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Cover design by Tom Hiatt, Western Pacific Regional Office, WHO. The front cover illustrates the contribution of different sources of funding to TB care and control in low-income countries, highlighting the importance of international donor funding (coloured blocks) compared with domestic contributions (grey band) as well as the role of the Global Fund (red line) that is the leading source of international donor funding globally; see Figure 5.5. The back cover illustrates the impressive reduction in TB prevalence in Cambodia, a low-income and high-burden country, between 2002 (when a baseline national TB prevalence survey was implemented) and 2011 (when a repeat national TB prevalence survey was implemented); see Box 2.7 in Chapter 2.

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Contents

Annexes

Abbreviations

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
BCG	Bacille-Calmette-Guérin
BRICS	Brazil, Russian Federation, India, China, South Africa
CDR	case detection rate
CPT	co-trimoxazole preventive therapy
CBC	community-based TB care
DOT	directly observed treatment
DOTS	the basic package that underpins the Stop TB Strategy
DR-TB	drug-resistant tuberculosis
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
GDP	gross domestic product
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)
IGRA	interferon-gamma release assay
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
PEPFAR	US President's Emergency Plan for AIDS Relief
POC	point-of-care
PPM	Public–Private Mix
SEAR	WHO South-East Asia Region
SRL	supranational reference laboratory
TB	tuberculosis
TB-TEAM	Tuberculosis Technical Assistance Mechanism
TST	tuberculin skin test
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, defined as MDR-TB plus resistance to a fluoroquinolone and at least one of three injectable second-line drugs (amikacin, kanamycin or capreomycin)
ZN	Ziehl Neelsen

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Executive Summary

The World Health Organization (WHO) *Global Tuberculosis Report 2012* provides the latest information and analysis about the tuberculosis (TB) epidemic and progress in TB care and control at global, regional and country levels. It is based primarily on data reported by WHO's Member States in annual rounds of global TB data collection. In 2012, 182 Member States and a total of 204 countries and territories that collectively have more than 99% of the world's TB cases reported data.

Key findings

- **Progress towards global targets for reductions in TB cases and deaths continues**. The Millennium Development Goal (MDG) target to halt and reverse the TB epidemic by 2015 has already been achieved. New cases of TB have been falling for several years and fell at a rate of 2.2% between 2010 and 2011. The TB mortality rate has decreased 41% since 1990 and the world is on track to achieve the global target of a 50% reduction by 2015. Mortality and incidence rates are also falling in all of WHO's six regions and in most of the 22 high-burden countries that account for over 80% of the world's TB cases. At country level, Cambodia demonstrates what can be achieved in a low-income and high-burden country: new data show a 45% decrease in TB prevalence since 2002.
- **However, the global burden of TB remains enormous**. In 2011, there were an estimated 8.7 million new cases of TB (13% co-infected with HIV) and 1.4 million people died from TB, including almost one million deaths among HIV-negative individuals and 430 000 among people who were HIV-positive. TB is one of the top killers of women, with 300 000 deaths among HIV-negative women and 200 000 deaths among HIV-positive women in 2011. Global progress also conceals regional variations: the African and European regions are not on track to halve 1990 levels of mortality by 2015.
- **Access to TB care has expanded substantially** since the mid-1990s, when WHO launched a new global TB strategy and began systematically monitoring progress. Between 1995 and 2011, 51 million people were successfully treated for TB in countries that had adopted the WHO strategy, saving 20 million lives.
- **Progress in responding to multidrug-resistant TB (MDR-TB) remains slow**. While the number of cases of MDR-TB notified in the 27 high MDR-TB burden countries is increasing and reached almost 60 000 worldwide in 2011, this is only one in five (19%) of the notified TB patients estimated to have MDR-TB. In the two countries with the largest number of cases, India and China, the figure is less than one in ten; scale-up is expected in these countries in the next three years.
- **There has been further progress in implementing collaborative TB/HIV activities** (first recommended by WHO in 2004). These saved an estimated 1.3 million lives between 2005 and the end of 2011. In 2011, 69% of TB patients were tested for HIV in the African Region, up from 3% in 2004. Globally, 48% of the TB patients known to be living with HIV in 2011 were started on antiretroviral therapy (ART); coverage needs to double to meet WHO's recommendation that all TB patients living with HIV are promptly started on ART. Kenya and Rwanda are top performers in HIV testing and provision of ART.
- **Innovations in diagnostics are being implemented**. The roll-out of Xpert MTB/RIF, a rapid molecular test that can diagnose TB and rifampicin resistance within 100 minutes, has been impressive. Between its endorsement by WHO in December 2010 and the end of June 2012, 1.1 million tests had been purchased by 67 low- and middle-income countries; South Africa (37% of purchased tests) is the leading adopter. A 41% price reduction (from US$ 16.86 to US$ 9.98) in August 2012 should accelerate uptake.
- **The development of new drugs and new vaccines is also progressing**. New or re-purposed TB drugs and novel TB regimens to treat drug-sensitive or drug-resistant TB are advancing in clinical trials and regulatory review. Eleven vaccines to prevent TB are moving through development stages.
- **There are critical funding gaps for TB care and control**. Between 2013 and 2015 up to US$ 8 billion per year is needed in low- and middle-income countries, with a funding gap of up to US$ 3 billion per year. International donor funding is especially critical to sustain recent gains and make further progress in 35 low-income countries (25 in Africa), where donors provide more than 60% of current funding.
- **There are also critical funding gaps for research and development**. US$ 2 billion per year is needed; the funding gap was US$ 1.4 billion in 2010.

