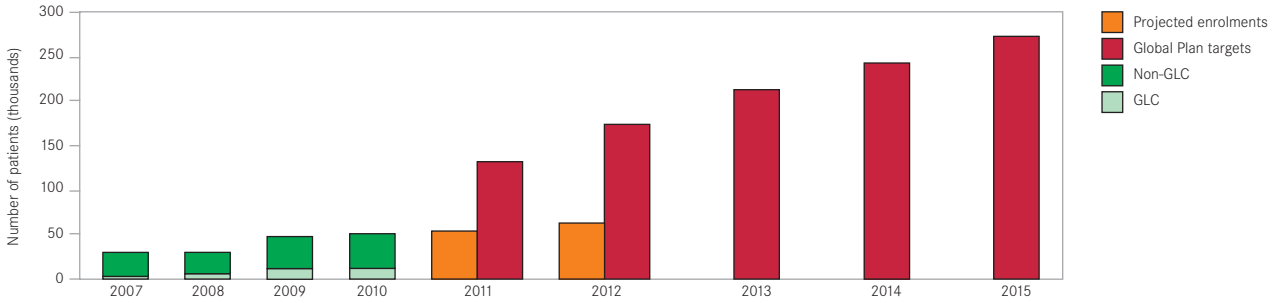
– Indicates data not available.

[a] Calculated by applying the best combined estimate of MDR to the notified cases of pulmonary TB in 2010.

[b] Percentage may exceed 100% as a result of notifications of cases from previous years, inadequate linkages between notification systems for TB and MDR-TB, and estimates of the number of cases of MDR-TB that are too conservative.

FIGURE 3.5

Notified cases of MDR-TB (2007–2010) and projected numbers of patients to be enrolled on treatment (2011–2012) in the 149 countries included in the Global Plan, compared with the targets included in the Global Plan to Stop TB 2011–2015.
The numbers represent smear and/or culture-positive cases of MDR-TB.



(Figure 3.5). Approaching these targets will require rapid expansion of diagnosis and treatment, notably in China and India.

3.5 Treatment outcomes

When the DOTS strategy was introduced in the mid-1990s, emphasis was given to the recording and reporting of treatment outcomes among patients with sputum smear-positive pulmonary TB: that is, the most infectious cases. Although efforts have been made to record and report the outcomes of treatment for other cases, the data for such cases are still incomplete. Among the countries reporting to WHO in 2010, 162 reported data on treatment outcomes among smear-negative and extrapulmonary cases.

As in previous reports in this series, the best available data on treatment outcomes are for sputum smear-positive cases of pulmonary TB (Table 3.6; for definitions of the categories used to report treatment outcomes see Box 3.6). Globally, the rate of treatment success for the 2.6 million new cases of sputum smear-positive pulmonary TB who were treated in the 2009 cohort was 87% (Table 3.6). This was the third successive year that the target of 85% (first set by the World Health Assembly in 1991) was exceeded globally. Among WHO's six regions, three met or exceeded the 85% target: the Eastern Mediterranean Region, the South-East Asia Region and the Western Pacific Region. The treatment success rate was 81% in the African Region (where there has been steady improvement since 1997), 76% in the Region of the Americas (where the rate has been relatively stable since 2002) and 66% in the European Region (where major efforts to increase treatment success rates are needed).

Of the 22 HBCs, 15 reached the 85% target. The seven countries that reported lower rates of treatment success were Brazil (72%), Ethiopia (84%), Nigeria (83%), the Russian Federation (55%), South Africa (77%), Uganda (67%) and Zimbabwe (78%). In Brazil and Uganda, low rates reflect a high proportion of patients for whom the outcome of treatment was not evaluated (11% and 16%, respectively) and high default rates (11% and 10%, respectively). In the Russian Federation, treatment failure rates are high, possibly linked to MDR-TB.

National data on treatment outcomes for cases of MDR-TB are limited. Data for cohorts of at least 200 patients are currently limited to 14 countries (Figure 3.6). Rates of treatment success are variable, ranging from below 50% (in the Republic of Moldova, South Africa and Romania) to 74% (in Kazakhstan). Most of these countries thus remain far from the Global Plan target of a treatment success rate of ≥75% as a result of high frequencies of treatment failure, death and default.

BOX 3.5

Infection control to prevent the transmission of TB

Outbreaks of MDR-TB and extensively drug-resistant TB (XDR-TB) in health-care facilities have highlighted the importance of proper infection control. Appropriate measures include personal protection (for example, masks), administrative controls (for example, in waiting areas for people attending outpatient services) and environmental measures such as ventilation systems. The best indicator to assess the quality of infection control in health-care settings is the ratio of the notification rate of TB among health-care workers to the notification rate among the general population (with appropriate adjustments for the age distribution of the two groups). This ratio should be approximately 1. The data required to calculate this indicator for 2010 were limited, and collection and reporting need to be improved. WHO is currently leading the development of guidance material on how to establish surveillance of TB among health-care workers.

Among the 149 low and middle-income countries from which data on infection control were requested, 34 had conducted a national assessment of infection control for TB, 49 had conducted an assessment of infection control in tertiary hospitals and 45 had a national plan for infection control (a plan was under development in a further 39 countries). Training related to infection control was implemented in 78 of these countries in 2010 and 79 had a focal point for infection control in at least one tertiary hospital.

TABLE 3.6

Treatment success for new smear-positive cases (%) and cohort size (thousands), 1995–2009

a. Treatment success (%)

	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Afghanistan	–	–	45	33	86	85	84	87	86	89	90	84	87	88	86
Bangladesh	71	63	73	77	79	81	83	84	85	90	91	92	92	91	92
Brazil	17	20	27	40	78	71	55	80	77	76	76	73	72	71	72
Cambodia	91	94	91	95	93	91	92	92	93	91	93	93	94	95	95
China	93	94	95	95	95	93	95	92	93	94	94	94	94	94	95
DR Congo	74	48	64	70	69	78	77	78	83	85	85	86	87	87	88
Ethiopia	61	71	72	74	74	80	76	76	70	79	78	84	84	84	84
India	25	21	18	27	21	34	54	60	76	82	86	86	87	87	88
Indonesia	91	81	54	58	50	87	86	86	87	90	91	91	91	91	91
Kenya	75	77	65	77	79	80	80	79	80	80	82	85	85	85	86
Mozambique	39	55	65	–	71	75	78	78	76	77	79	83	79	84	85
Myanmar	67	79	82	82	81	82	81	81	81	84	84	84	85	85	85
Nigeria	49	32	73	73	75	79	79	79	78	73	75	76	82	78	83
Pakistan	70	–	67	23	70	74	77	78	79	82	83	88	91	90	91
Philippines	60	35	78	71	87	88	88	88	88	87	89	88	89	88	89
Russian Federation	65	57	67	68	65	68	67	67	61	60	58	58	58	57	55
South Africa	58	61	68	72	57	63	61	68	67	69	71	74	74	76	77
Thailand	64	78	58	68	77	69	75	74	73	74	75	77	83	82	86
Uganda	44	33	40	62	61	63	56	60	68	70	73	70	75	70	67
UR Tanzania	73	76	77	76	78	78	81	80	81	81	82	85	88	88	88
Viet Nam	89	89	85	92	92	92	93	92	92	93	92	93	92	92	92
Zimbabwe	53	32	69	70	73	69	71	67	66	54	68	60	78	74	78
High-burden countries	**53**	**50**	**56**	**62**	**60**	**67**	**72**	**75**	**81**	**84**	**86**	**87**	**87**	**87**	**88**
AFR	60	56	64	70	68	71	70	73	73	74	76	75	80	80	81
AMR	50	51	58	67	79	76	69	81	80	79	79	76	79	77	76
EMR	79	66	73	57	79	81	82	84	82	83	83	86	88	88	88
EUR	67	58	72	63	75	75	74	74	75	70	72	70	71	70	67
SEAR	33	31	29	40	34	50	63	68	79	84	87	87	88	88	89
WPR	80	72	91	92	91	90	91	90	91	91	92	92	92	92	93
Global	**57**	**54**	**60**	**64**	**64**	**69**	**73**	**76**	**80**	**83**	**85**	**84**	**86**	**86**	**87**

b. Cohort size (thousands)

	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009
Afghanistan	–	–	2.0	2.9	2.0	3.1	6.3	7.8	6.8	10	10	12	13	13	12
Bangladesh	11	30	34	38	38	38	41	47	54	63	85	102	104	106	109
Brazil	46	45	43	30	27	34	41	29	38	43	42	48	38	41	41
Cambodia	4.4	9.1	12	13	16	15	14	17	19	19	21	19	19	20	18
China	131	175	189	210	208	214	190	194	267	385	473	470	466	464	449
DR Congo	16	25	26	33	35	36	41	45	54	62	65	63	66	66	72
Ethiopia	5.1	11	12	15	21	30	32	37	40	41	39	37	38	41	45
India	265	291	293	284	345	349	384	396	420	489	507	553	592	616	625
Indonesia	3.0	12	21	40	46	52	54	76	93	129	159	175	161	166	169
Kenya	6.5	13	19	22	27	28	31	31	34	41	40	39	38	37	37
Mozambique	11	13	11	–	12	13	14	15	16	17	18	18	18	19	20
Myanmar	7.9	9.7	9.2	10	12	17	21	24	27	31	37	40	43	41	42
Nigeria	9.5	24	11	13	15	16	17	21	28	34	35	40	44	46	45
Pakistan	0.8	–	2.8	29	3	4.1	6.3	15	20	32	48	66	89	100	102
Philippines	90	126	27	21	37	50	55	59	68	78	81	86	87	85	89
Russian Federation	0.05	43	0.7	0.7	1.5	3.6	4.1	5.2	6.3	26	26	31	32	32	32
South Africa	28	45	55	37	81	86	101	99	114	127	135	140	143	144	135
Thailand	20	0.1	3.7	8	14	23	20	27	28	28	30	29	30	33	28
Uganda	15	15	18	13	14	14	17	19	20	21	21	20	21	23	23
UR Tanzania	20	21	22	24	24	24	24	24	25	26	25	25	25	24	25
Viet Nam	38	48	54	55	53	53	54	57	56	58	55	56	54	53	51
Zimbabwe	9.7	12	12	13	13	14	17	16	14	15	13	16	11	10	10
High-burden countries	**739**	**967**	**879**	**912**	**1 044**	**1 119**	**1 186**	**1 260**	**1 450**	**1 776**	**1 965**	**2 087**	**2 132**	**2 181**	**2 179**
AFR	178	233	268	235	323	365	409	452	491	552	564	566	577	591	602
AMR	129	134	125	111	110	111	102	105	110	121	119	132	116	109	122
EMR	46	51	60	89	66	64	52	76	81	98	114	132	156	167	167
EUR	34	94	24	48	22	41	50	54	60	75	81	98	108	114	91
SEAR	318	360	376	399	473	512	550	604	661	780	856	938	974	1 011	1 022
WPR	296	372	294	313	353	360	346	357	439	575	663	663	661	657	632
Global	**1 001**	**1 245**	**1 147**	**1 195**	**1 347**	**1 453**	**1 510**	**1 649**	**1 842**	**2 200**	**2 396**	**2 529**	**2 591**	**2 649**	**2 637**

– Indicates no data reported.

BOX 3.6

Definitions of treatment outcomes for patients treated for drug-susceptible TB used for reporting at global level

Cured A patient who was initially smear-positive and who was smear-negative in the last month of treatment and on at least one previous occasion.

Completed treatment A patient who completed treatment but did not meet the criteria for cure or failure. This definition applies to pulmonary smear-positive and smear-negative patients and to patients with extrapulmonary disease.

Died A patient who died from any cause during treatment.

Failed A patient who was initially smear-positive and who remained smear-positive at month 5 or later during treatment.

Defaulted A patient whose treatment was interrupted for 2 consecutive months or more.

Not evaluated A patient whose treatment outcome is not known.

Successfully treated A patient who was cured or who completed treatment.

Cohort A group of patients in whom TB has been diagnosed, and who were registered for treatment during a specified time period (e.g. the cohort of new smear-positive cases registered in the calendar year 2005). This group forms the denominator for calculating treatment outcomes. The sum of the above treatment outcomes, plus any cases for whom no outcome is recorded (including those "still on treatment" in the European Region) should equal the number of cases registered. Some countries monitor outcomes among cohorts defined by smear and/or culture, and define cure and failure according to the best laboratory evidence available for each patient.

BOX 3.7

Definitions of treatment outcomes for patients treated for MDR-TB

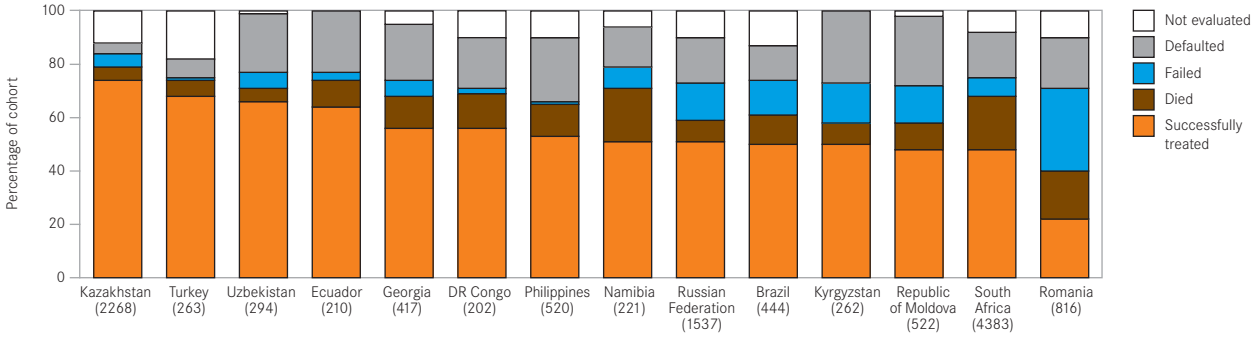
The categories used to assess treatment outcomes for patients with MDR-TB are the same as those for patients with drug-susceptible TB (see Box 3.6). The main differences are the definitions of cure and failure, which are recognized to be too complex for routine surveillance. In 2011, WHO initiated a consultation on updating the definitions of cases and treatment outcomes in the context of new diagnostic tests. It is anticipated that updated definitions will be agreed upon by the end of 2011. The definitions for cured and failed that are currently in use are summarized below.

Cured A patient who has completed a course of anti-TB treatment according to programme protocol and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment. If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.

Failed Anti-TB treatment will be considered to have failed if two or more of the five cultures recorded in the final 12 months of therapy are positive, or if any one of the final three cultures is positive. Treatment will also be considered to have failed if a clinical decision has been made to terminate treatment early because of poor clinical or radiological response or adverse events. These latter failures can be indicated separately in order to do sub-analysis.

FIGURE 3.6

Treatment outcomes for patients diagnosed with MDR-TB in 14 countries, 2008 cohorts. The total number of patients starting treatment in each cohort is shown under each country.[a]



[a] Only countries reporting outcomes for >200 MDR-TB cases with <20% not evaluated are shown. Countries are ranked by the proportion successfully treated (cured+completed).

CHAPTER 4

Financing TB care and control

KEY MESSAGES

- In 2012, funding for TB control is expected to reach US$ 3.3 billion in the 22 high-burden countries (HBCs) that account for 80% of the world's TB cases, up from US$ 1.3 billion in 2002.
- Among 97 countries for which trends can be assessed since 2006, funding is expected to reach US$ 4.4 billion in 2012. This is an increase from US$ 3.5 billion in 2006, but funding has levelled off since 2009.
- Almost three quarters of the funding for TB control in the 22 HBCs is accounted for by domestic funding in BRICS (Brazil, the Russian Federation, India, China and South Africa). However, in the other 17 HBCs, donor funding increased more than six-fold during the period 2002–2010, accounting for about half of the total TB expenditures of US$ 0.6 billion in these countries in 2010.
- International donor funding for TB control has increased by 50% since 2006, from US$ 0.4 billion to an expected US$ 0.6 billion in 2012, but still falls far short of funding for malaria (US$ 1.8 billion in 2009) and HIV (US$ 6.9 billion in 2010).
- Across 97 countries that reported data, the Global Fund is expected to account for 82% of the US$ 0.6 billion of donor funding for TB in 2012. Overall, donor funding accounted for 14% of total funding.
- Funding for MDR-TB has increased since 2009, but large funding gaps constrain plans to scale up diagnosis and treatment.
- Funding gaps reported by national TB control programmes for 2012 amount to US$ 0.8 billion, of which US$ 0.5 billion is accounted for by the 22 HBCs.
- Funding gaps in the 17 HBCs outside BRICS could be halved, from US$ 0.4 billion to US$ 0.2 billion, if donor funding for BRICS was redirected to these countries. The US$ 0.2 billion per year of donor funding for BRICS is almost sufficient to scale up the diagnosis and treatment of MDR-TB in low-income countries according to the targets included in the Global Plan to Stop TB 2011–2015.
- Expenditure tracking and reporting need to be improved; 3 HBCs have been unable to report expenditure data for at least the past two years.

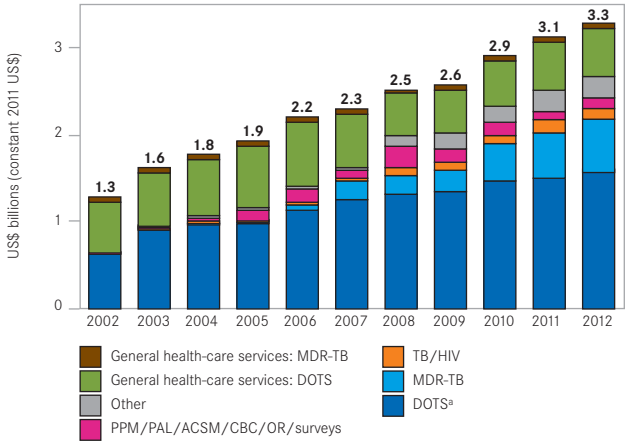
Progress in TB prevention, care and control requires adequate funding. WHO began monitoring of funding for TB in 2002, and the global TB database holds data from 2002 up to 2012. The data compiled to date allow assessment of trends in funding during the period 2002–2012 in the 22 high-burden countries (22 HBCs) that account for about 80% of the world's TB cases, and for a much larger set of countries since 2006. The first part of this chapter summarizes trends in funding for TB in the 22 HBCs, quantifies the funding gaps reported by these countries, compares levels of domestic and international funding, and summarizes estimates of the cost per patient treated. The second part of the chapter assesses a similar set of data for a group of 97 countries (22 HBCs and 75 other countries). Ambitious targets for scaling up diagnosis and treatment of multidrug-resistant TB (MDR-TB) between 2011 and 2015 have been set (**Chapter 1**), but the costs of treatment are several times higher than those for drug-susceptible TB. In this context, the third part of the chapter gives special attention to the funding needs, sources of funding and funding gaps for MDR-TB. The final part of the chapter compares available funding for TB with the resource requirements set out in the Global Plan to Stop TB 2011–2015.

4.1 Funding for TB care and control in the 22 high-burden countries

The funding available for TB control in the 22 HBCs has increased year-on-year since 2002, and is expected to reach US$ 3.3 billion in 2012 (**Figure 4.1**, **Figure 4.2**, **Figure 4.3**). Most of this funding has been used to support diagnosis and treatment with first-line drugs (labelled "DOTS" in **Figure 4.1**). However, it is noticeable that funding for the diagnosis and treatment of MDR-TB has increased since 2009, and is expected to reach US$ 0.6 billion in 2012 (**Figure 4.1**). This may be linked to increasing political commitment following a high-level ministerial conference on MDR-TB that was held in Beijing, China, in April 2009. The relatively small amounts of funding reported for collaborative TB/HIV activities (see **Chapter 6** for further details) reflect the fact that funding for most of these interventions (including the most expensive, antiretroviral treatment) is usually channelled to national HIV programmes and nongovernmental organizations rather than to national TB control programmes (NTPs).