Additional highlights by topic

Burden of disease

Geographically, the burden of TB is highest in Asia and Africa. India and China together account for almost 40% of the world's TB cases. About 60% of cases are in the South-East Asia and Western Pacific regions. The African Region has 24% of the world's cases, and the highest rates of cases and deaths per capita.

Worldwide, 3.7% of new cases and 20% of previously treated cases were estimated to have MDR-TB.

India, China, the Russian Federation and South Africa have almost 60% of the world's cases of MDR-TB. The highest proportions of TB patients with MDR-TB are in eastern Europe and central Asia.

Almost 80% of TB cases among people living with HIV reside in Africa.

Estimating the burden of TB in children (aged less than 15) is difficult; estimates are included in the report for the first time. There were an estimated 0.5 million cases and 64 000 deaths among children in 2011.

Case notifications and treatment success

In 2011, 5.8 million newly diagnosed cases were notified to national TB control programmes (NTPs) and reported to WHO, up from 3.4 million in 1995 but still only two-thirds of the estimated total of 8.7 million people who fell ill with TB in 2011.

Notifications of TB cases have stagnated in recent years. New policy measures, including mandatory case notification by all care providers via an electronic web-based system in India, could have a global impact on the number of TB cases notified in future years. Intensified efforts by NTPs to engage the full range of care providers using public-private mix (PPM) initiatives are also important; in most of the 21 countries that provided data, 10–40% of notifications were from non-NTP care providers.

Globally, treatment success rates have been maintained at high levels for several years. In 2010 (the latest year for which treatment outcome data are available), the treatment success rate among all newly-diagnosed cases was 85% and 87% among patients with smear-positive pulmonary TB (the most infectious cases).

Responding to drug-resistant TB

Measurement of drug resistance has improved considerably. Data are available for 135 countries worldwide (70% of WHO's 194 Member States) and by the end of 2012 will be available from all 36 countries with a high burden of TB or MDR-TB.

Extensively drug-resistant TB, or XDR-TB, has been reported by 84 countries; the average proportion of MDR-TB cases with XDR-TB is 9.0%.

The target treatment success rate of 75% or higher for patients with MDR-TB was reached by only 30 of 107 countries that reported treatment outcomes.