FIGURE 4.1

Funding available for TB control by line item, 22 high-burden countries, 2002–2012



[a] DOTS includes the available funding for first-line drugs, NTP staff, programme management and supervision, and laboratories.

FIGURE 4.2

Funding available for TB control by source of funding, 22 high-burden countries, 2002–2012

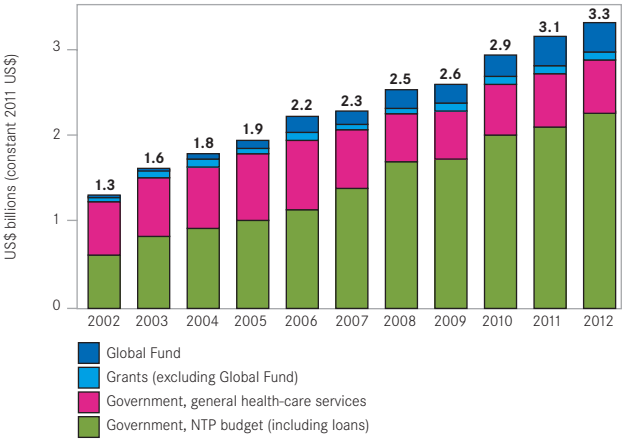


FIGURE 4.3

Funding available for TB control by country, 22 high-burden countries, 2002–2012

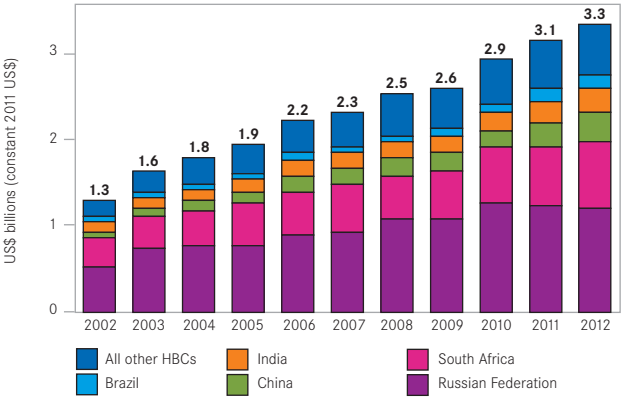
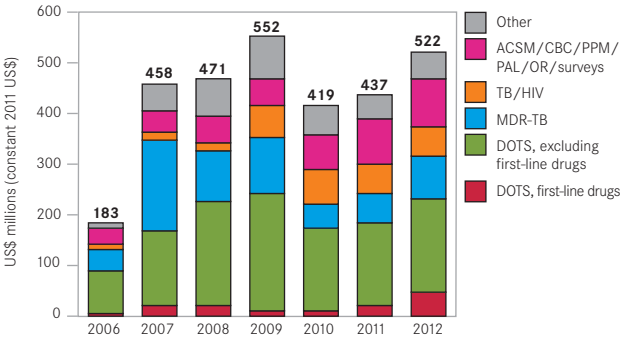


FIGURE 4.4

Funding gaps reported by NTPs, 22 high-burden countries, 2006–2012



Across all of the 22 HBCs, domestic funding from national governments is the single largest source of funding (**Figure 4.2**), accounting for 87% of total expected funding in 2012.[1] Nonetheless, the Global Fund has contributed a growing amount of funding since 2004, and is expected to reach US$ 362 million in 2012. The Global Fund is now easily the largest source of donor funding for TB; funding from other donor sources is expected to amount to only US$ 86 million in 2012.

In absolute terms, 60% of the funding expected for TB in the 22 HBCs in 2012 is accounted for by just two countries: the Russian Federation and South Africa (**Figure 4.3**). Brazil, the Russian Federation, India, China and South Africa (BRICS) account for 83% of expected funding, with 60% of all notified cases in the 22 HBCs (**Chapter 3**). Funding expected in the remaining 17 HBCs (which accounted for 40% of notified cases in HBCs in 2010) amounts to US$ 571 million in 2012, equivalent to 17% of the total funding expected in the 22 HBCs.

Despite increases in funding and 10 completed rounds of proposals[2] to the Global Fund, NTPs in the 22 HBCs continue to report funding gaps (**Figure 4.4**). Since 2007, these gaps have been in the range US$ 0.4–0.5 billion per year. In 2012, funding gaps are anticipated for several elements of TB care and control, including first-line drugs (for which the gap amounts to US$ 48 million in 2012).

[1] Domestic funding includes funding for outpatient visits and inpatient care in hospitals, the costs of which are not usually included in NTP budgets and expenditures. The amount of domestic funding for these inputs to TB treatment are estimated by combining data on the average number of outpatient visits and days in hospital per TB patient reported by countries with WHO estimates of the unit costs of outpatient visits and bed-days (see www.who.int/choice).

[2] The first round was completed in 2003. Round 10 was completed in 2010.

TABLE 4.1

NTP budgets, available funding, cost of utilization of general health-care services and total funding required according to country plans, 2012 (US$ millions)

	NTP BUDGET	AVAILABLE FUNDING				FUNDING GAP[a]	COST OF GENERAL HEALTH-CARE SERVICES (ESTIMATED)[b]	TOTAL FUNDING REQUIRED[c]
		GOVERNMENT (EXCLUDING LOANS)	LOANS	GRANTS (EXCLUDING GLOBAL FUND)	GLOBAL FUND			
Afghanistan	11	0.4	0	3.7	4.5	2.0	5.2	16
Bangladesh	48	1.2	0	2.2	10	35	5.1	53
Brazil	87	71	0	1.4	0.9	13	75	162
Cambodia	40	1.2	0	8.9	4.5	26	4.8	45
China	350	220	0	3.6	95	32	0	350
DR Congo	62	–	–	–	–	–	0.7	63
Ethiopia	52	8.8	0	15	15	13	13	64
India	210	43	87	0	80	0	84	293
Indonesia	102	16	0	0.2	47	39	19	121
Kenya	53	6.1	1.7	0.5	12	33	8.8	62
Mozambique	39	1.9	0.7	19	2.8	15	10	49
Myanmar	29	0.6	0	2.0	8.1	19	2.9	32
Nigeria	43	6.6	0	6.8	13	17	24	67
Pakistan	64	2.8	0	2.9	5.7	53	5.9	70
Philippines	79	24	0	0	24	31	58	137
Russian Federation	1 204	1 204	0	0	0	0	35	1 239
South Africa	–	–	–	–	–	–	–	–
Thailand	45	34	0	4.5	3.2	3.5	3.4	48
Uganda	20	0.1	0.2	2.4	3.5	14	0.3	20
UR Tanzania	42	7.3	0	6.8	5.2	23	2.4	45
Viet Nam	74	4.6	0	1.0	9.2	59	26	100
Zimbabwe	–	–	–	–	–	–	–	–
High-burden countries[d]	**2 653**	**1 654**	**90**	**80**	**343**	**425**	**383**	**3 036**
AFR[e]	1 035	590	4.0	65	143	233	355	1 390
AMR	175	111	0	12	17	35	151	327
EMR	168	63	0	8.9	30	67	64	233
EUR	1 632	1 339	0	2.1	51	240	347	1 979
SEAR	449	105	87	15	147	95	108	557
WPR	595	309	1.0	14	121	149	183	777
Global[e]	**4 054**	**2 517**	**92**	**117**	**509**	**819**	**1 209**	**5 263**

– indicates not available.

[a] Calculated as the NTP budget minus all the available funding.

[b] See text for an explanation of how these costs are estimated.

[c] Calculated as the NTP budget plus the cost of utilization of general health-care services.

[d] These totals do not include estimates for DR Congo, South Africa and Zimbabwe and are therefore lower than those in Figures 4.1–4.5.

[e] The regional and global totals include estimates for those countries that did not report data for 2012 and are in constant 2011 US$, consistent with totals presented elsewhere in this report.

Trends in funding, funding gaps and expenditures in the 22 HBCs as a whole conceal important variation among countries, and differences between BRICS and the other 17 HBCs are especially striking (**Table 4.1**, **Figure 4.5**, **Figure 4.6**).

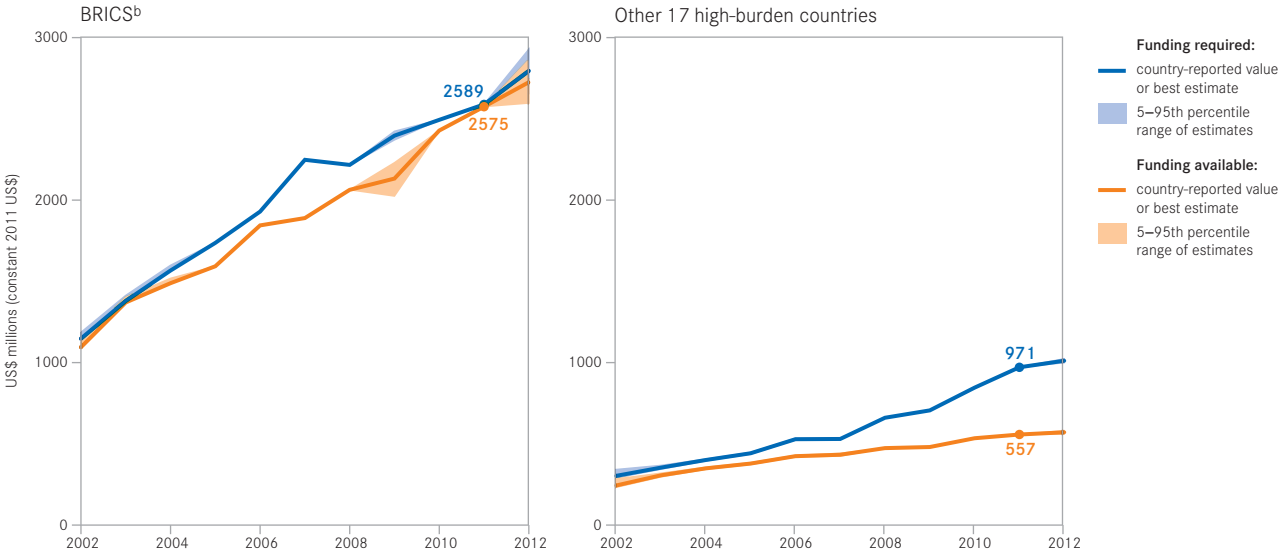
The funding estimated to be required in BRICS has steadily increased since 2002 (see **blue** line in **Figure 4.5**), and the available funding has kept pace (see **orange** line in **Figure 4.5**). In the other 17 HBCs, the amount of funding estimated to be required and the funding available have also increased, but large funding gaps have persisted and widened over the past decade. The 17 HBCs outside BRICS have reported a funding gap of US$ 0.4 billion in 2012, ranging from US$ 2 million in Afghanistan to US$ 59 million in Viet Nam (**Table 4.1**). Funding gaps in the 17 HBCs outside BRICS could be halved in 2012, from US$ 0.4 billion to US$ 0.2 billion, if all donor funding for BRICS was redirected to these countries.

In BRICS, most funding (95% in 2010) for NTPs comes from domestic sources (**Figure 4.6**), although India was an outlier at around 50%.[1] In the other 17 HBCs, only 33% of the funding for NTPs was from domestic sources in 2010. When the resources that are used to pro-

[1] Further details for individual countries can be found in **Annex 2**, and in finance country profiles for around 100 countries that are available online at **www.who.int/tb/data**.

FIGURE 4.5

Funding required[a] and funding available for TB control, 22 high-burden countries, 2002–2012

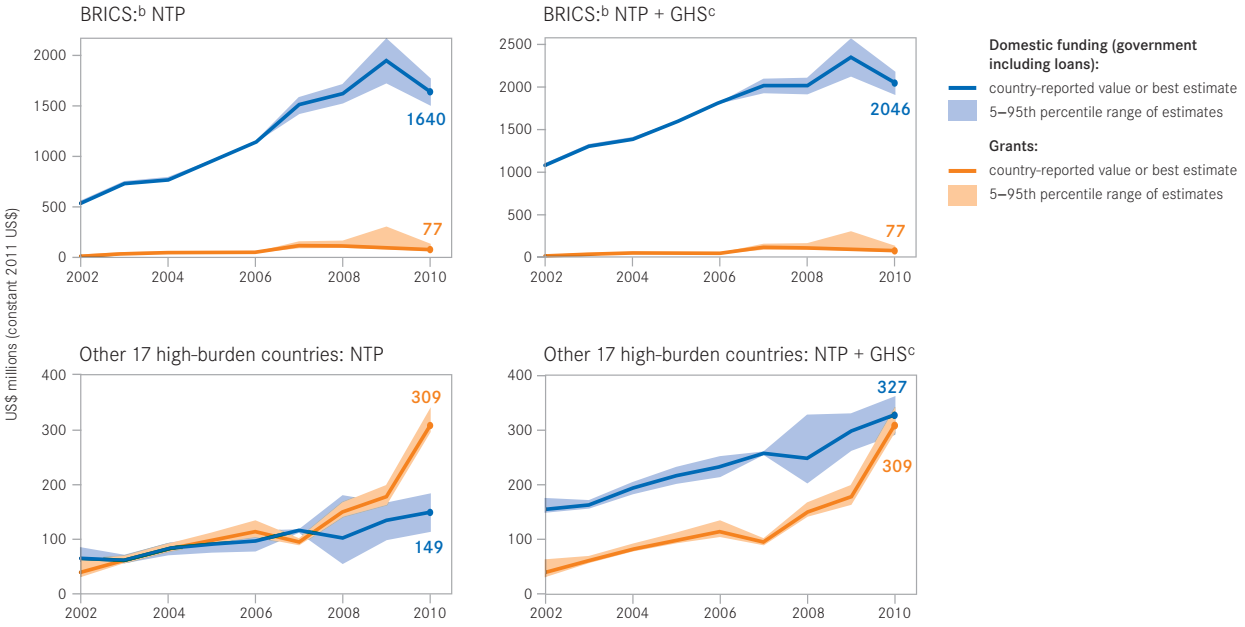


[a] Funding required is the sum of the funds needed to fully fund NTP budgets plus the funds needed for outpatient visits and hospital stays (general health-care services) if these are not already included in NTP budgets. The difference between the funding required and the funding available is the funding gap reported by NTPs.

[b] Brazil, the Russian Federation, India, China and South Africa.

FIGURE 4.6

TB expenditures by source of funding,[a] 22 high-burden countries, 2002–2010



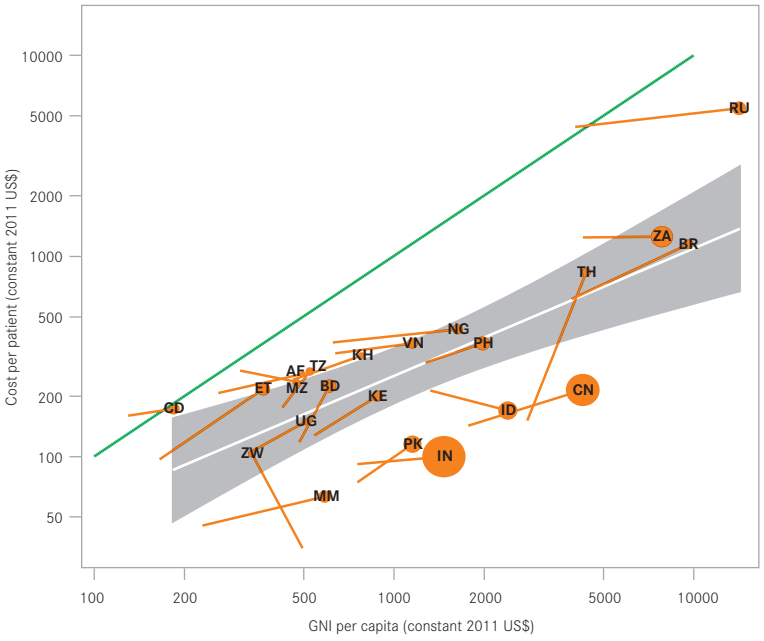
[a] Total expenditures may be less than funding available in **Figure 4.5**, as not all funding commitments translate into disbursements and not all disbursements translate into expenditures.

[b] Brazil, the Russian Federation, India, China and South Africa.

[c] GHS is the cost of resources used for TB treatment in the general health system that are not usually managed by the NTP. It includes the costs associated with hospital stays and outpatient visits.

FIGURE 4.7

Cost per TB patient treated with first-line drugs,[a] 22 high-burden countries,[b] 2004 and 2010[c]



- The size of the orange circle is proportional to the number of cases treated in 2010.
- The tail attached to each circle depicts the change in cost per patient and GNI per capita between 2004 and 2010.
- The grey area depicts the 95% confidence interval for the prediction (= white line) of the unweighted log–log regression of cost per patient on GNI per capita in 2010.
- The green line marks where cost per patient equals GNI per capita.

[a] Costs include all resources used for treatment (not only first-line drugs), i.e. all items included in Figure 4.1 with the exception of those for MDR-TB.

[b] **AF** Afghanistan; **BD** Bangladesh; **BR** Brazil; **CN** China; **CD** Democratic Republic of the Congo; **ET** Ethiopia; **ID** Indonesia; **IN** India; **KE** Kenya; **KH** Cambodia; **MM** Myanmar; **MZ** Mozambique; **NG** Nigeria; **PK** Pakistan; **PH** Philippines; **RU** Russian Federation; **TH** Thailand; **TZ** United Republic of Tanzania; **UG** Uganda; **VN** Viet Nam; **ZA** South Africa; **ZW** Zimbabwe.

[c] Costs per patient treated are based on 3-year averages, 2002–2004 and 2008–2010, to minimize distortions associated with non-annual expenses on items such as buildings, equipment and buffer stocks of drugs.

vide TB diagnosis and treatment within the general health system (that is, the staff and health facilities used for outpatient and inpatient care) are added to the resources included in NTP budgets, the share of funds contributed from domestic sources increases in both sets of countries (**Figure 4.6**). Nonetheless, the share still only reached 51% in the 17 countries outside BRICS in 2010.[1] Between 2009 and 2010 there was a marked reduction in expenditures in BRICS (driven by the Russian Federation although there were falls in spending in Brazil and China as well), and expenditures also declined in Mozambique and Viet Nam.

The estimated cost per patient treated for TB with first-line drugs is shown for each of the 22 HBCs in **Figure 4.7**. The cost generally lies in the range US$ 100–500 per patient treated. The exceptions are Myanmar (under US$ 100), Thailand (US$ 830) and Brazil, the Russian Federation and South Africa (above US$ 1000). Between 2004 and 2010, the cost per patient treated has increased in almost all of the HBCs, as has GNI [gross national income] per capita, with the exception of Indonesia and Mozambique. It is noticeable that in all of the HBCs, the cost per patient treated is less than GNI per capita (that is, all values lie below the solid **green** line in **Figure 4.7**). Besides GNI, a further explanation for variation in costs appears to be the scale at which treatment is provided. Some of the countries with relatively low costs for their income level (for example, China, India, Indonesia and Pakistan) are countries where the total number of patients treated each year is comparatively high (as shown by the size of the circles in **Figure 4.7**).

As in previous years, the cost of treating TB patients with first-line drugs in the Russian Federation is higher than might be expected for the country's income level. The relatively high cost is due in large part to an extensive network of hospitals and sanatoria that are used for lengthy inpatient care. Nevertheless, there is evidence that some costs are starting to fall, with decreasing expenditures on staff and gradual reductions in the use of inpatient care. In addition, the number of dedicated beds for TB patients fell from 103 000 in 2007 to less than 97 000 in 2010, and the average length of stay for a TB patient fell from 106 to 84 days. It should also be highlighted that the characteristics of the patient population in the Russian Federation (such as high rates of alcohol abuse and unemployment, and a comparatively high proportion of ex-prisoners) may also warrant additional investments in some aspects of TB care. Examples include patient enablers and incentives to support outpatient care, and psychosocial support.

4.2 Funding for TB care and control in the 22 high-burden countries and 75 other countries

Besides the 22 HBCs, 75 other countries have reported financial data to WHO since 2006 that allow assessment of trends in funding for TB control. These 97 countries accounted for 92% of the world's notified cases of TB in 2010.

Funding for TB control in these 97 countries has grown from US$ 3.5 billion in 2006 to a projected US$ 4.4 billion in 2012 (**Figure 4.8**, **Figure 4.9**); funding has levelled off

[1] Further details for individual countries can be found in **Annex 2**, and in finance country profiles for around 100 countries that are available online at **www.who.int/tb/data**.

FIGURE 4.8

Funding available for TB control by line item and funding gap, 22 high-burden countries and 75 other countries,[a] 2006–2012

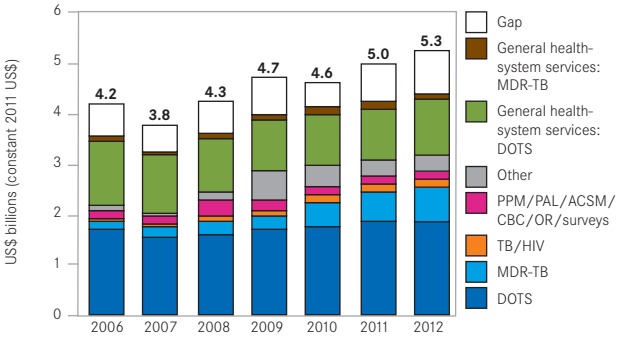
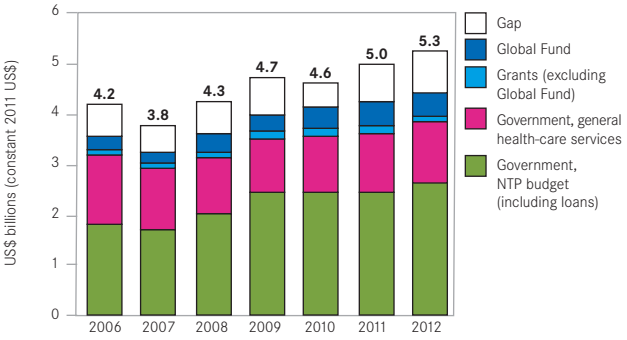


FIGURE 4.9

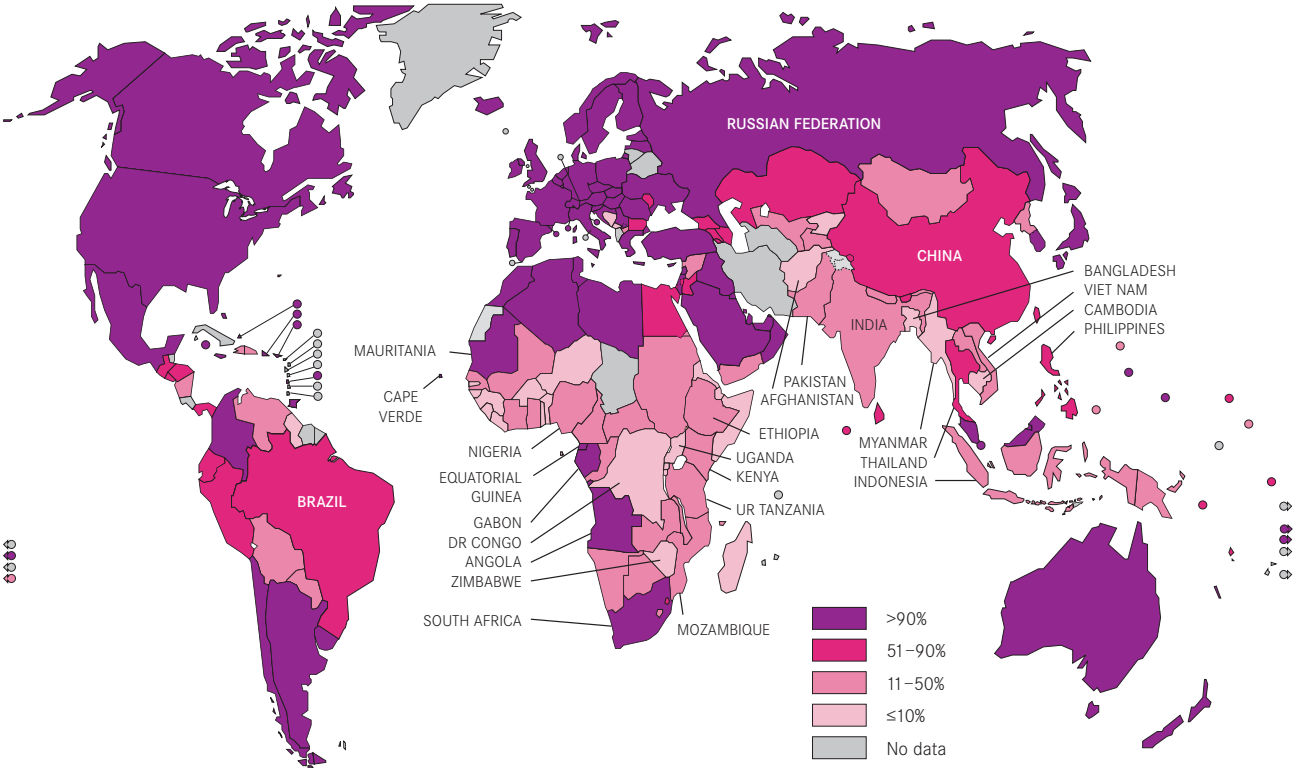
Funding available for TB control by source of funding and funding gap, 22 high-burden countries and 75 other countries,[a] 2006–2012



[a] These countries together account for 92% of the total number of drug-susceptible TB cases notified globally in 2010.

FIGURE 4.10

Domestic funding as a percentage of total funding available to the NTP, 2011



since 2009. As in the 22 HBCs, the largest share of funding is for TB diagnosis and treatment with first-line drugs (labelled "DOTS" in **Figure 4.8**); an increasing amount is for MDR-TB. National governments account for 86% of the funding expected in 2012, followed by the Global Fund (US$ 515 million, or 12% of total funding) and then by grants from donors besides the Global Fund (US$ 113 million, or 2%). International donor funding for TB control has increased by 50% since 2006, from US$ 0.4 billion to an expected US$ 0.6 billion in 2012, but still falls far short of funding for malaria (US$ 1.8 billion in 2009)[1] and HIV (US$ 6.9 billion in 2010).[2]

Funding gaps in the 97 countries amounted to US$ 0.7 billion in 2011 and are anticipated to reach US$ 0.8 billion in 2012 (**Figure 4.9**).

Global aggregates conceal wide variation in the share of funding from domestic sources at country level (**Figure 4.10**). For example, in most countries of sub-Saha-

[1] *World malaria report 2010*. Geneva, World Health Organization, 2010.

[2] *Financing the response to AIDS in low and middle-income countries. international assistance from donor governments in 2010*. UNAIDS and the Kaiser Family Foundation, 2010. Available at **www.unaids.org**

FIGURE 4.11

Cost per TB patient treated with first-line drugs (US$), 2010

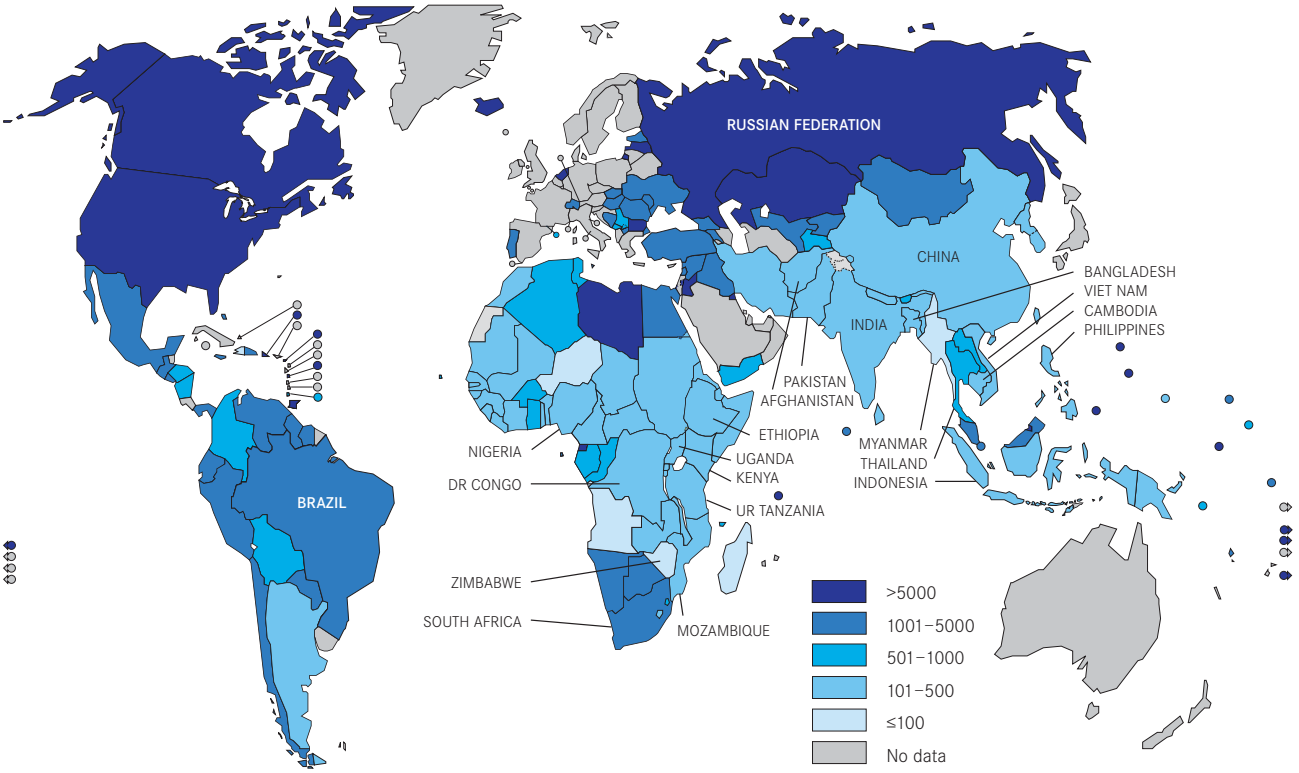
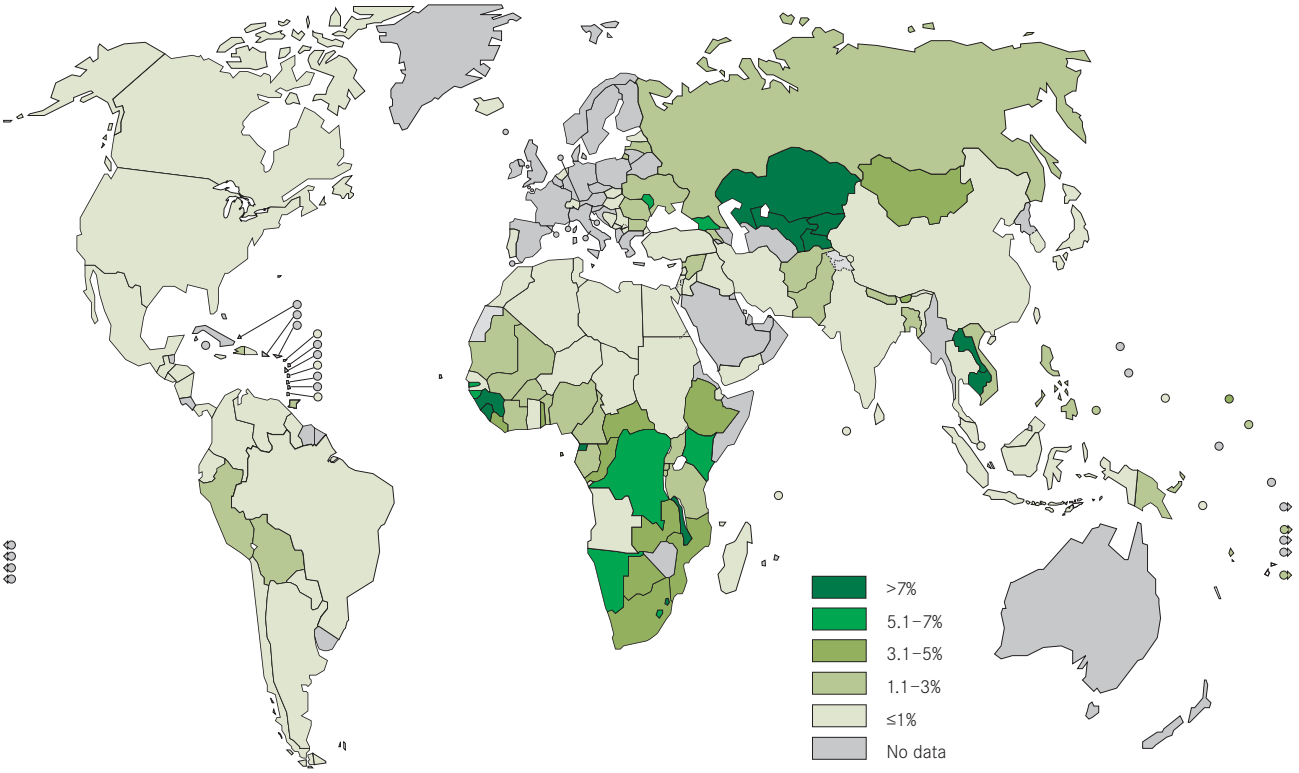


FIGURE 4.12

The cost of TB control as a percentage of total health expenditures by the public sector, 2009



ran Africa the share of funding from domestic sources is below 50% (the exceptions are Angola, Cape Verde, Equatorial Guinea, Gabon and South Africa – all high-income or middle-income countries).

The cost of treating a patient with first-line drugs at country level is summarized in **Figure 4.11**. In most countries in the African, South-East Asia and Western Pacific regions, the cost per patient treated is under US$ 1000 (exceptions include Botswana, Namibia and South Africa in the African Region, and Malaysia in the Western Pacific Region). Costs are higher in the Region of the Americas and the European Region.

In general, the cost of TB control as a proportion of public health expenditures[1] is relatively low (**Figure 4.12**).[2] In most countries, TB control accounts for <3% of public health expenditures. Cambodia, Kazakhstan, Kyrgyzstan, Lao PDR, Tajikistan and Uzbekistan stand out as countries that have high levels of spending on TB relative to total health expenditure. Part of the explanation is that these countries are among the list of 27 high MDR-TB burden countries,[3] and treatment for MDR-TB is comparatively expensive. Other reasons include continued use of models of care for all forms of TB that rely extensively on inpatient care. For example, in Kazakhstan, 84% of smear-negative cases and 96% of smear-positive cases[4] are hospitalized, with average lengths of stay of 60 and 105 days respectively; 35% of cases of MDR-TB are hospitalized for 180 days. In Kyrgyzstan, Tajikistan and Uzbekistan, more than 50% of new cases are hospitalized, for an average of more than 50 days.

Further details for all of the 97 countries that reported financial data are provided in regional and country finance profiles that are available online.[5]

Improvements to the methods used to analyse financial data, ongoing data challenges and ways in which the quantity and quality of financial data can be improved are described in **Box 4.1**.

4.3 Funding needs and gaps for MDR-TB care and control

Of the estimated 290 000 cases of MDR-TB among notified cases of pulmonary TB in 2010, only around 50 000 were reported to have been enrolled on treatment (**Chapter 3**). China and India account for 44% of the estimated cases (about 130 000), but reported only small numbers of cases as enrolled on treatment (just over 4000). In the Russian Federation, which ranks third in terms of the estimated number of cases of MDR-TB among notified cases of pulmonary TB (about 31 000 cases), almost 14 000 patients were enrolled on treatment. In European countries excluding the Russian Federation, there were an estimated 22 000 people with MDR-TB among notified cases of pulmonary TB (8% of the global total) in 2010, just under 19 000 of which were enrolled on treatment. Kazakhstan enrolled more cases on treatment (5705, or 13% of the total) than any other country apart from the Russian Federation. With 5402 patients enrolled on treatment in 2010, South Africa ranked third.

The funding available for MDR-TB treatment in 106 countries that reported data increased from US$ 0.2 billion in 2006 to US$ 0.7 billion in 2011 (**Figure 4.13**).[6] Second-line drugs accounted for 30–50% of the total, depending on the year. In 2011, three countries account for most of the funding: in descending order, they are South Africa, the Russian Federation and Kazakhstan, with a combined total of US$ 0.5 billion.[7] Much of the remaining funding is accounted for by China (US$ 35 million) and India (US$ 47 million). Although the amounts of funding for MDR-TB in China and India are small relative to the other three countries, they represent a large increase compared with amounts of US$ 0.2 million and US$ 1.9 million respectively in 2006.

Much of the reported funding for MDR-TB is from domestic sources, but the share varies from year to year. Since 2006, domestic financing has represented 60–94%

[1] Source: World Health Organization National Health Account database (**www.who.int/nha/en**) accessed via **http://data.worldbank.org/indicator/SH.XPD.PUBL.ZS** in July 2011.

[2] In some countries in Africa, estimates appear to be too high because of a denominator that is underestimated. A good example is the Democratic Republic of the Congo; here, the explanation may be a lack of data on expenditures by regional governments.

[3] For the list of 27 countries, see **Chapter 2** and **Chapter 3**.

[4] For case definitions, see **Chapter 3**.

[5] **www.who.int/tb/data**

[6] These amounts include the estimated value of resources used for inpatient care and outpatient visits, which are not usually part of the budgets and expenditures reported by NTPs. They exclude laboratory supplies and equipment, since amounts for MDR-TB specifically are not distinguished in the WHO data collection form.

[7] Financial data were not reported to WHO by South Africa in 2011. The funding available was estimated using data reported in previous years as well as a detailed budget developed using the WHO TB planning and budgeting tool in 2007 (see **Box 4.1**).

BOX 4.1

Improved methods for data analysis and ongoing data challenges

Improved methods for data analysis

Uncertainty about estimates of total NTP budgets, available funding and expenditures was more rigorously accounted for in the time-series presented in this chapter, compared with previous reports in this series. Missing values were estimated using a regression model in which the budget requested for period *t* in a specific country was assumed to depend on a combination of the final budget requested for period *t-1* and/or the number of TB cases in period *t*. One or both of these variables were included in a stepwise regression, with forward selection based on p-values. In the absence of any significant explanatory variables, a linear time-trend was fitted to the reported budget values and missing values were interpolated. For countries that have reported budget data but have never reported expenditures, expenditure data reported by other countries within the same income group were used to estimate the proportion of the required budget that was ultimately funded and spent. A full description of the methods will be made available in a paper for a peer-reviewed journal.

Weaknesses in financial data reported to WHO

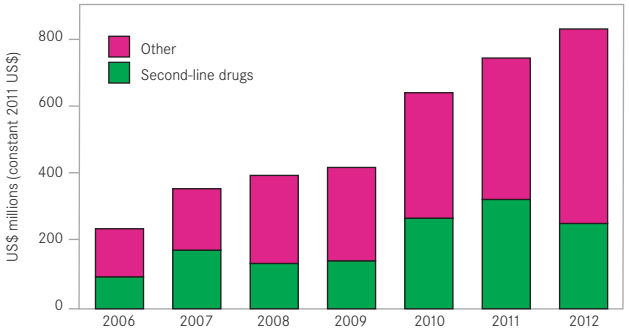
During WHO's annual process of data collection, review and follow-up, considerable efforts are made to maintain and improve the quality and completeness of financial reports. Despite these efforts, expenditure data are consistently less complete than budget data. Examples of HBCs where there have been persistent difficulties with reporting expenditures include South Africa (since 2006), Uganda (since 2005) and Thailand (since 2008). In Uganda, reasons include difficulties in compiling data from four administrative regions and 111 districts. In South Africa, it has proved difficult to compile expenditures from the nine provinces and 44 district municipalities. Wide uncertainty bands on the estimates of expenditures in these and other countries illustrate the need for investments in financial management systems, especially in countries where responsibility for budget allocation and monitoring of expenditures is decentralized to subnational levels (such as states and provinces), to ensure that TB expenditures can be tracked at all levels.