Scaling up TB-HIV collaboration

Globally, 40% of TB patients had a documented HIV test result and 79% of those living with HIV were provided with co-trimoxazole preventive therapy in 2011.

Interventions to detect TB promptly and to prevent TB among people living with HIV, that are usually the responsibility of HIV programmes and general primary health-care services, include regular screening for TB and isoniazid preventive therapy (IPT) for those without active TB. The number of people in HIV care who were screened for TB increased 39% (2.3 million to 3.2 million) between 2010 and 2011. Nearly half a million people without active TB were provided with IPT, more than double the number started in 2010 and mostly the result of progress in South Africa.

Research and development to accelerate progress

Research to develop a point-of-care diagnostic test for TB and MDR-TB continues, and other diagnostic tests are in the pipeline.

Today, standard treatment for TB patients lasts six months and the regimen for most patients with drug-resistant TB takes 20 months. Treatment for MDR-TB is costly and can have serious side-effects. Of the 10 anti-TB drugs in clinical trials, two new drugs are being evaluated to boost the effectiveness of MDR-TB regimens. A novel regimen that could be used to treat both drug-sensitive TB and MDR-TB and shorten treatment duration has shown encouraging results in clinical trials.

There is no effective vaccine to prevent TB in adults. Progress in the past decade means that it is possible that at least one new vaccine could be licensed by 2020.

Financing for TB care and control

About US$ 1 billion per year of international donor funding is needed for TB care and control (excluding TB/HIV interventions) in low and middle-income countries from 2013 to 2015, double existing levels. Up to an additional US$ 1 billion per year is needed for TB/HIV interventions, mostly for ART for HIV-positive TB patients.

National contributions provide the bulk of financing for TB care and control in Brazil, the Russian Federation, India, China and South Africa (BRICS). However, they remain insufficient for scaling up the diagnosis and treatment of MDR-TB; BRICS account for about 60% of the world's estimated cases of MDR-TB.

The Global Fund provides almost 90% of international donor funding for TB.

CHAPTER 1

Introduction

BOX 1.1

Basic facts about tuberculosis (TB)

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 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.

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]

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. Following recent developments in TB diagnostics, the use of rapid molecular tests for the diagnosis of TB and drug-resistant TB is increasing, as highlighted in **Chapter 6** of this report. In countries with more developed laboratory capacity, cases of TB are also diagnosed via culture methods (the current reference standard).

Treatment for new cases of drug-susceptible TB consists of a 6-month regimen of four first-line drugs: isoniazid, rifampicin, ethambutol and pyrazinamide. Treatment for multidrug-resistant TB (MDR-TB), defined as resistance to isoniazid and rifampicin (the two most powerful anti-TB drugs) is longer, and requires more expensive and toxic drugs. For most patients with MDR-TB, the current regimens recommended by WHO last 20 months.

[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.

Tuberculosis (TB) remains a major global health problem. It causes ill-health among millions of people each year and ranks as the second leading cause of death from an infectious disease worldwide, after the human immunodeficiency virus (HIV). The latest estimates included in this report are that there were almost 9 million new cases in 2011 and 1.4 million TB deaths (990 000 among HIV-negative people and 430 000 HIV-associated TB deaths). This is despite the availability of treatment that will cure most cases of TB. Short-course regimens of first-line drugs that can cure around 90% of cases have been available since the 1980s.

The World Health Organization (WHO) declared TB a global public health emergency in 1993. Starting in the mid-1990s, efforts to improve TB care and control intensified at national and international levels. WHO developed the DOTS strategy, a five-component package comprising political commitment, diagnosis using sputum smear microscopy, a regular supply of first-line anti-TB drugs, short-course chemotherapy and a standard system for recording and reporting the number of cases detected by national TB control programmes (NTPs) and the outcomes of treatment. Within a decade, almost all countries had adopted the strategy and there was considerable progress towards global targets established for 2005: the detection of 70% of the estimated number of smear-positive pulmonary cases (the most infectious cases) and the successful treatment of 85% of these cases. In 2005, the numbers of cases reported by NTPs grew to over 5 million and treatment success rates reached 85%.