Efforts to improve the quantity and quality of financial data

WHO continues to promote and train countries to use the TB Planning and Budgeting tool to improve the quality of the data being reported (and to make it easier for countries to report to WHO). By mid-2011, the tool had been used to develop plans and budgets in 13 of the 22 HBCs and a further 28 countries. An assessment of the tool by users in 2011 will help to make further improvements; input can be provided via WHO's Stop TB Department web site (www.who.int/tb). For some countries, specific studies following the established methods of national health accounts may be required on a periodic basis to better track TB expenditures.

FIGURE 4.13

Funding available for MDR-TB by line item, 106 countries,[a] 2006–2012



[a] These countries accounted for 96% of the total number of MDR-TB cases enrolled on treatment in 2010.

of the NTP budget; on the assumption that hospital care and outpatient visits during treatment (typically not included in NTP budgets) are domestically financed, this figure for domestic financing increases to 79–96% of the total funding available for MDR-TB. The value of grants for MDR-TB from the Global Fund is growing, and reached US$ 0.13 billion in 2011 (equivalent to 91% of total grant financing for MDR-TB). According to country reports, the biggest grants are for India and China, at US$ 36 million and US$ 31 million respectively.

The funding that is available for MDR-TB is much lower than the funding requirements set out in the Global Plan 2011–2015.[1] The estimates in the plan are that US$ 7 billion is needed over five years, increasing from US$ 0.9 billion in 2011 to US$ 1.9 billion in 2015 (see also **section 2.4**), for the cumulative treatment of 1.1 million people with MDR-TB, including 270 000 in 2015. To reach the plan targets, substantial resource mobilization will be needed. A new analysis suggests that most of the funding required for scaling up MDR-TB diagnosis and treatment could come from domestic funding in BRICS and other middle-income countries (**Box 4.2**).

[1] *The Global Plan to Stop TB, 2011–2015*. Geneva, World Health Organization, 2010 (WHO/HTM/STB/2010.2).

BOX 4.2

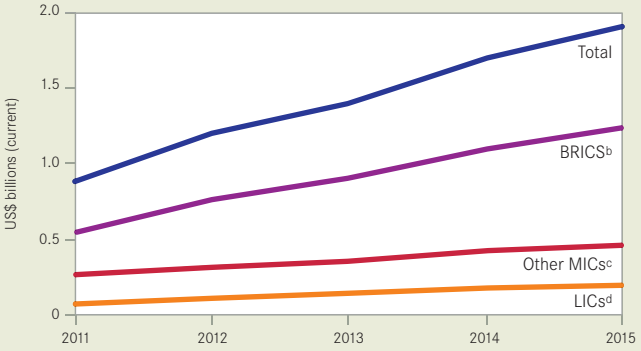
Financing the expansion of diagnosis and treatment of MDR-TB

In a new analysis conducted for this report, the funding needs for MDR-TB set out in the Global Plan to Stop TB 2011–2015 were estimated for three groups of countries: BRICS (Brazil, the Russian Federation, India, China and South Africa), other middle-income countries (MICs), and low-income countries (LICs). These groupings were defined with the rationale that BRICS as well as other MICs should have the capacity to fund the diagnosis and treatment of MDR-TB from domestic sources, while LICs will need financial support from grant sources. Estimates of funding requirements for each group were developed using projections of the number of patients that would need to be treated in each country to reach the Global Plan target, and estimates of the cost per patient treated for individual countries that underpinned the analyses conducted for the Global Plan.

Funding needs in the three groups of countries are illustrated in the figure (right). BRICS account for more than 60% of the required funding in each year and almost 70% of overall funding (US$ 4.6 billion for 2011–2015). Other MICs require US$ 0.2–0.4 billion per year, and US$ 1.8 billion in total. The LICs require US$ 0.1–0.2 billion per year, and US$ 0.7 billion in total.

Donor funding for MDR-TB amounted to US$ 0.14 billion in 2011. If prioritized for LICs, current levels of donor funding would be almost sufficient to finance the scale-up of MDR-TB diagnosis and treatment in line with the targets included in the Global Plan.

Funding required for MDR-TB, Global Plan to Stop TB, 2011–2015[a]



[a] Total funding required is the best estimate from the range of plausible values reported in the Global Plan to Stop TB, 2011–2015.
[b] Brazil, the Russian Federation, India, China and South Africa.
[c] Other middle-income countries (not including BRICS).
[d] Low-income countries.

It should also be highlighted that there is scope to lower the costs of treatment. The average (median) cost per patient implied by data reported by the 27 high MDR-TB burden countries 2009–2011 is US$ 8200 (interquartile range, US$ 6200–21 700). Besides the more expensive drug regimens that are needed for treatment, a major reason for relatively high costs (compared with those for first-line treatments shown in **Figure 4.7**) is that people are treated for lengthy periods of time in hospital. The latest WHO guidelines on the programmatic management of MDR-TB include a conditional recommendation for outpatient treatment, based on a systematic review of the cost and cost-effectiveness of models of care in Estonia, Peru, the Philippines and Tomsk (Russian Federation).[1,2] The outpatient models cost less than US$ 4000 per patient.

[1] Fitzpatrick C, Floyd K. A systematic review of the cost and cost-effectiveness of treatment for multidrug-resistant tuberculosis. *PharmacoEconomics*, 2011 [accepted for publication].

[2] *Guidelines for the programmatic management of drug-resistant tuberculosis, 2011 update*. Geneva, World Health Organization, 2011. **www.who.int/tb/challenges/mdr/programmatic_guidelines_for_mdrtb**

4.4 Comparisons of funding available for TB care and control with the resource requirements estimated in the Global Plan to Stop TB 2011–2015

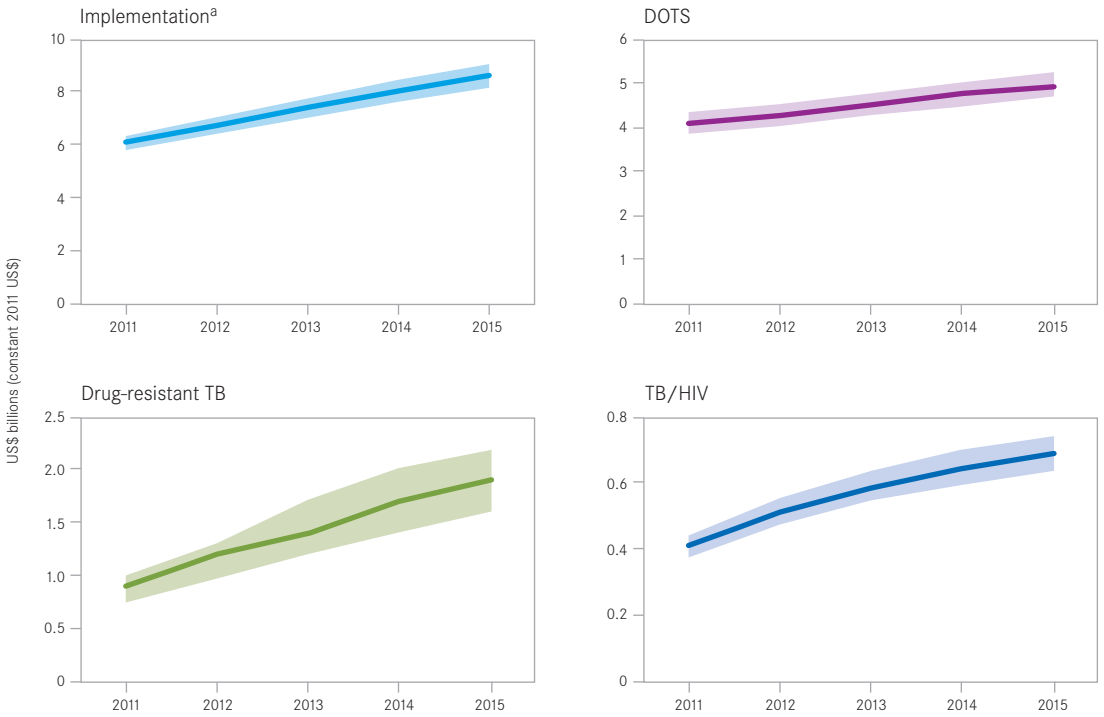
The Global Plan to Stop TB 2011–2015 was developed by the Stop TB Partnership in 2010.[1] It sets out what needs to be done to achieve the global targets for TB control set for 2015,[2] and the associated funding requirements (**Table 4.2**, **Figure 4.14**). The total requirement over five years amounts to US$ 47 billion. Excluding research and development for new TB drugs, diagnostics and vaccines (**Chapter 7**), which are not the responsibility of NTPs, the total is US$ 37 billion. This rises from around US$ 6 billion in 2011 to US$ 8 billion in 2015 (**Figure 4.14**). Diagnosis and treatment following the DOTS approach requires the largest single share of funding – US$ 4 billion in 2011 increasing to around US$ 5 billion in 2015. The second largest component is diagnosis and treatment of MDR-TB, for which the funding requirement is estimated at US$ 1 billion in 2011, rising to almost US$ 2 billion in 2015.

A comparison of the funding requirements set out in the Global Plan with the funding available in the 149 low-income and middle-income countries considered in the plan is provided in **Figure 4.15**.[3] Overall, funding falls about US$ 2 billion short of the requirements estimated in the Global Plan in 2012. This includes a gap of about

[1] *The Global Plan to Stop TB, 2011–2015*. Geneva, World Health Organization, 2010 (WHO/HTM/STB/2010.2).
[2] For a summary of the targets set in the plan, see **Chapter 1**.
[3] The total funding available in the 97 countries for which data were available was adjusted upwards according to the fraction of cases for which they accounted, to allow direct comparison with the group of 149 countries considered in the Global Plan. The Global Plan excludes high-income countries.

FIGURE 4.14

Funding required to implement the Global Plan to Stop TB, 2011–2015



[a] Implementation includes DOTS, Drug-resistant TB, TB/HIV, Laboratory strengthening and Technical assistance.

FIGURE 4.15

Funding required according to the Global Plan to Stop TB, 2011–2015, funding required according to country plans and funding available for TB control, 2010–2012, 149 countries

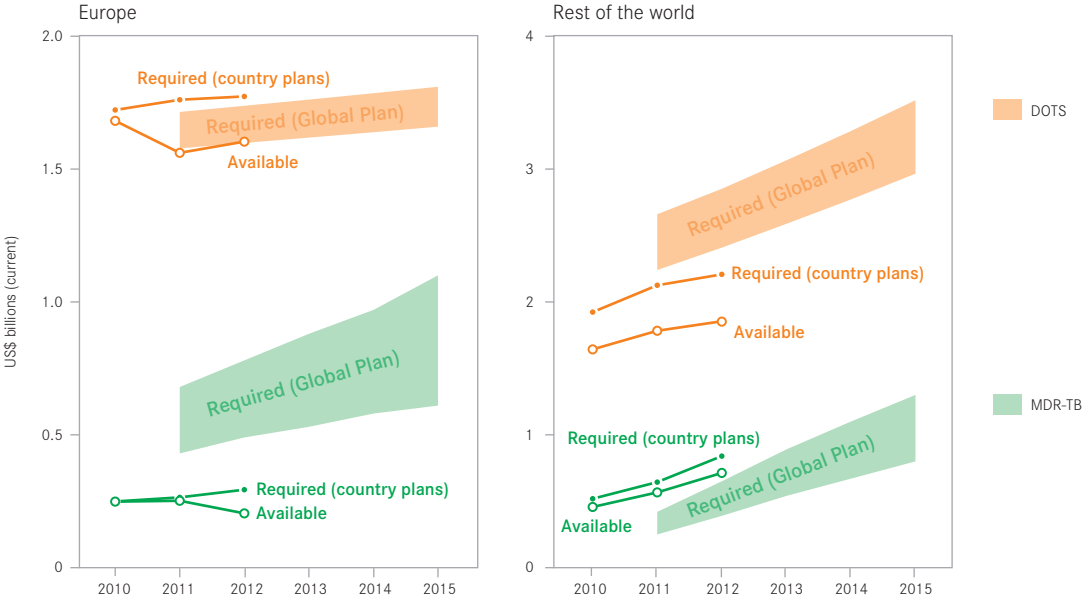


TABLE 4.2

Summary of funding requirements for TB control during the period 2011–2015, as set out in the Global Plan to Stop TB

PLAN COMPONENT	TOTAL FUNDING REQUIRED (US$ BILLIONS) [% OF TOTAL]	PLAUSIBLE RANGE
Implementation	**36.9 [79%]**	**36.1–37.7**
DOTS	22.6 [48%]	22.1–23.2
MDR-TB	7.1 [15%]	6.6–7.7
TB/HIV	2.8 [6%]	2.7–2.9
Laboratory strengthening	4.0 [8%]	3.7–4.2
Technical assistance	0.4 [1%]	
Research and development	**9.8 [21%]**	
Fundamental research	2.1 [5%]	
New diagnostics	1.7 [4%]	not estimated
New drugs	3.7 [8%]	
New vaccines	1.9 [4%]	
Operational research	0.4 [1%]	
All components	**46.7 [100%]**	**45.9–47.5**

US$ 1 billion for treatment with first-line drugs (labelled "DOTS" in **Figure 4.15**) in countries outside Europe, and US$ 0.5 billion for treatment of patients with MDR-TB in eastern Europe. These gaps reflect the funding gaps reported by countries (as reported in **section 4.1** and **section 4.2**), but also planning for the implementation of TB control that is less ambitious than the targets set out in the Global Plan (especially the targets set for MDR-TB, as discussed in **Chapter 3**). It should be emphasized that although funding for MDR-TB appears to exceed the funding required in the group of countries outside eastern Europe (labelled "rest of the world" in **Figure 4.15**), this funding is heavily concentrated in one country: South Africa.

CHAPTER 5

New diagnostics and laboratory strengthening for TB

KEY MESSAGES

- The landscape of TB diagnostics is rapidly evolving and WHO has established a dynamic and systematic process for timely formulation of policy. Between July 2010 and July 2011, this process resulted in the endorsement of a new test for rapid diagnosis of TB and drug-resistant TB – Xpert MTB/RIF as well as a negative policy on the use of commercial serodiagnostics for the diagnosis of active TB.
- The Xpert MTB/RIF assay provides the foundation for a revolution in the diagnosis of TB and drug-resistant TB.
- Global roll-out of the Xpert MTB/RIF assay and associated GeneXpert instruments has started. By 30 June 2011, 26 of the 145 countries that are eligible to purchase instruments and Xpert MTB/RIF cartridges at concessional prices had done so.
- Conventional laboratory capacity remains inadequate in many countries. In 2010, 8 of the 22 high-burden countries (HBCs) that account for 80% of the world's TB cases did not meet the target of 1 microscopy centre per 100 000 population. Among the 36 countries that are in the combined list of 22 HBCs and 27 high MDR-TB burden countries, 20 had less than the recommended capacity of 1 laboratory to perform culture and drug susceptibility testing per 5 million population.
- Implementation of diagnostics endorsed between 2007 and 2009 appears to be most advanced in the European Region, where 51% of countries reported using liquid culture and rapid speciation and 43% reported use of line probe assays.
- Laboratory strengthening must be accelerated to reach global targets for the diagnosis of drug-resistant TB and HIV-associated TB, as is currently happening in countries that are participating in the EXPAND-TB project.

There were an estimated 8.8 million new and recurrent cases of TB in 2010, of which 5.7 million were diagnosed and notified to national TB control programmes (NTPs); among notified cases, there were an estimated 290 000 cases of multidrug-resistant TB (MDR-TB), of which only 53 000 (18%) were reported to have been diagnosed and enrolled on appropriate treatment (**Chapter 2**, **Chapter 3**). Earlier and improved detection of TB cases and expanded capacity to diagnose cases of MDR-TB are thus global priorities for TB control, requiring new diagnostic tests, clear policies on which diagnostic tests to use (and which not to use) and strengthened laboratories in which tests can be safely and effectively carried out.

This chapter has two main parts. The first part highlights two landmarks in TB diagnostics in 2010/2011: the endorsement of a new rapid test for TB and drug-resistant TB called Xpert MTB/RIF at the end of 2010, and new policy guidance on the use of commercial serological tests for the diagnosis of active TB disease. The second part discusses the status of laboratory capacity in 2010, and recent progress in strengthening laboratories including the adoption of policy guidance from WHO. Particular attention is given to the countries that carry the highest burden of TB and MDR-TB as well as to a project in 27 countries called EXPAND-TB and the roll-out of Xpert MTB/RIF in the first six months of 2011.

5.1 New diagnostic tests and WHO policies

The landscape of TB diagnostics is rapidly evolving, and in this context WHO has established a dynamic and systematic process for timely formulation of policy. The process involves four main steps. First, the available evidence is synthesized through systematic reviews and meta-analyses of data. Second, findings are reviewed by an external Expert Group. Third, the evidence and public health impact of new tools and technologies are assessed using the recommended GRADE approach.[1] Fourth, detailed policy guidance is developed, followed by dissemination to Member States and other stakeholders.[2]

Between July 2010 and July 2011, this process resulted in the endorsement of a new test for rapid diagnosis of TB and drug-resistant TB – Xpert MTB/RIF as well as a

[1] **www.gradeworkinggroup.org**

[2] WHO policies on TB diagnostics are available at: **www.who.int/tb/laboratory/policy_statements**

BOX 5.1

Serodiagnostics: the evidence base for "negative" policy guidance

In 2010, a systematic review identified 67 studies on the use of commercially available serodiagnostic tests to diagnose active pulmonary TB disease. There were 32 studies from low-income and middle-income countries. The results demonstrated that the sensitivity and specificity values from individual studies were highly variable. Pooled results of the most widely used test showed sensitivities of 76% and 59% and specificities of 92% and 91% in patients with smear-positive and smear-negative pulmonary TB, respectively.

For extrapulmonary TB, 25 studies were identified in a systematic review, including 10 studies from low-income and middle-income countries. The results demonstrated that sensitivity and specificity values from individual studies were highly variable. Pooled sensitivity was 64% for TB of the lymph nodes and 46% for TB of the pleura. The pooled results for the sensitivity and specificity of the most widely used test were 81% and 85%, respectively. In one study involving HIV-infected patients, the sensitivity of the test was 33%.

negative policy on the use of commercial serodiagnostics for the diagnosis of active TB disease.

5.1.1 Xpert MTB/RIF

Xpert MTB/RIF is a TB-specific automated, cartridge-based nucleic amplification assay based on the GeneXpert multi-disease platform. It was developed by Cepheid, Inc. (Sunnyvale, USA) in partnership with the Foundation for Innovative New Diagnostics (FIND) and the University of Medicine and Dentistry of New Jersey (Newark, USA) with support from the US National Institutes of Health and the Bill & Melinda Gates Foundation. Xpert MTB/RIF detects *Mycobacterium tuberculosis* as well as mutations conferring resistance to rifampicin directly from sputum in an assay that provides results within 100 minutes. Results from field demonstration studies found that a single Xpert MTB/RIF test can detect TB in 99% of patients with smear-positive pulmonary TB and >80% of patients with smear-negative pulmonary TB (see **Chapter 3**, **Box 3.1** for definitions of different types of TB case). The demonstration studies also showed that while HIV coinfection substantially decreases the sensitivity of microscopy, it does not significantly affect the performance of Xpert MTB/RIF. Furthermore, Xpert MTB/RIF can detect rifampicin resistance with 95.1% sensitivity and exclude resistance with 98.4% specificity.

WHO endorsed the Xpert MTB/RIF assay in December 2010. The test has the capacity to revolutionize the diagnosis of TB and drug-resistant TB, since it can greatly increase case finding and overcomes several of the barriers to establishing diagnostic capacity at country level, including human resource and biosafety constraints.

It should be emphasized that countries will continue to require adequate laboratory services for microscopy and culture to monitor treatment progress and to detect resistance to drugs other than rifampicin. Moreover, several operational conditions need to be met for successful implementation of Xpert MTB/RIF, including revised diagnostic algorithms, definition of the risk groups and levels of the health system in which the test would be used first, and analysis of logistic considerations to optimize the use and benefits of the technology.

The use of technologies such as Xpert MTB/RIF must be accompanied by rapid expansion and access to treatment services. WHO therefore recommends that health authorities should roll out Xpert MTB/RIF in phases, within the context of national plans for appropriate treatment and care of TB, MDR-TB and HIV-associated TB. Global recommendations on the operational aspects of implementing Xpert MTB/RIF are available in key WHO documents on a dedicated web site.[1]

5.1.2 Commercial serological antibody tests to diagnose TB disease

Dozens of commercial serological antibody tests for the diagnosis of active TB disease are marketed in many parts of the world,[2] despite the previously reported poor performance of these tests. In 2010, WHO commissioned a systematic review to synthesize the latest evidence on the diagnostic accuracy of these tests, both for pulmonary and extrapulmonary TB. Overall it was found that commercial serological tests provide inconsistent and imprecise results with highly variable values for sensitivity and specificity, and high proportions of false-negative and false-positive results. There was no evidence that existing commercial serological assays improve outcomes that are important to patients. Following the findings of this review, WHO issued "negative" policy guidance that strongly recommends that commercial serological tests should not be used for the diagnosis of pulmonary and extrapulmonary TB. A summary of the main evidence used for policy formulation is provided in **Box 5.1**; the full policy document is available from WHO.[3]

[1] **www.who.int/tb/laboratory/mtbrifrollout**

[2] These tests should be distinguished from interferon-gamma release assays (IGRAs) which are used to test for latent infection (as opposed to active disease).

[3] **www.who.int/tb/laboratory/policy_statements**

5.2 Laboratory capacity and progress in laboratory strengthening at country level

A total of 36 countries (see **Table 5.1** and **Table 5.2**) are in the combined list of 22 high-burden countries (HBCs) that account for about 80% of the world's estimated cases of TB and the 27 high MDR-TB burden countries that account for about 85% of the world's estimated cases of MDR-TB. In 2010, 20 of these 36 countries had less than the recommended capacity of 1 laboratory to perform culture and drug susceptibility testing (DST) per 5 million population (**Table 5.1**). Capacity to perform sputum smear microscopy also remains insufficient in many settings: 8 of the 22 HBCs do not meet the target of 1 microscopy centre per 100 000 population and at the regional level the Western Pacific and the Eastern Mediterranean regions had only 0.5 and 0.9 microscopy centres, respectively, per 100 000 population.

Globally, almost three quarters of countries indicated the existence of a designated national TB reference laboratory (NRL). The African Region reported the highest proportion of countries (87%) with an NRL, although their functionality and/or performance have not been fully verified.

The Global Plan to Stop TB 2011–2015[1] includes a target that all patients who have been previously treated for TB should be tested for MDR-TB using rapid tests by 2015. Given the slower, conventional methods for DST, globally only 6% of previously treated patients received DST by any method in 2010 (see **Chapter 3**).

The uptake at country level of WHO laboratory policy guidance, with particular attention to the rapid diagnosis of drug-resistant TB, is described in **Table 5.2**. Capacity to conduct conventional DST for the detection of drug resistance exists in about 50% of countries. The uptake of newer diagnostics is slower: only 38% of countries reported use of liquid culture and rapid speciation in 2010, and only 23% reported use of line probe assays (LPAs) to detect rifampicin resistance. At the regional level, implementation appears to be most advanced in the European Region, where 51% of countries reported using liquid culture and rapid speciation and 43% reported use of LPAs. Uptake in the Region of the Americas appears slowest; only 23% of countries reported using liquid culture and rapid speciation, and 2% reported use of LPAs.

The availability of conventional DST and the uptake of new, rapid technologies in the combined list of 36 high-burden countries is better than the global average. Conventional DST is being rolled out in almost all of these countries. However, the coverage of liquid culture is still not adequate: 15 of the 22 HBCs (68%) and 17 of the 27 high MDR-TB burden countries (63%) had implemented liquid culture by 2010; the figures were 10/22 (45%) and 16/27 (59%), respectively, for LPAs. The slightly higher rate of implementation among HBCs is due in part to the EXPAND-TB project, a multi-partner initiative to establish new and rapid TB diagnostic technologies in 27 countries.

Launched in 2008 and expected to continue until 2013, the EXPAND-TB project aims to improve capacity to diagnose MDR-TB in upgraded laboratory services in 27 countries, 15 of which are in the list of 22 HBCs or 27 high MDR-TB burden countries (**Figure 5.1**). The project is a collaboration among WHO, the Global Laboratory Initiative, FIND and the Global Drug Facility, and funded by UNITAID and other partners. As this report went to press, new laboratory infrastructure and successful transfer of liquid culture and LPA technologies had been established in 18 countries. Among these 18 countries, six were routinely diagnosing patients with MDR-TB and rapid increases in patient numbers were evident (**Figure 5.2**).

FIGURE 5.1

The EXPAND-TB project - progress by July 2011

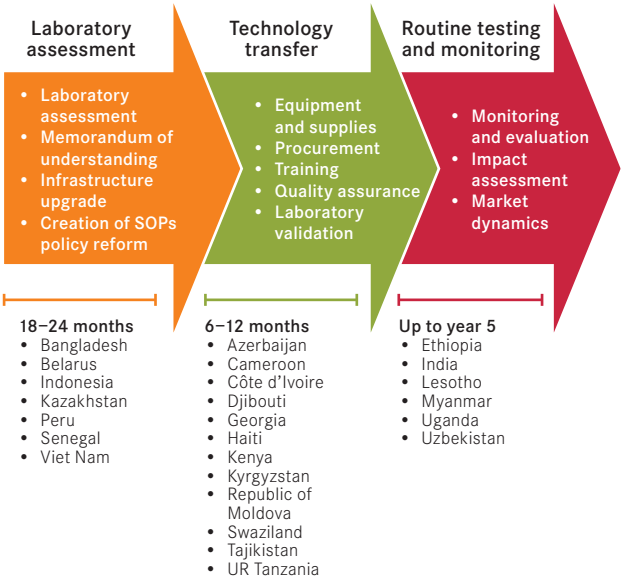
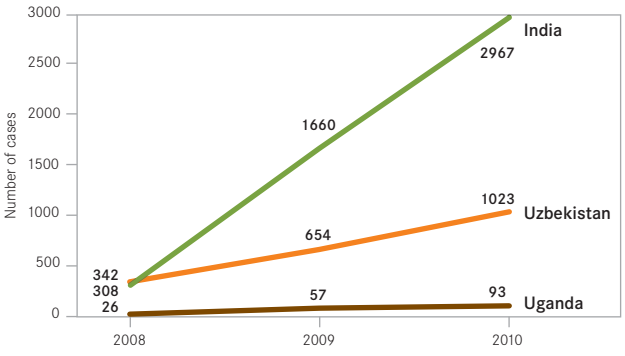


FIGURE 5.2

Cases of MDR-TB reported by selected countries participating in the EXPAND-TB project, 2008–2010



[1] *The Global Plan to Stop TB, 2011–2015*. Geneva, World Health Organization, 2010 (WHO/HTM/STB/2010.2).

TABLE 5.1

Laboratory capacity, 2010

■ Yes □ No	HIGH TB BURDEN	HIGH MDR-TB BURDEN	SMEAR LABORATORIES (PER 100 000 POPULATION)	CULTURE LABORATORIES (PER 5 MILLION POPULATION)[a]	DRUG SUSCEPTIBILITY TESTING LABORATORIES (PER 5 MILLION POPULATION)[a]	LINE-PROBE ASSAY RIFAMPICIN LABORATORIES (PER 5 MILLION POPULATION)	NATIONAL REFERENCE LABORATORY
Afghanistan	■	□	1.9	0.2	0	0	■
Armenia	□	■	1.4	1.6	1.6	1.6	■
Azerbaijan	□	■	0.8	1.1	1.1	–	–
Bangladesh	■	■	0.7	<0.1	<0.1	0	■
Belarus	□	■	–	–	–	–	–
Brazil	■	□	2.0	6.5	1.0	0	■
Bulgaria	□	■	0.5	20	14	0.7	■
Cambodia	■	□	1.5	1.1	0.4	0	■
China	■	■	0.2	3.3	0.7	<0.1	■
DR Congo	■	■	2.2	<0.1	<0.1	0	■
Estonia	□	■	0.4	7.5	7.5	7.5	■
Ethiopia	■	■	2.3	0.1	0.1	0.1	■
Georgia	□	■	0.7	2.3	1.1	1.1	■
India	■	■	1.1	<0.1	<0.1	<0.1	■
Indonesia	■	■	2.1	0.9	0.1	0	■
Kazakhstan	□	■	2.9	31	6.9	0	□
Kenya	■	□	3.3	0.7	0.5	0.4	■
Kyrgyzstan	□	■	2.3	7.5	2.8	0.9	■
Latvia	□	■	0.7	8.9	2.2	2.2	■
Lithuania	□	■	0.4	9.0	9.0	1.5	■
Mozambique	■	□	1.9	0.4	0.4	0	■
Myanmar	■	■	0.9	0.2	0.2	0.2	■
Nigeria	■	■	0.6	0.2	0.1	<0.1	■
Pakistan	■	■	0.7	0.4	0.3	0	■
Philippines	■	■	2.1	0.4	0.1	0	■
Republic of Moldova	□	■	1.7	5.6	5.6	1.4	■
Russian Federation	■	■	2.8	14	9.5	–	□
South Africa	■	■	0.5	1.5	1.5	1.4	■
Tajikistan	□	■	1.4	2.2	0.7	0	■
Thailand	■	□	1.6	4.7	1.1	0.1	■
Uganda	■	□	2.9	1.2	0.6	0.5	■
Ukraine	□	■	2.2	11	5.1	–	■
UR Tanzania	■	□	1.6	0.4	0.2	0.2	■
Uzbekistan	□	■	1.1	0.7	0.4	0.4	■
Viet Nam	■	■	0.9	1.3	0.1	0.1	■
Zimbabwe	■	□	0.9	0.8	0.8	0	■
High-burden countries			**1.0**	**2.0**	**0.7**	**<0.1**	**95%**
High MDR-TB burden countries			**0.9**	**2.1**	**0.8**	**<0.1**	**85%**
AFR			1.4	0.7	0.4	0.2	87%
AMR			2.5	17	0.9	<0.1	74%
EMR			0.9	2.0	0.4	0.1	77%
EUR			1.3	12	5.9	1.1	62%
SEAR			1.2	0.4	0.1	<0.1	82%
WPR			0.5	4.6	0.7	0.1	72%
Global			**1.1**	**4.4**	**1.0**	**0.1**	**74%**

– Indicates no data reported.

[a] The revised WHO target for both culture and DST capacity is 1 laboratory per 5 million population. While these processes previously had separate indicators, the revised combined indicator is the result of the introduction of new technologies for which culture and DST are invariably performed together.

TABLE 5.2

Implementation of WHO policy guidance for diagnosis of TB, 2010

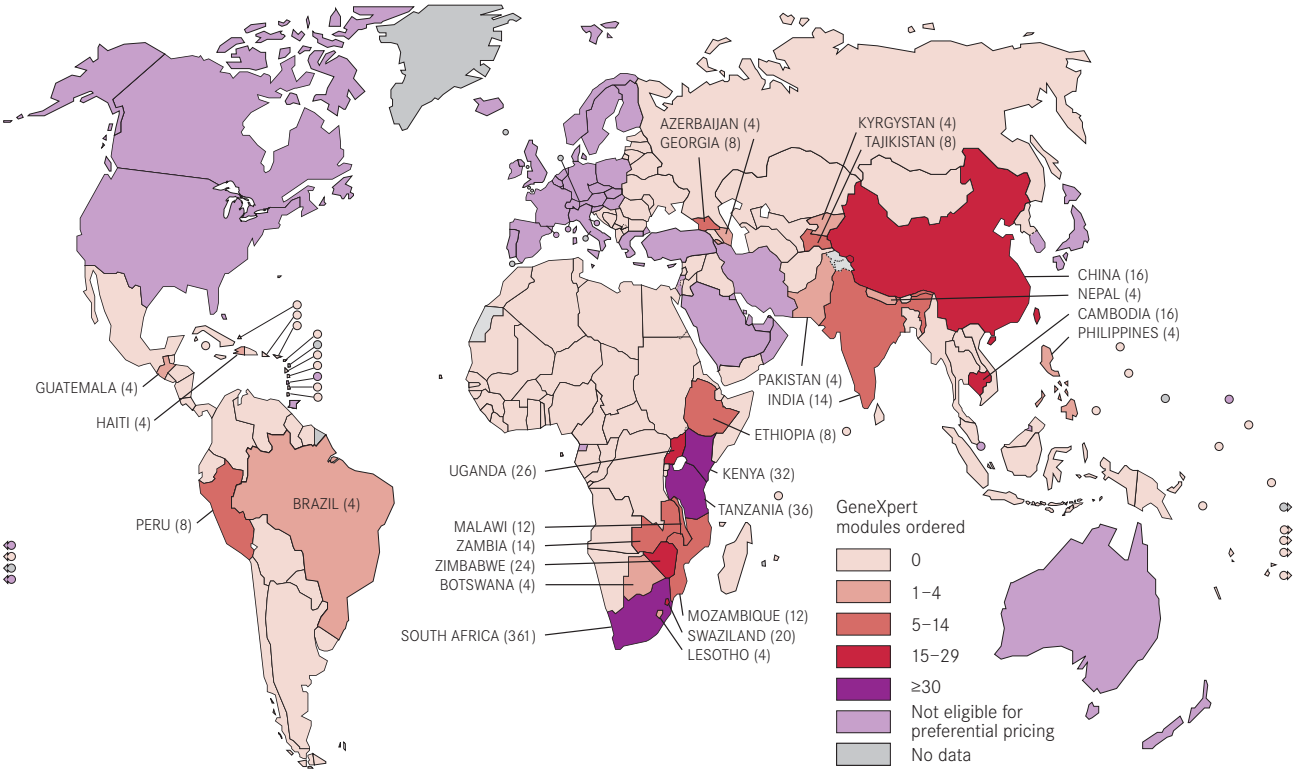
■ Yes
□ No

	HIGH TB BURDEN	HIGH MDR-TB BURDEN	CONVENTIONAL DRUG SUSCEPTIBILITY TESTING (DST)		LIQUID CULTURE AND RAPID SPECIATION TEST		LINE-PROBE ASSAY FOR DETECTING RESISTANCE TO RIFAMPICIN		ALGORITHM FOR THE DIAGNOSIS OF TB IN HIV-POSITIVE PEOPLE	
			INCORPORATED INTO POLICY	BEING ROLLED OUT	INCORPORATED INTO POLICY	BEING ROLLED OUT	INCORPORATED INTO POLICY	BEING ROLLED OUT	INCORPORATED INTO POLICY	BEING ROLLED OUT
Afghanistan	■	□	□	□	□	□	□	□	□	□
Armenia	□	■	■	■	■	■	■	■	□	□
Azerbaijan	□	■	–	–	–	–	–	–	–	–
Bangladesh	■	■	■	■	□	□	□	□	■	■
Belarus	□	■	–	–	–	–	–	–	–	–
Brazil	■	□	■	■	■	■	□	□	■	■
Bulgaria	□	■	■	■	■	■	□	■	■	■
Cambodia	■	□	□	□	□	□	□	□	■	■
China	■	■	■	■	■	■	□	□	■	■
DR Congo	■	■	■	■	□	□	□	□	■	■
Estonia	□	■	■	■	■	■	■	■	■	■
Ethiopia	■	■	■	■	■	■	■	■	□	□
Georgia	□	■	■	□	■	□	■	□	■	□
India	■	■	■	■	■	■	■	■	■	■
Indonesia	■	■	■	■	■	■	□	□	■	■
Kazakhstan	□	■	■	■	□	□	■	■	□	□
Kenya	■	□	■	■	■	■	■	■	■	■
Kyrgyzstan	□	■	■	■	■	■	□	■	■	–
Latvia	□	■	■	■	■	■	■	■	■	■
Lithuania	□	■	■	■	■	■	□	■	■	■
Mozambique	■	□	■	■	□	■	□	□	■	■
Myanmar	■	■	■	■	□	■	□	■	□	□
Nigeria	■	■	■	■	■	■	■	■	□	□
Pakistan	■	■	■	■	■	□	■	□	□	□
Philippines	■	■	■	■	□	□	□	□	■	□
Republic of Moldova	□	■	■	■	■	■	■	■	■	■
Russian Federation	■	■	■	■	■	■	■	■	■	■
South Africa	■	■	■	■	■	■	■	■	■	■
Tajikistan	□	■	■	□	□	□	□	□	■	■
Thailand	■	□	■	■	■	■	■	■	■	■
Uganda	■	□	■	■	■	■	■	■	■	■
Ukraine	□	■	■	■	□	□	□	□	□	■
UR Tanzania	■	□	■	■	□	□	□	□	□	■
Uzbekistan	□	■	■	■	■	■	■	■	■	■
Viet Nam	■	■	■	■	■	■	■	■	■	■
Zimbabwe	■	□	■	■	■	■	□	□	■	■
High-burden countries			**91%**	**91%**	**64%**	**68%**	**45%**	**45%**	**77%**	**73%**
High MDR-TB burden countries			**93%**	**85%**	**67%**	**63%**	**52%**	**59%**	**70%**	**59%**
AFR			52%	48%	48%	46%	33%	24%	57%	54%
AMR			40%	34%	32%	23%	4%	2%	34%	30%
EMR			68%	55%	45%	36%	32%	18%	59%	59%
EUR			60%	57%	51%	51%	42%	43%	38%	34%
SEAR			82%	64%	45%	36%	27%	27%	36%	36%
WPR			50%	50%	31%	31%	22%	22%	42%	50%
Global			**54%**	**49%**	**42%**	**38%**	**27%**	**23%**	**44%**	**43%**

– Indicates no data reported.

FIGURE 5.3

Progress in the roll-out of Xpert MTB/RIF, as of June 2011



As the newly endorsed Xpert MTB/RIF assay is rolled out worldwide, WHO is systematically compiling and sharing information on progress, including the plans of countries and partners, information on sales of instrument modules[1] and cartridges and reports of problems from the field. Of the 145 countries that are eligible to purchase GeneXpert instrument modules and Xpert MTB/RIF cartridges at concessional prices agreed between FIND and the manufacturer,[2] 26 countries had ordered a total of 681 instrument modules by 30 June 2011 (**Figure 5.3**); 361 were ordered by South Africa alone.

In addition to equipping laboratories with new diagnostic technologies, implementation of external quality assurance (EQA) systems is critical to ensure the high-quality functioning of laboratories. Of the 36 countries in the combined list of 22 HBCs and 27 high MDR-TB burden countries, 29 provided information on the number of microscopy centres that participated in an EQA scheme in 2010. Coverage was far from adequate, with ≥80% of microscopy centres participating in an EQA scheme in only 21 of the 29 countries. Similarly, of the 30 countries that provided information on the number of DST laboratories that participated in an EQA scheme, only 20 reported that all DST laboratories participated in 2010. More positively, all of the 36 countries that reported less than 100% participation in EQA schemes in 2010 had plans to increase the coverage of their EQA schemes for both microscopy and DST in 2011.

In addition to advancing policies and initiatives to accelerate the uptake of new, rapid diagnostics, two priority themes to strengthen laboratories in 2011 are promoting laboratory accreditation and laboratory biosafety (**Box 5.2**).[3]

[1] The most common configuration is a four-module instrument, which allows for 16–20 tests per day.