WHO's currently-recommended approach to TB care and control is the Stop TB Strategy, launched in 2006 (**Box 1.2**). This strategy was linked to new global targets for reductions in TB cases and deaths that were set for 2015 (**Box 1.3**) as part of the Millennium Development Goals (MDGs) and by the Stop TB Partnership. The targets are that TB incidence should be falling by 2015 (MDG Target 6.c) and that prevalence and death rates should be halved compared with their levels in 1990.

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 has been described in Global Plans developed by the Stop TB Partnership. The latest plan covers the period 2011–2015 and

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

TABLE 1.1 **Targets for the scale-up of interventions for TB care and control set in the Global Plan to Stop TB 2011–2015**

PLAN COMPONENT AND INDICATORS	2015 TARGET
Diagnosis and treatment of drug-susceptible TB	
Number of cases diagnosed, notified and treated according to the DOTS approach (per year)	6.9 million
Treatment success rate (in annual cohort)	90%
Number of countries with ≥1 laboratory with sputum-smear microscopy services per 100 000 population	149
Diagnosis and treatment of drug-resistant TB	
Percentage of previously treated TB patients tested for MDR-TB	100%
Percentage of new bacteriologically-positive TB patients tested for MDR-TB	20%
Number of countries among the 22 HBCs and 27 high MDR-TB burden countries with ≥1 culture laboratory per 5 million population	36
Percentage of confirmed cases of MDR-TB enrolled on treatment according to international guidelines	100%
Number of confirmed cases of MDR-TB enrolled on treatment according to international guidelines	~270 000
Treatment success rate among confirmed cases of MDR-TB	≥75%
Collaborative TB/HIV activities	
Percentage of TB patients tested for HIV	100%
Percentage of HIV-positive TB patients treated with CPT	100%
Percentage of HIV-positive TB patients treated with ART	100%
Percentage of people living with HIV attending HIV care services who were screened for TB at their last visit	100%
Percentage of people living with HIV attending HIV care services who were enrolled on IPT, among those eligible	100%
Laboratory strengthening (additional to those above)	
Percentage of national reference laboratories implementing a quality management system (QMS) according to international standards	≥50%

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

comes with a price tag of US$ 47 billion.[1] The main indicators and associated targets for 2015 are summarized in Table 1.1.

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 and WHO's recommended strategy for achieving these targets. This 2012 edition – the 17th in the series – continues the tradition. 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 (Box 1.4). In 2012, a total of 204 countries and territories that account for over 99% of the world's estimated cases of TB reported data (Table 1.2).

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

Chapter 2 contains the latest estimates of the burden of disease caused by TB and assessment of progress towards the 2015 targets at global, regional and country levels. The chapter puts the spotlight on Cambodia as a new success story in TB control at country level and for the first

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

BOX 1.3

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

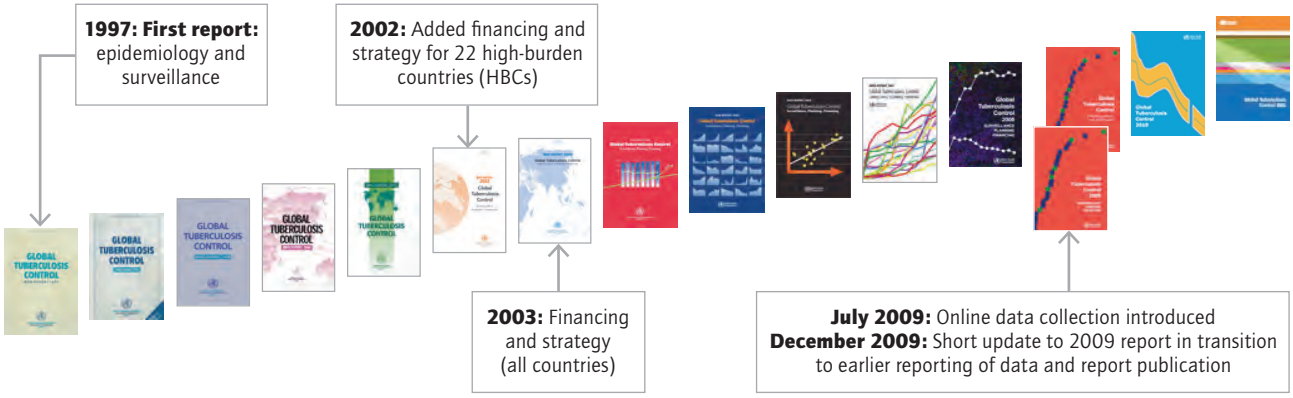
Indicator 6.10: Proportion of TB cases detected and cured under DOTS

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

FIGURE 1.1 **Sixteen annual WHO reports on TB in 15 years, 1997–2011**



BOX 1.4

Data collected in WHO's 2012 round of global TB data collection

Data were requested on the following topics: TB case notifications and treatment outcomes, including breakdowns by case type, age, sex, HIV status and drug resistance 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; TB infection control; engagement of all care providers in TB control; the budgets of national TB control programmes (NTPs) in 2012 and 2013; utilization of general health services (hospitalization and outpatient visits) during treatment; and NTP expenditures in 2011. 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$ 12 475 in 2011, as defined by the World Bank)[1] 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.[2] In 2012, the online system was opened for reporting on 16 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). 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.

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. Following corrections and updates by countries, the data used for the main part of this report were the data available in July 2012. Annex 4 was produced on 25 September 2012, by which time additional data had been reported by a few European countries.[3]

Besides the data reported through the standard TB questionnaire, data about screening for TB among people living with HIV and provision of isoniazid preventive therapy to those without active TB were collected by the HIV department in WHO and UNAIDS. The data were jointly validated and imported into the global TB database.

[1] http://data.worldbank.org/about/country-classifications
[2] www.stoptb.org/tme
[3] For this reason, there may be slight discrepancies between the main part of the report and Annex 4.

time includes estimates of the burden of TB in children. The latest status of efforts to improve measurement of TB cases and deaths at country level, with guidance and support from WHO's Global Task Force on TB Impact Measurement, is described.

Chapter 3 presents data on the numbers of cases notified to NTPs and reported to WHO and their treatment outcomes, including breakdowns of cases by type of TB disease, sex and age.

Chapter 4 focuses on drug-resistant TB, covering progress in drug resistance surveillance and associated estimates of the proportion of TB patients that have MDR-TB and extensively drug-resistant TB (XDR-TB), and the latest data on the coverage of testing for MDR-TB among new and previously treated TB patients, notifications of cases of MDR-TB and enrolments on treatment, and treatment outcomes.

Chapter 5 assesses financing for TB care and control. Trends since 2006 are described by source of funding and category of expenditure. Important contrasts in the extent to which different country groups rely upon domestic and donor financing are illustrated. Funding gaps, the unit costs of TB treatment and the cost-effectiveness of TB interventions are discussed as well.

TABLE 1.2 **Reporting of data in the 2012 round of global TB data collection**

WHO REGION OR SET OF COUNTRIES	COUNTRIES AND TERRITORIES		MEMBER STATES	
	NUMBER	NUMBER THAT REPORTED DATA	NUMBER	NUMBER THAT REPORTED DATA
African Region	46	46	46	46
Eastern Mediterranean Region	23	23	22	22
European Region[a]	54	42	53	41
Region of the Americas	46	46	35	35
South-East Asia Region	11	11	11	11
Western Pacific Region	36	36	27	27
High-burden countries (HBCs)[b]	22	22	22	22
WORLD	**216**	**204**	**194**	**182**

[a] Countries that did not report by the deadlines were mostly low-incidence countries in Western Europe.
[b] The HBCs are 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.