[2] The list of eligible countries is available at **www.finddiagnostics.org/about/what_we_do/successes/find-negotiated-prices/xpert_mtb_rif.html**

[3] For the most up-to-date WHO policies and resources on TB diagnostics and laboratory strengthening, visit **www.who.int/tb/laboratory/policy_statements**. Resources of the GLI, a Working Group of the Stop TB Partnership, are available at **www.stoptb.org/wg/gli**

BOX 5.2

Priority themes for strengthening laboratories in 2011: accreditation and biosafety

Accreditation. The Global Plan to Stop TB 2011–2015 includes a target that more than half of all national TB reference laboratories (NRLs) should have implemented an accredited quality management system by 2015. Accreditation programmes for laboratories provide both guidance and an incentive for improving laboratory quality. While such programmes are required components of TB laboratory services in most industrialized countries, they have been largely absent in resource-constrained settings.

International standards (so-called ISO standards) for clinical laboratory services have been developed by the International Organization for Standardization. However, because of the specific technical nature of TB diagnostic services and the corresponding biosafety needs, these general standards need to be translated into practical guidelines and TB-specific requirements. Partners of the Global Laboratory Initiative (GLI), including the Union, the United States Centers for Disease Control and Prevention, the Royal Tropical Institute in the Netherlands and WHO have developed a guide to assist countries to implement a quality management system at the level of the NRL. This guide facilitates a step-wise approach to achieving relevant ISO standards, and will be field tested in countries starting in 2011.

Biosafety. A combination of good laboratory practices together with administrative controls, containment principles, safety equipment and laboratory facilities are essential in TB laboratories to minimize the generation of infectious aerosols and thus prevent laboratory-acquired infections. Different types and combinations of test procedures require different containment precautions, equipment and facilities. WHO has therefore developed a risk assessment approach to determine the minimum biosafety measures required for TB laboratories based on the actual procedures performed in the laboratory. It is important to note that the risk-based approach to laboratory biosafety moves away from the traditional approach of assigning different "biosafety levels" to a much more focused approach taking into account the actual procedures performed in the laboratory.

The resulting three-tiered system is based on "low", "moderate" and "high" TB risk precautions, described below; respective minimum requirements are described in detail in biosafety guidance under development in 2011.

Low TB risk precautions. Procedures: direct AFB microscopy, Xpert MTB-RIF

Moderate TB risk precautions. Procedures: processing sputum specimens for primary culture inoculation on solid media, direct nitrate reductase assay (NRA), direct microscopic observation of drug susceptibility (MODS) assay or direct line-probe assay on sputum-positive specimens

High TB risk precautions – containment laboratory. Procedures: manipulating cultures for identification and drug susceptibility testing (DST) with indirect phenotypic methods such as liquid culture, or for line probe assays

CHAPTER 6

Addressing the co-epidemics of TB and HIV

KEY MESSAGES

- HIV testing of TB patients is now standard practice in many countries, especially in the African Region. In 68 countries and territories including 22 countries in the African Region, ≥75% of TB patients knew their HIV status in 2010. Further efforts are needed to achieve similar results at global level. In 2010, 34% of notified TB patients (2.1/6.2 million) knew their HIV status.
- The highest rates of HIV coinfection in TB patients are in the African Region, where 44% of TB patients with an HIV test result in 2010 were HIV-positive (range among high TB/HIV burden countries, 8%–82%), followed by the Region of the Americas (17%).
- The global coverage of antiretroviral therapy (ART) for TB patients living with HIV remains low (only 46%), despite the large increase in HIV testing among TB patients and the WHO recommendation that ART should be provided to all TB patients living with HIV regardless of their CD4 cell count. The provision of ART to TB patients living with HIV must be enhanced, including the use of TB services and infrastructure to allow decentralization of care delivery according to national guidelines and the local context.
- Implementation of WHO guidelines on TB screening and isoniazid preventive therapy among people living with HIV can result in a rapid expansion of TB prevention, diagnosis and treatment.
- The recording and reporting of the outcomes of TB treatment disaggregated by HIV status needs to be improved, using WHO-recommended TB registers (which should also be used by HIV service providers including in ART clinics).

People living with HIV who are also infected with TB are about 21–34 times more likely to develop TB disease compared with those who are HIV-negative.[1] Starting in the 1980s, the HIV epidemic led to a major upsurge in TB cases and TB mortality in many countries that persisted throughout the 1990s and up to around 2004, especially in southern and east Africa (**Chapter 2**, **Chapter 3**). Globally, just over one in ten of the almost 9 million people who develop TB each year is HIV-positive, equivalent to 1.1 million new TB cases among people living with HIV in 2010 (**Chapter 2**, **Table 2.1**). In the African Region, which accounted for 82% of the new TB cases that were living with HIV in 2010, an estimated 900 000 (39%) of the 2.3 million people who developed TB in 2010 were HIV-positive. Globally in 2010, there were an estimated 0.35 million deaths (range, 0.32 million–0.39 million) from TB among people who were HIV-positive. WHO, UNAIDS and the Stop TB Partnership have set a target that by 2015, TB mortality rates among people who are HIV-positive should be reduced by 50%, compared with 2004 (the year in which TB mortality among HIV-positive people is estimated to have peaked).[2]

WHO has provided clear recommendations about the interventions needed to prevent, diagnose and treat TB in people living with HIV since 2004.[3] The recommended interventions are collectively known as collaborative TB/HIV activities. They include HIV testing of TB patients, provision of antiretroviral therapy (ART) and co-trimoxazole preventive therapy (CPT) to TB patients living with HIV, HIV prevention services for TB patients, intensified TB case-finding among people living with HIV, isoniazid preventive therapy (IPT) for people living with HIV who do not have active TB, and infection control in health-

[1] The probability of developing TB among people living with HIV divided by the probability of developing TB among HIV-negative people is the incidence rate ratio (IRR). The median value of the IRR in countries with a generalized HIV epidemic was 21 (inter-quartile range 14–25) in 2010. A generalized epidemic is defined by UNAIDS as a prevalence of HIV infection >1% in those aged 15–49 years old. The IRR was 34 (inter-quartile range 20–34) in 115 other countries with low-level or concentrated HIV epidemics.

[2] *Getting to zero. 2011–2015 strategy*. Geneva, Joint United Nations Programme on HIV/AIDS.

[3] *Policy on collaborative TB/HIV activities*. Geneva, World Health Organization, 2004 (WHO/HTM/TB/2004.330; WHO/HTM/HIV/2004.1).

TABLE 6.1

HIV testing, treatment for HIV-positive TB patients and prevention of TB among people living with HIV, 41 high TB/HIV burden countries and WHO regions, 2010. Numbers in thousands except where indicated

	HIV-POSTIVE INCIDENT TB CASES			NUMBER OF TB PATIENTS WITH KNOWN HIV STATUS	% OF NOTIFIED TB PATIENTS TESTED FOR HIV	% OF TESTED TB PATIENTS HIV-POSITIVE	% OF IDENTIFIED HIV-POSITIVE TB PATIENTS STARTED ON CPT	% OF IDENTIFIED HIV-POSITIVE TB PATIENTS STARTED ON ART	NUMBER OF HIV-POSITIVE PEOPLE SCREENED FOR TB	NUMBER OF HIV-POSITIVE PEOPLE PROVIDED WITH IPT
	BEST	LOW	HIGH							
Angola	5.2	3.7	7.1	2.4	4.9	28	18	12	–	–
Botswana	6.5	5.8	7.3	6.1	80	65	79	45	0.2	0.7
Brazil	18	15	22	37	45	23	–	93	–	–
Burkina Faso	1.6	1.4	1.9	4.3	83	18	96	41	–	–
Burundi	2.5	2.2	2.8	5.5	71	23	95	40	–	–
Cambodia	4.0	3.4	4.7	32	77	6.6	65	45	–	0.5
Cameroon	14	11	17	19	78	40	–	–	–	–
Central African Republic	5.3	4.0	6.8	2.6	39	33	–	62	–	–
Chad	9.2	6.4	12	3.8	39	17	–	–	–	–
China	18	10	28	150	16	3.1	–	45	65	–
Congo	1.2	1.0	1.4	9.7	94	7.8	2.9	2.9	0.1	–
Côte d'Ivoire	6.7	5.7	7.6	17	73	24	80	26	31	–
Djibouti	0.6	0.5	0.8	2.2	52	11	–	11	–	–
DR Congo	18	13	24	29	24	18	24	9.3	3.9	–
Ethiopia	–	–	–	67	43	15	69	39	44	6.6
Ghana	4.9	4.3	5.6	10	69	23	86	20	57	–
Haiti	4.6	3.8	5.5	9.5	67	20	13	9.8	6.2	4.1
India	110	75	160	480	32	8.6	90	57	200	–
Indonesia	18	9.9	29	–	–	–	–	–	3.2	–
Kenya	50	45	55	97	91	41	100	48	–	–
Lesotho	11	9.2	12	11	84	77	96	27	–	–
Malawi	21	19	22	20	88	63	94	46	230	–
Mali	1.5	1.0	2.0	2.3	43	17	100	40	25	0
Mozambique	77	53	110	41	88	61	97	25	0.4	8.9
Myanmar	37	21	57	4.4	3.2	22	100	94	6.4	0.5
Namibia	7.6	7.1	8.1	9.5	76	55	92	42	25	14
Nigeria	51	25	87	72	79	25	59	33	57	1.8
Russian Federation	8.1	6.8	9.4	170	100	6.2	–	82	–	–
Rwanda	3.6	3.2	4.0	6.9	98	32	97	–	13	–
Sierra Leone	4.0	3.3	4.8	9.7	74	10	6.4	19	–	–
South Africa	300	240	350	210	53	60	74	54	760	120
Sudan	7.1	4.8	9.9	11	41	6.2	58	54	1.5	–
Swaziland	13	10	15	9.5	86	82	93	35	–	–
Thailand	15	13	18	53	77	16	71	53	25	–
Togo	5.4	4.3	6.5	2.3	78	20	–	–	–	–
Uganda	38	30	46	37	81	54	90	24	400	–
Ukraine	6.0	5.0	7.1	35	95	13	–	–	–	5.0
UR Tanzania	30	28	32	57	90	38	92	35	320	–
Viet Nam	7.6	4.6	11	42	43	8.3	62	43	–	1.3
Zambia	40	36	44	41	83	65	77	47	12	–
Zimbabwe	60	47	76	38	80	75	18	30	–	–
High TB/HIV burden countries	**1 000**	**960**	**1 100**	**1 900**	**39**	**25**	**77**	**46**	**2 300**	**170**
AFR	900	820	980	880	59	44	76	42	2 000	160
AMR	35	31	38	100	46	17	47	65	15	13
EMR	12	9.8	15	46	11	3.4	51	37	6.8	0.3
EUR	20	19	22	290	80	6.0	48	77	5.6	6.6
SEAR	190	140	230	540	23	9.5	87	57	230	0.6
WPR	35	26	45	250	19	4.8	55	41	69	2.0
Global	**1 100**	**1 000**	**1 200**	**2 100**	**34**	**23**	**77**	**46**	**2 300**	**180**

care and congregate settings (the latter three activities are referred to as the "*Three Is for HIV/TB*").

Testing TB patients for HIV and providing CPT to TB patients living with HIV are typically the responsibility of national TB control programmes (NTPs). National HIV programmes are usually responsible for initiating intensified case-finding for TB among people living with HIV as well as providing IPT to those without active TB. Provision of ART to TB patients living with HIV has often been the responsibility of national HIV programmes, but should also be done by NTPs. When NTPs do not provide ART directly, they are responsible for referring TB patients living with HIV to ART services. The latest policy guidance from WHO recommends that ART should be provided to all TB patients living with HIV, irrespective of their CD4 count (and to all people living with HIV with a CD4 cell count ≤350).[1]

WHO began monitoring the implementation and expansion of collaborative TB/HIV activities in 2004. This chapter presents the latest status of progress, using data for 2003 up to 2010.[2] The need for better data on treatment outcomes for TB patients living with HIV, and the recent and rapid expansion of TB screening among people living with HIV and associated uptake of IPT following new policy guidance in Cambodia and South Africa are also highlighted.

6.1 HIV testing, co-trimoxazole preventive therapy and antiretroviral therapy for patients with TB

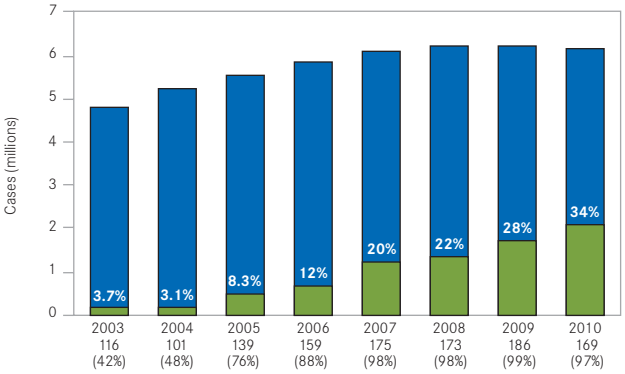
The number of TB patients who knew their HIV status reached 2.1 million in 2010, equivalent to 34% of notified cases of TB (**Table 6.1**). This was an improvement from 28% in 2009 and almost 10 times better than the 3.7% reported in 2003 (**Figure 6.1**). The coverage of HIV testing for TB patients was particularly high in the African and European regions, where 59% and 80% of TB patients respectively knew their HIV status. Impressively, ≥75% of TB patients living in almost half of the countries in the African Region (22 out of 46 countries) knew their HIV status in 2010. This was an increase from 16 in 2009 and double the 11 countries that achieved testing rates of ≥75% in 2008. More than three quarters of the African countries that reported data (31/41) achieved ≥50% (**Figure 6.2**). Five African countries did not report data for 2010: Algeria, Cape Verde, Comoros, Eritrea and Gabon. Globally, the percentage of TB patients who knew their HIV status was ≥75% in 68 countries and territories in 2010, up from 55 countries in 2009.

Among TB patients with an HIV test result in 2010, 23% were HIV-positive at the global level (**Table 6.1**). Among the 41 countries identified as priorities for TB/HIV at the global level in 2002 (listed in **Table 6.1**), 25% were HIV-positive. Much higher rates of HIV coinfection were reported for TB patients in the African Region,

FIGURE 6.1

HIV testing for TB patients, all countries, 2003–2010

The number of notified new and retreatment cases is shown in blue and the number of cases for which the HIV status was recorded in the TB register is shown in green. The percentage of notified TB cases with known HIV status is indicated above the green bars.[a]



[a] The numbers under each year show the number of countries reporting data on HIV testing followed by the percentage of total estimated HIV-positive TB cases accounted for by reporting countries.

where 44% of those tested were found to be HIV-positive. The percentage of TB patients found to be HIV-positive in the 31 African countries in the list of 41 priority countries ranged from 8% in Congo to 82% in Swaziland. Besides Swaziland, more than half of the TB patients who were tested were HIV-positive in Botswana, Lesotho, Malawi, Mozambique, Namibia, South Africa, Uganda, Zambia and Zimbabwe.

In the Region of the Americas, the percentage of TB patients found to be HIV-positive was 17%. In the Eastern Mediterranean, European, South-East Asia and Western Pacific regions, less than 10% of TB patients tested for HIV were HIV-positive. Among the 11 countries identified as priorities for TB/HIV at the global level in 2002 that are outside the African Region, the percentage of TB patients who were HIV-positive ranged from 3% in China to 23% in Brazil in 2010.

Globally, the number of TB patients living with HIV who were enrolled on CPT levelled off between 2009 and 2010, at just over 0.3 million (**Figure 6.3**). This was equivalent to 77% of TB patients known to be HIV-positive (**Table 6.1**, **Figure 6.4**). Further progress is needed to reach the target of 100% that is included in the Global Plan to Stop TB, 2011–2015[3] (see **Chapter 1**). The African

[1] **www.who.int/hiv/pub/arv/advice**

[2] This chapter does not discuss infection control or services aimed at HIV prevention among TB patients. Data for the former are limited for most countries, but available data can be accessed at www.who.int/tb/data. Data on HIV prevention services for TB patients are not part of routine recording and reporting in TB registers, and are not requested on the annual WHO TB data collection form.

[3] *The Global Plan to Stop TB, 2011–2015*. Geneva, World Health Organization, 2010 (WHO/HTM/STB/2010.2).

FIGURE 6.2

HIV testing for TB patients, by country, 2010

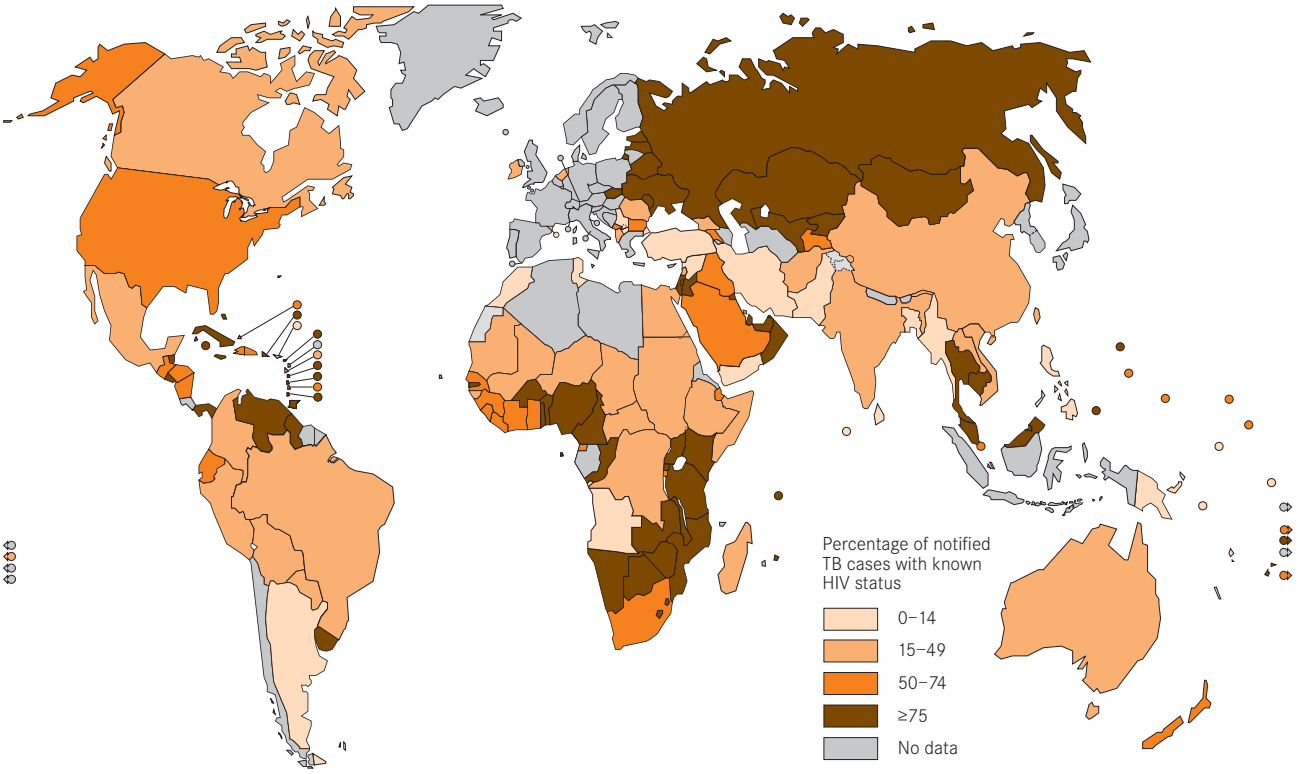
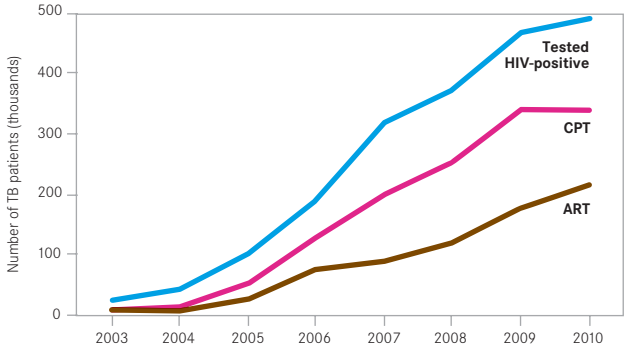


FIGURE 6.3

Co-trimoxazole preventive therapy (CPT) and antiretroviral therapy (ART) for HIV-positive TB patients, 2003–2010



and South-East Asia regions achieved particularly high levels of enrolment on CPT, with 76% and 87% of TB patients known to be living with HIV provided with CPT, respectively (**Table 6.1**). Countries that achieved the highest rates of enrolment on CPT in 2010 included Burkina Faso (96%), Burundi (95%), India (90%), Kenya (100%), Lesotho (96%), Mozambique (97%), Malawi (94%), Mali (100%), Myanmar (100%), Namibia (92%), Rwanda (97%), Swaziland (93%), the United Republic of Tanzania (92%) and Uganda (90%).