Chapter 6, on TB diagnostics and laboratory strengthening, summarizes recent policy development and analyses laboratory capacity in 2011. The development of laboratory capacity through the EXPAND-TB project and the latest data on progress in rolling out Xpert MTB/RIF since endorsement of this rapid molecular test in 2010 are given particular attention.

Chapter 7 contains the most recent data on progress in implementing collaborative TB/HIV activities to jointly address the epidemics of TB and HIV. The lives saved by these interventions since WHO policy was issued in 2004 and the need to further increase the coverage of antiretroviral therapy for TB patients living with HIV are highlighted.

Chapter 8 discusses research and development for new TB diagnostics, drugs and vaccines. After years of stagnation, considerable progress has occurred in the last decade and the development pipelines as of mid-2012 are described and discussed.

The report also has four annexes. **Annex 1** explains the methods used to produce estimates of the burden of disease caused by TB. **Annex 2** contains country profiles for the 22 high-burden countries (HBCs) that collectively account for about 80% of the world's TB cases (profiles for all countries are available online[1]). **Annex 3** contains regional profiles. **Annex 4** consists of summary tables that provide data on key indicators for the world, WHO's six regions and individual countries.

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

CHAPTER 2

The burden of disease caused by TB

KEY FACTS AND MESSAGES

- There has been major progress in reducing TB cases and deaths in the past two decades.
- The 2015 MDG target of halting and reversing TB incidence has been achieved, with TB incidence falling globally for several years and declining at a rate of 2.2% between 2010 and 2011. Globally, the TB mortality rate has fallen by 41% since 1990 and the world is on track to reach the global target of a 50% reduction by 2015.
- Mortality and incidence rates are falling in all of WHO's six regions and in most of the 22 HBCs that account for over 80% of the world's TB cases.
- Cambodia provides an important new success story for TB control in a HBC: a national population-based survey completed in 2011 showed that TB prevalence had fallen 45% since a baseline survey in 2002.
- Despite this encouraging progress, the global burden of TB remains enormous. There were an estimated 8.7 million incident cases of TB in 2011 (13% co-infected with HIV). There were also 1.4 million deaths from TB (990 000 deaths among HIV-negative individuals and 430 000 among people who were HIV-positive). These deaths included 0.5 million among women, making TB one of the top killers of women worldwide.
- Geographically, the burden of TB is highest in Asia and Africa. India and China combined have almost 40% of the world's TB cases; the South-East Asia and Western Pacific Regions of which they are a part account for 60%. The African Region has approximately one quarter of the world's cases, and the highest rates of cases and deaths relative to population.
- Globally, 3.7% of new cases and 20% of previously treated cases are estimated to have MDR-TB.
- Estimates of the burden of disease caused by TB are being continuously improved at country level, supported by WHO's Global Task Force on TB Impact Measurement.

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).

This chapter presents estimates of TB incidence, prevalence and mortality (absolute numbers and rates) between 1990 and 2011 and (for prevalence and mortality) forecasts up to 2015 (in **sections 2.1–2.3**). These data are used to assess progress towards achieving the global targets for TB control 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 1990 (**Box 1.3** in **Chapter 1**). Key aspects of the methods used to produce the estimates are provided at the beginning of each section.[1] **Section 2.4** contains estimates of the number of prevalent cases of multidrug-resistant TB (MDR-TB) in 2011, and estimates of the proportion of MDR-TB cases globally, regionally and in high TB-burden countries (HBCs).[2]

In response to increasing demand and global attention, this 2012 global report is the first to feature estimates of the number of TB cases and deaths among children and the first to include estimates of TB mortality among women that include HIV-associated TB deaths.[3] The chapter also puts the spotlight on Cambodia, which provides a new success story for TB control at country level. A national survey in 2011 showed that TB prevalence had fallen by 45% in the 9 years since a baseline survey in 2002.

There is uncertainty in all estimates of the burden of disease caused by TB. **Section 2.5** profiles efforts to improve measurement of the burden of the disease 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.

[1] A detailed description is provided in **Annex 1**.

[2] **Chapter 4** includes a much fuller discussion of the MDR-TB epidemic and the latest data on progress in the diagnosis and treatment of MDR-TB.

[3] In previous reports, estimates were restricted to the number of TB deaths among women who were HIV-negative.

BOX 2.1

Uncertainty in estimates of TB incidence, prevalence and mortality

Measuring the incidence of TB at national level has never been done because it 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; costs range from US$ 1 to US$ 4 million per survey.[1] Between 2009 and 2015, an unprecedented number of national TB prevalence surveys are being conducted in countries where TB is endemic. In low and medium-burden countries, sample sizes and costs become prohibitively large. 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. Sample VR systems covering representative areas of the country (as in China) provide an interim solution. Mortality surveys can also be used to directly measure deaths caused by TB. In 2011, 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 systems are in place because 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. The methods used to produce best estimates and uncertainty intervals are described in detail in **Annex 1**.

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

2.1 Incidence

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 revised between 2009 and 2012 in regional or country workshops (**Figure 2.1**) 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 not diagnosed at all, was documented. Reliance on expert opinion is one of the reasons why estimates are uncertain (**Box 2.1**); strengthening surveillance and better quantifying the extent of under-reporting (i.e. the number of cases that are missed by surveillance systems) are needed to reduce this uncertainty (efforts to do so are discussed in **Section 2.5**). For countries not covered in workshops, estimates are based on extending previous time-series or on updates using mortality data from VR systems combined with evidence about the case fatality rate (see **Annex 1** for details).

In 2011, there were an estimated 8.7 million incident cases of TB (range, 8.3 million–9.0 million) globally, equivalent to 125 cases per 100 000 population (**Table 2.1**, **Table 2.2**, **Figure 2.3**, **Figure 2.4**, **Figure 2.5**). Most of the estimated number of cases in 2011 occurred in Asia (59%) and Africa (26%);[1] smaller proportions of cases occurred in the Eastern Mediterranean Region (7.7%), the European Region (4.3%) 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 82% of all estimat-

FIGURE 2.1 **Progress in applying the Task Force framework for assessment of TB surveillance data, as of July 2012[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, national workshops were also held in China in June 2011, in India in July 2011 and July 2012, in Cambodia in February 2012 and in Indonesia in March 2012. Further details about these workshops are provided in **ANNEX 1**.