The number of HIV-positive TB patients on ART has grown steadily from a very low level in 2004 (**Figure 6.3**), reaching over 200 000 in 2010.[1] Among TB patients known to be living with HIV, 46% were on ART globally (**Table 6.1**, **Figure 6.4**). In the African Region, 42% of TB patients known to be living with HIV were on ART in 2010 and only a few countries (Botswana, Central African Republic, Kenya, Malawi, South Africa and Zambia, at 47–62%) exceeded this level, despite the WHO recommendation that all HIV-positive TB patients are eligible for ART irrespective of their CD4 cell count. Most of the ART being provided to TB patients living with HIV is accounted for by African countries, notably South Africa

[1] In the annual WHO TB data collection form, countries are asked to report the number of TB patients living with HIV who "started or continued on ART".

BOX 6.1

Better reporting of the outcomes of TB treatment by HIV status is urgently needed

The Stop TB Partnership, WHO and UNAIDS have set a target of halving the number of TB deaths among HIV-positive people by 2015 compared with 2004 (the year in which TB mortality among HIV-positive people is estimated to have peaked). Earlier and prompt diagnosis and treatment of TB as well as antiretroviral therapy (ART) and co-trimoxazole preventive therapy (CPT) can cut mortality rates among TB patients living with HIV. To assess whether the goal is achieved, data on mortality rates among HIV-positive TB patients during TB treatment are needed. In turn, this requires that treatment outcomes for TB patients are disaggregated by HIV status; that is, outcomes are available for HIV-positive and HIV-negative TB patients separately.

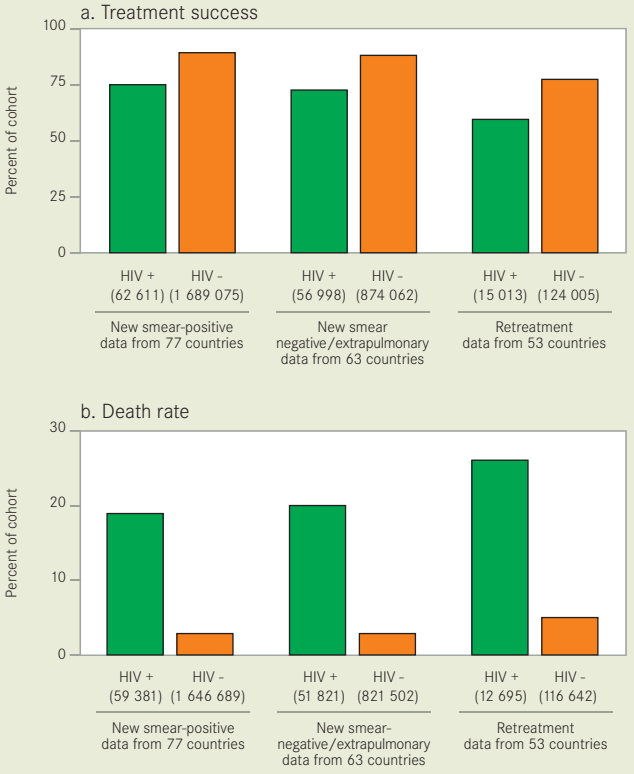
In 2010, a large number of countries (n=81) reported data on the outcomes of TB treatment disaggregated by HIV status (these data are for 2009, given the lag-time in reporting of treatment outcomes). However, these countries accounted for only 21% of the estimated global number of HIV-related TB cases. The treatment success and death rates reported for HIV-positive TB cases in 2009 were 72% and 20%, respectively, compared with 88% and 3% among HIV-negative TB cases (see figure right); the remaining patients had treatment outcomes of failed treatment, transferred out of the district during treatment or their treatment outcome was not evaluated.[1] Among the 63 high TB/HIV burden countries (see list below),[2] less than half (n=28) reported treatment outcomes disaggregated by HIV status.

The recording and reporting of the outcomes of TB treatment disaggregated by HIV status needs to be improved, using WHO-recommended TB registers (which should also be used by HIV service providers including in ART clinics).

[1] The death rate for HIV-positive TB cases cited here assumes that those who were recorded as having defaulted from treatment also died from TB.

[2] The 63 high TB/HIV burden countries are a combination of 41 countries that were identified as priorities for TB/HIV at global level in 2002 and that account for 97% of estimated HIV-positive TB cases globally, plus 22 additional countries that UNAIDS has defined as having a generalized HIV epidemic. The 41 countries are listed in **Table 6.1**. The other 22 countries are (in alphabetical order) the Bahamas, Barbados, Belize, Benin, the Dominican Republic, Equatorial Guinea, Eritrea, Estonia, Gabon, Guatemala, Guinea, Guinea-Bissau, Guyana, Honduras, Jamaica, Liberia, Madagascar, the Niger, Panama, Somalia, Suriname, and Trinidad and Tobago.

Treatment outcomes for HIV-positive and HIV-negative TB patients, 2009. Numbers under bars indicate the number of patients in each cohort, which are slightly larger for a. because patients "not evaluated" are included.



(**Figure 6.5**, **Figure 6.6**). The highest rates of enrolment on ART were reported by countries in the Region of the Americas, notably Brazil at 93% (**Figure 6.6**).

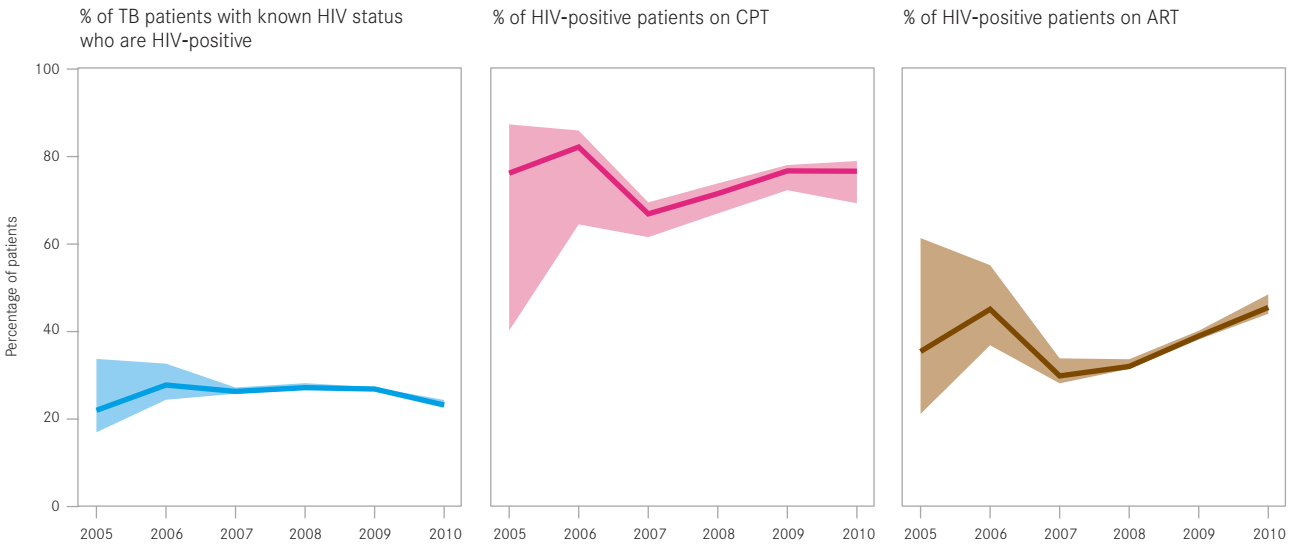
A substantial improvement in ART provision will be needed to reach the Global Plan target of providing ART to all TB patients known to be living with HIV by 2015. This could be facilitated by using TB services and infrastructure to allow decentralization of care delivery according to national guidelines and the local context.

6.2 Intensified case-finding and isoniazid preventive therapy among people living with HIV

Until 2010, data on intensified screening for TB among people living with HIV and provision of IPT to those without active TB were requested from NTPs as part of the global TB data collection form. In 2011, in an effort to streamline efforts to collect data and improve the quality of data, information about these two interventions was collected by the WHO's HIV department from national HIV programmes. It should be noted that monitoring of access to these two interventions at country level is considered weaker than for interventions such as ART, and thus the reported data need to be interpreted with some caution.

FIGURE 6.4

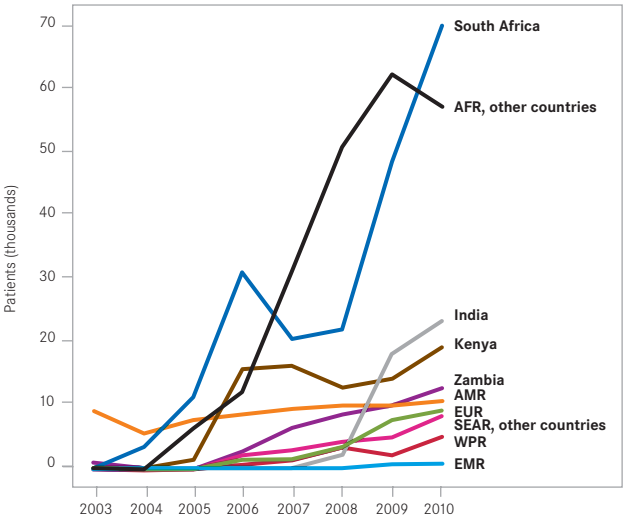
TB patients with known HIV status who are HIV-positive and HIV-positive TB patients on co-trimoxazole preventive therapy (CPT) and antiretroviral therapy (ART), 2005–2010[a]



[a] The solid lines show values for countries that reported data. The shaded areas show upper and lower limits when countries that did not report data are considered.

FIGURE 6.5

Antiretroviral therapy for HIV-positive TB patients by WHO region and selected countries, 2003–2010



The data reported indicate that TB screening among people living with HIV and provision of IPT have steadily increased, particularly since 2007 (**Figure 6.7**, **Figure 6.8**). In 2010, 2.3 million were screened for TB (up from 1.7 million in 2009) and 178 000 of those without active TB were enrolled on IPT (double the level achieved in 2009).

The number of people living with HIV who were screened for TB was equivalent to more than half (58%, 2 302 680/3 956 326) of the reported number of people who were enrolled in HIV care worldwide in 2010. The number started on IPT was 12% (178 144/1 464 579) of the reported number of people living with HIV newly enrolled in HIV care in 2010. Intensified efforts are needed to approach the Global Plan's targets of providing screening for TB for all those enrolled in HIV care and providing IPT to all those attending HIV care services who are eligible for it by 2015. The examples of Cambodia and South Africa illustrate the major progress that can be achieved in a short time when new WHO guidelines are adopted and implemented (**Box 6.2**).

FIGURE 6.6

ART provision and percentage of HIV-positive TB patients on ART, 2010. The area of each box represents the number of HIV-positive TB patients on ART

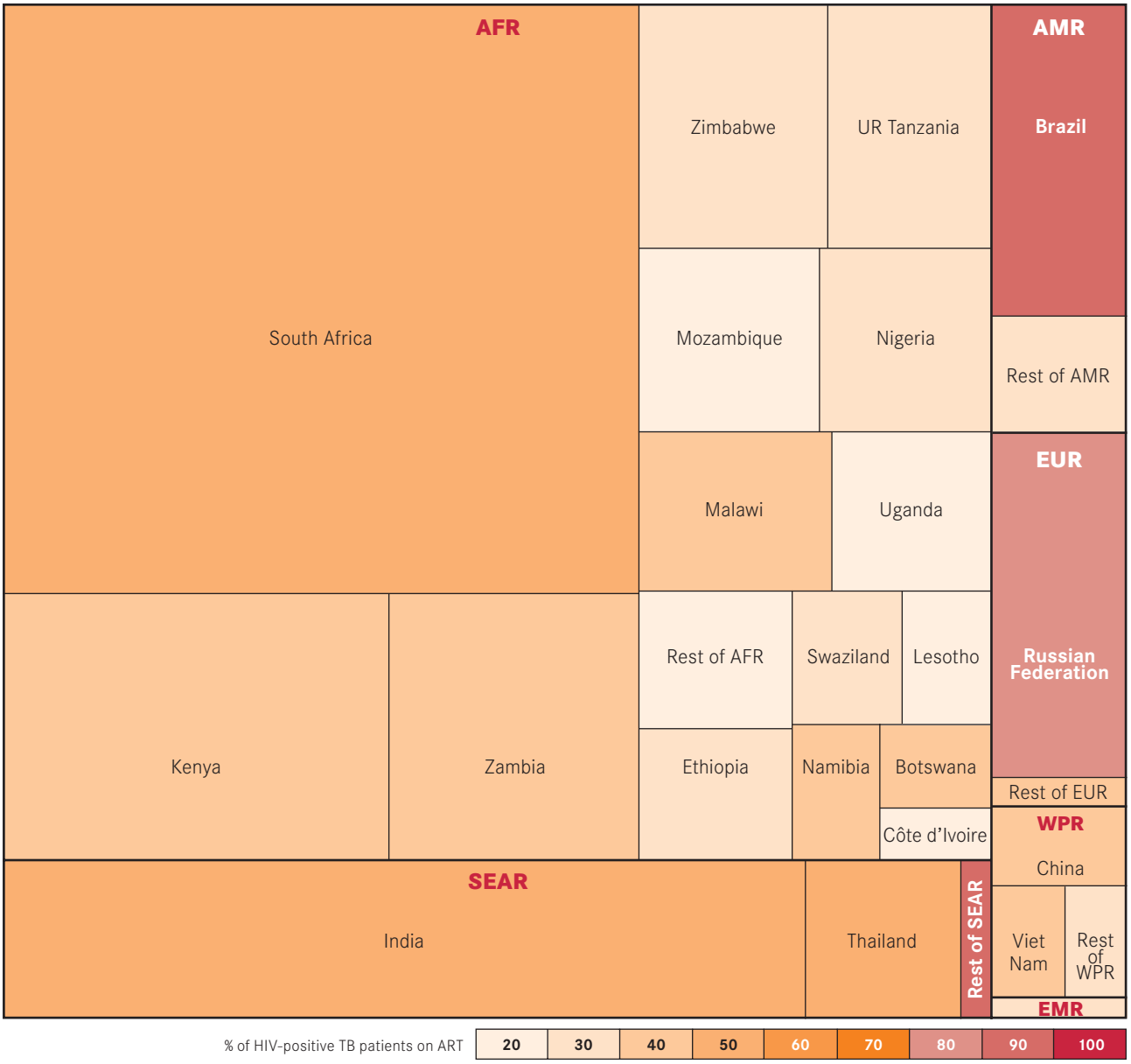


FIGURE 6.7

Intensified TB case-finding among HIV-positive people, 2005–2010

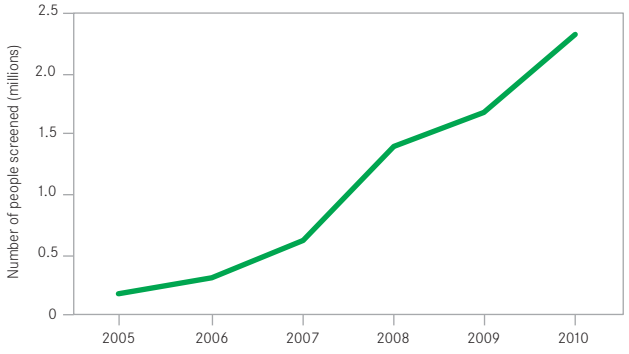
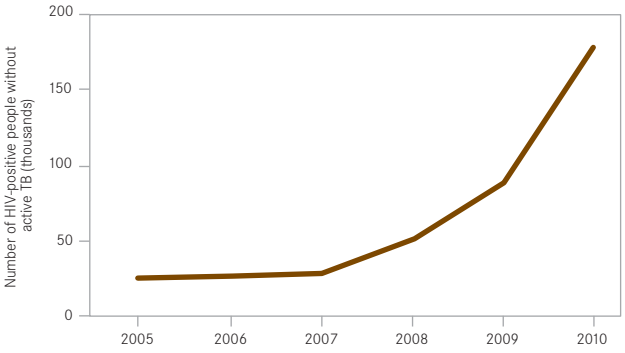


FIGURE 6.8

IPT provision among HIV-positive people, 2005–2010



BOX 6.2

Uptake of new WHO guidelines leads to rapid scale up of isoniazid preventive therapy

Recent WHO guidelines on TB screening and isoniazid preventive therapy (IPT) among people living with HIV were adopted and implemented by Cambodia and South Africa in 2010. The guidelines recommend screening using four symptoms (current cough, fever, weight loss and night sweats) and providing IPT if these symptoms are absent.[1] This symptom-based screening algorithm has been found to have a negative predictive value of 97.7% (95%confidence interval, 97.4–98.0) in settings where the prevalence of TB among people living with HIV is 5%.[2]

An HIV counselling and testing campaign in South Africa in 2010 aimed at all sexually-active individuals aged >12 years included TB screening based on the new guidelines. The guidelines were also reflected in planning and implementation of collaborative TB/HIV activities in Cambodia in 2010.

In South Africa, the number of people living with HIV who were provided with IPT increased by more than five-fold in one year, from 23 583 in 2009 to 124 049 in 2010. In Cambodia, the numbers provided with IPT increased seven-fold in one year, from 66 in 2009 to 491 in 2010.

To complement this large and rapid scale-up in the provision of IPT, emphasis on adherence to therapy as well as monitoring of resistance to isoniazid are needed.

[1] *Guidelines for intensified tuberculosis case finding and isoniazid preventive therapy for people living with HIV in resource constrained settings*. Geneva, World Health Organization, 2010.

[2] Getahun H et al. Development of a standardized screening rule for tuberculosis in people living with HIV in resource constrained settings: individual participant data meta-analysis of observational studies. *PLoS Medicine*, 2011, 8(1) e1000391 (doi:10.1371/journal.pmed).

CHAPTER 7

Research and development

KEY MESSAGES

- Progress in TB care and control is constrained by old technologies.
- During the past decade, efforts to develop new diagnostics, drugs and vaccines for TB have intensified and considerable progress has been made.
- Several new diagnostic tests or methods have been endorsed by WHO since 2007, including Xpert MTB/RIF that has the potential to transform the diagnosis of TB and rifampicin-resistant TB. Other new tests, including point-of-care tests, are in the pipeline.
- For the first time in 40 years, there is a coordinated portfolio of promising new drugs on the horizon. There are 10 new or repurposed TB drugs in trials, which have the potential to shorten the treatment of drug-susceptible TB and to improve the treatment of multidrug-resistant TB (MDR-TB). Results from three Phase III trials of 4-month regimens for the treatment of drug-susceptible TB are expected between 2012 and 2013. Results from two Phase II trials of new drugs for the treatment of MDR-TB are expected in 2012.
- There are 9 vaccine candidates for the prevention of TB in Phase I or Phase II trials. It is hoped that one or two of the candidates currently in a Phase II trial will enter a Phase III trial in the next 2–3 years, with the possibility of licensing at least one new vaccine by 2020.
- Funding for TB research and development has increased in recent years, reaching US$ 614 million in 2009, but still falls far short of the annual target of US$ 1.8 billion that is included in the Global Plan to Stop TB 2011–2015.

Major progress in TB care and control has been achieved since the introduction of the DOTS strategy in the mid-1990s and the launch of its successor, the Stop TB Strategy, in 2006 (**Chapters 2–6**). However, progress is constrained by old technologies. To achieve the Stop TB Partnership's target of eliminating TB by 2050 (**Chapter 1**), a transformation in TB prevention, diagnosis and treatment is required.[1]

During the past decade, efforts to develop new diagnostics, drugs and vaccines for TB have intensified. Three public–private partnerships have been created: the Foundation for Innovative New Diagnostics (in 2003), which works on the development of novel diagnostics for TB among a range of other diseases; the TB Alliance (in 2000) for new anti-TB drugs; and Aeras (in 2003) for new TB vaccines. The Stop TB Partnership has established working groups for new diagnostics, new drugs and new vaccines. Although the total funding available for TB research and development falls short of the US$ 1.8 billion per year that is called for in the *Global Plan to Stop TB 2011–2015*,[2] funding increased from US$ 363 million in 2005 to US$ 614 million in 2009.[3] Sources of funding include the United States National Institutes of Health, the Bill & Melinda Gates Foundation, the European Union, the European and Developing Countries Clinical Trials Partnership (EDCTP) and several other national, bilateral and multilateral agencies and philanthropic organizations.

This chapter presents the status of progress in the development of new diagnostics, new drugs and new vaccines for TB in mid-2011, using information provided by the respective Working Groups of the Stop TB Partner-

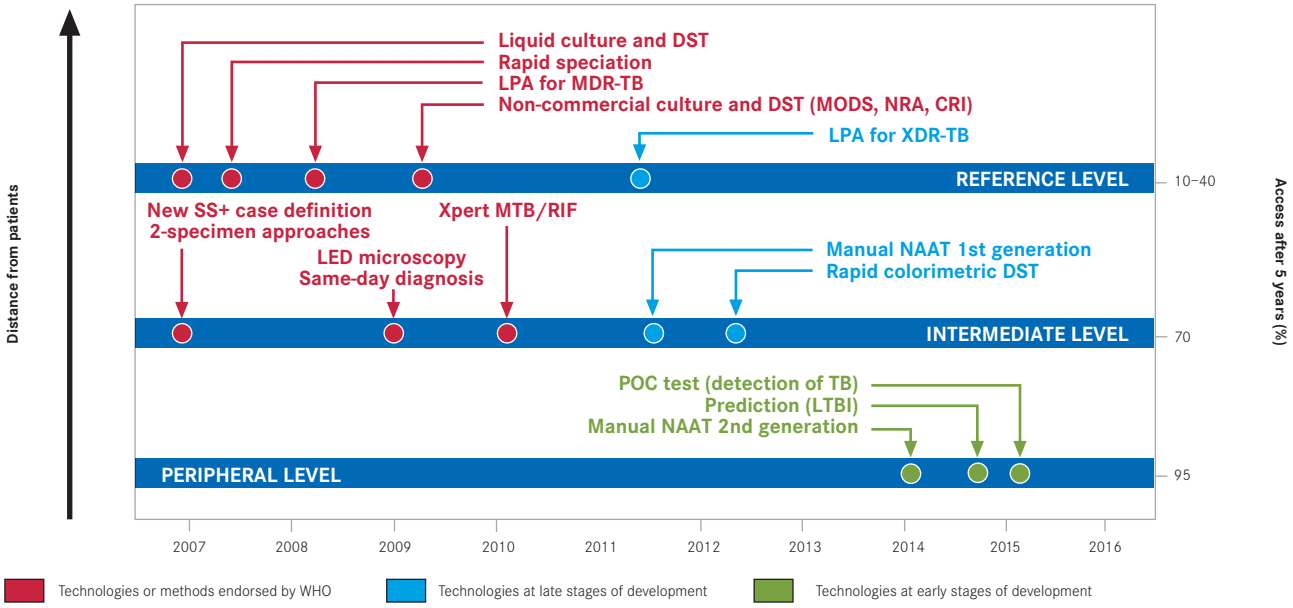
[1] Abu-Raddad LJ et al. Epidemiological benefits of more effective tuberculosis vaccines, drugs and diagnostics. *Proceedings of the National Academy of Sciences of the United States of America*, 2009, 106(33):13980–139805. The analysis in this paper indicated that TB incidence could be reduced by 71% by 2015 in the South-East Asia Region with the combined use of a neonatal pre-exposure vaccination, a 2-month drug regimen with high efficacy for drug-susceptible and drug-resistant TB, and a rapid test to diagnose TB. To achieve elimination (defined as less than one case per million population per year) would require new delivery strategies such as mass vaccination campaigns, and new products targeted at people with latent TB infection.

[2] *The Global Plan to Stop TB, 2011–2015*. Geneva, World Health Organization, 2010 (WHO/HTM/STB/2010.2).

[3] *2010 report on tuberculosis research funding trends, 2005–2009*. Treatment Action Group, 2010.

FIGURE 7.1

The development pipeline for new diagnostics, 2011



Abbreviations: **DST** Drug susceptibility test; **NAAT** Nucleic acid amplification test; **LTBI** Latent TB infection; **POC** Point of care; **MODS** Microscopic observation drug-susceptibility; **NRA** Nitrate reductase assay; **CRI** Colorimetric redox indicator assay; **LED** Light-emitting diode; **LPA** Line probe assay

ship. It also highlights two documents finalized in 2011 that address the continuum of research from fundamental science to operational research.

7.1 New diagnostics for TB

The most commonly used diagnostic test for TB, sputum smear microscopy, is over 100 years old. It is a relatively insensitive test and it cannot be used to identify paucibacillary or extrapulmonary TB. Diagnosis using culture methods – the current gold standard – requires laboratory infrastructure that is not widely available in countries with a high burden of TB (**Chapter 5**), and results take weeks. Conventional methods used to diagnose MDR-TB also rely on culturing of specimens followed by drug susceptibility testing (DST); results take weeks and not all laboratories with capacity to perform DST for first-line drugs have the capability to perform DST for second-line drugs. New diagnostic tests that are comparable to culture in terms of accuracy but which also allow rapid diagnosis and can be used at the lowest level of health systems are needed. The ideal is a simple, rapid, point-of-care test that can be used to diagnose both TB and MDR-TB outside the setting of a conventional laboratory.

The status of the pipeline for new diagnostics in July 2011 is illustrated in **Figure 7.1**.

Various new tests and methods have been endorsed by WHO in the past four years. Since 2007, endorsed tests and methods include liquid culture and rapid speciation for faster diagnosis of TB and MDR-TB, molecular line probe assays (LPAs) for rapid testing for MDR-TB, non-commercial culture methods for rapid DST, light-emitting diode (LED) fluorescence microscopes for better diagnosis using smear microscopy, and Xpert MTB/RIF for the rapid diagnosis of TB and rifampicin-resistant TB. These are beginning to be implemented in countries (**Chapter 5**), and Xpert MTB/RIF in particular (a fully automated, cartridge-based, nucleic acid amplification test) has the potential to transform the diagnosis of TB and drug-resistant TB. It is suitable for use at district and sub-district levels, and results are available within 2 hours. As Xpert MTB/RIF is rolled out worldwide (**Chapter 5**), data are also being collected to evaluate its performance in programmatic conditions.[1] It should be emphasized that countries implementing Xpert MTB/RIF still need to establish conventional laboratory capacity to monitor treatment progress and to perform DST for drugs other than rifampicin. The EXPAND-TB project is helping to accelerate access to such laboratory capacity in many countries (**Chapter 5**).

Tests that are in the late stages of development include a second-generation LPA for rapid testing for extensively drug-resistant TB in reference laboratories and a rapid test for detection of TB in microscopy centres. Technologies that are in the early stages of development include point-of care tests for TB and tests for prediction of latent TB infection.

[1] www.stoptb.org/wg/gli/xpert

7.2 New drugs for the treatment and prevention of TB

The anti-TB drugs used in first-line treatments are around 50 years old. The regimen that is currently recommended by WHO for new cases of drug-susceptible TB is highly efficacious, with cure rates of around 90% in HIV-negative patients. Nonetheless, it entails 6 months of treatment with first-line drugs (a combination of rifampicin, isoniazid, ethambutol and pyrazinamide for 2 months, followed by a 4-month continuation phase of rifampicin and isoniazid). Recommended regimens for MDR-TB require at least 20 months of treatment with second-line drugs, are associated with multiple (and sometimes serious) side-effects, and cure rates are lower (usually in the range 60–75%). There are also interactions between TB treatment and antiretroviral therapy (ART) for people living with HIV. New drugs are required to shorten and simplify treatment, to improve the efficacy and tolerability of treatment for MDR-TB and to improve the simultaneous treatment of TB and HIV among people living with HIV. New drugs could also help to treat latent TB infection in people without active TB disease; at present, preventive therapy usually consists of 6–9 months of isoniazid monotherapy.

The status of the pipeline for new anti-TB drugs in July 2011 is illustrated in **Figure 7.2**.

For the first time in 40 years, there is a coordinated portfolio of promising new compounds on the horizon, some of which have the potential to become the cornerstone drugs of TB treatment in the future. There are 10 new or repurposed TB drugs under clinical investigation, one of which is in a Phase I (safety) trial, seven are in Phase II (early bactericidal activity and sputum culture conversion) trials, and three are in Phase III (efficacy) trials (rifapentine is being evaluated in both a Phase II and a Phase III trial).

Two of the Phase III trials are evaluating 4-month regimens (in which a fluoroquinolone – either gatifloxacin or moxifloxacin – is used in place of ethambutol or isoniazid) for the treatment of drug-susceptible TB, and results are expected between 2012 and 2013. The third Phase III trial is evaluating the use of rifapentine (a rifamycin that has a longer half-life than rifampicin) as part of a 4-month regimen. The use of rifapentine in combination with isoniazid for a shorter (3 months) treatment of latent TB infection is also being evaluated.

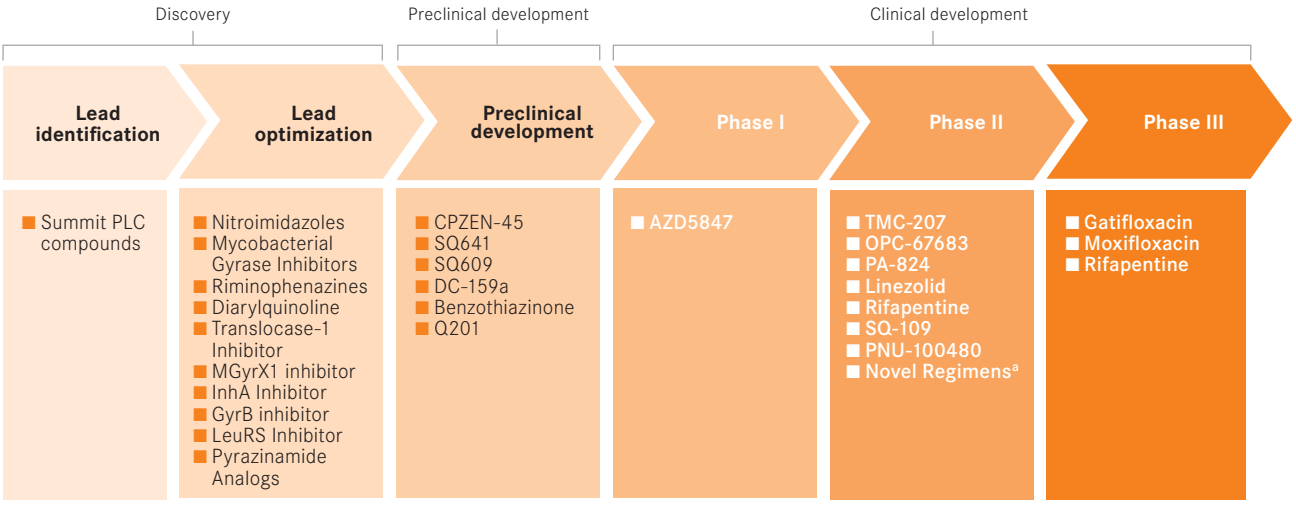
Of the compounds in Phase II trials, two are in the advanced stages of being tested for the treatment of MDR-TB. These are TMC-207 (bedaquiline) and OPC-67683 (delamanid). Both compounds have been evaluated in Phase IIb trials in newly-diagnosed MDR-TB patients, in which either the investigational drug or a placebo were added to an optimized background regimen. Final results are expected in 2012.

Other compounds in Phase II trials include linezolid, which is being tested for the treatment of extensively drug-resistant TB (XDR-TB) at a dose of 600 mg (in the Republic of Korea) and at a dose of 300 mg for the treatment of MDR-TB (in South Africa); PNU-100480 (a close analogue of linezolid); PA-824; and SQ-109 (a derivative of ethambutol). In November 2010, the first clinical trial of a novel TB drug regimen (NC001), investigating the bactericidal activity of a three-drug combination of PA-824, moxifloxacin and pyrazinamide, was initiated; results are very encouraging.

These major advances in TB drug development mean that multiple trials will be needed in various high-burden

FIGURE 7.2

The development pipeline for new drugs, 2011

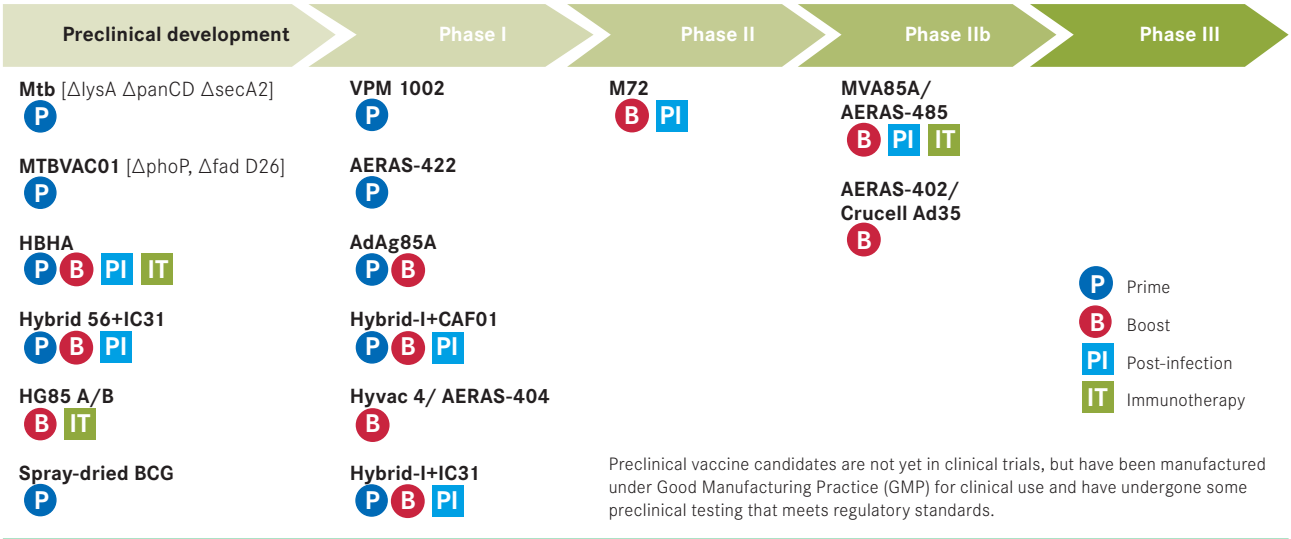


Note: This table only includes projects that have identified a promising molecule (known as a "lead" compound).

[a] The first clinical trial (NC001) of a novel TB drug regimen testing the three-drug combination of PA-824, moxifloxacin and pyrazinamide was initiated in November 2010.

FIGURE 7.3

The development pipeline for new vaccines, 2011



countries. This presents several challenges. Trials are lengthy and costly, since patients need to be followed for an extended period of time after completing treatment. New drugs have to be tested in specified drug combinations with current and/or newly re-purposed drugs; to facilitate this, novel biomarkers for treatment response and sterilizing activity, new approaches to the design of clinical trials and increased capacity (including staff and infrastructure) to implement trials in accordance with international standards are required. The recent establishment of the Critical Path to New TB Drug Regimens (CPTR) initiative, whose goal is to accelerate the development of novel regimens that will shorten TB treatment, is an important step in this direction. The CPTR is a broad coalition of stakeholders spearheaded by the Bill & Melinda Gates Foundation, the TB Alliance and the Critical Path Institute, and includes almost all pharmaceutical companies with compounds in clinical trials for TB treatment.

7.3 New vaccines for the prevention of TB

The Bacille-Calmette-Guérin (BCG) vaccine to prevent TB is almost 100 years old. It has been shown to provide protection against severe forms of TB in children (meningitis and miliary TB), but its efficacy in preventing pulmonary TB in adults varies among countries. BCG is not recommended for use in infants known to be infected with HIV, due to the risk of disseminated BCG disease. Historic opportunities for the development of new TB vaccines arose during the 1990s, following the development of techniques for genetic manipulation of mycobacteria and completion of the genome sequence of *Mycobacterium tuberculosis*.

There are two main approaches to improving TB vaccination. The first is a "prime-boost" strategy in which BCG is given to neonates (as now) and then a new vaccine is given as a booster dose. The new vaccine would be delivered to infants alongside other vaccines at 3–9 months of age and/or as a separate booster in young adults. The second approach is to develop vaccines that would replace BCG (i.e. new "prime" vaccines), such as an improved version of BCG or an attenuated live *Mycobacterium tuberculosis* vaccine. It is anticipated that a booster vaccine on top of BCG will lead the way to replacement of BCG.

The status of the pipeline for new vaccines in July 2011 is illustrated in **Figure 7.3**. There are 9 vaccine candidates in clinical trials, of which six are in Phase I trials, one is in a Phase II trial and two are in Phase IIb trials. Phase I trials are conducted with a small number of healthy volunteers (40–90 people) to ensure that the vaccine candidate is safe, to assess immunological reactions, and to begin to determine dosage levels. Phase II trials involve larger numbers of volunteers (from a few hundred to a few thousand) to continue testing safety as well as to determine optimal dosage levels and the timing of vaccination. In Phase IIb trials, preliminary data on protective efficacy are also collected. Phase III trials involve many thousands of participants and are used to determine the protective efficacy of a vaccine; the quality of data must meet the standards required for a vaccine to be licensed.

Of the vaccines that are currently being tested, MVA85A is at the most advanced stage of clinical development. It is being tested in Phase IIb trials in Africa, including among people living with HIV. It is hoped that one or two of the candidates currently in Phase IIb trials will enter a Phase III trial in the next 2–3 years, with the possibility of licensing at least one new vaccine by 2020, either alone or in combination.

It should be highlighted that capacity (staff and infra-

structure) for large-scale trials of vaccines needs to be increased in several endemic countries. At the same time, cohort studies in infants and adolescents that are under way in several countries need to be continued to provide important baseline data about TB incidence and to help determine the suitability of sites for large-scale vaccine efficacy trials.

7.4 Fundamental science and operational research

Besides the research and development discussed in **sections 7.1–7.3**, fundamental science and operational research are essential for improved TB care and control. The former is required to better characterize *Mycobacterium tuberculosis* and to improve understanding of the interaction between the bacillus and the human host, as a basis for maintaining the flow of new technologies into the product pipeline. The latter is required to identify the most effective ways of using available tools.

In the past year, the TB Research Movement of the Stop TB Partnership has developed a road map that sets out research priorities across the continuum from fundamental science to operational research.[1] A document on operational research specifically has also been developed in the last year by the Stop TB Partnership, WHO and the Global Fund.[2] This defines the critical questions to be addressed by operational research, and the appropriate study methods to use.

[1] The roadmap is available at **www.stoptb.org/global/research**

[2] *Priorities in operational research to improve tuberculosis care and control*. Available at **www.stoptb.org/assets/documents/resources/publications/technical**