[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)**

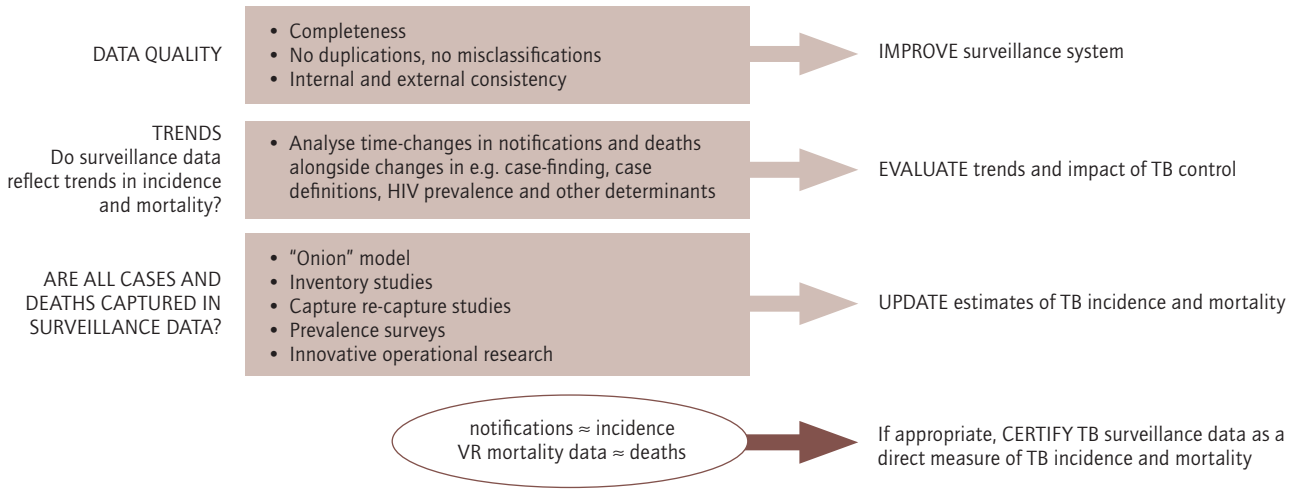


TABLE 2.1 **Estimated burden of disease caused by TB, 2011.** Numbers in thousands.[a]

		MORTALITY[b]			PREVALENCE			INCIDENCE			HIV-POSITIVE INCIDENT TB CASES		
	POPULATION	BEST[c]	LOW	HIGH	BEST	LOW	HIGH	BEST	LOW	HIGH	BEST	LOW	HIGH
Afghanistan	32 358	13	5.3	23	110	55	190	61	51	73	0.3	0.2	0.4
Bangladesh	150 494	68	29	120	620	300	1 100	340	280	400	0.6	0.3	1.0
Brazil	196 655	5.6	4.6	6.8	91	36	170	83	69	97	16	13	19
Cambodia	14 305	9.1	4.2	16	120	99	140	61	52	70	3.1	2.6	3.6
China	1 347 565	47	45	49	1 400	1 200	1 600	1 000	890	1 100	13	8.6	17
DR Congo	67 758	36	16	65	350	180	570	220	190	250	34	27	41
Ethiopia	84 734	15	11	20	200	160	240	220	160	280	38	28	49
India[d]	1 241 492	300	190	430	3 100	2 100	4 300	2 200	2 000	2 500	94	72	120
Indonesia	242 326	65	29	120	680	310	1 200	450	380	540	15	11	20
Kenya	41 610	9.2	4.7	15	120	63	200	120	110	120	47	45	49
Mozambique	23 930	11	4.0	22	120	56	200	130	91	180	83	58	110
Myanmar	48 337	23	11	40	240	190	310	180	160	210	18	15	22
Nigeria	162 471	27	6.1	64	280	71	620	190	90	330	50	23	86
Pakistan	176 745	59	26	110	620	280	1 100	410	340	490	1.5	1.0	2.1
Philippines	94 852	28	25	31	460	400	520	260	210	310	1.1	0.6	1.6
Russian Federation	142 836	22	22	23	180	72	330	140	120	160	9.3	7.4	11
South Africa	50 460	25	11	44	390	200	630	500	410	600	330	270	390
Thailand	69 519	9.8	4.2	18	110	51	200	86	71	100	13	10	15
Uganda	34 509	5.0	2.1	9.0	63	33	100	67	54	81	35	28	42
UR Tanzania	46 218	6.4	3.3	11	82	43	130	78	73	83	30	28	32
Viet Nam	88 792	30	12	55	290	130	500	180	140	220	14	11	18
Zimbabwe	12 754	6.0	2.4	11	70	37	110	77	59	96	46	36	58
High-burden countries	**4 370 719**	**820**	**680**	**980**	**9 700**	**8 300**	**11 000**	**7 100**	**6 800**	**7 500**	**890**	**810**	**970**
AFR	857 382	220	180	270	2 500	2 100	3 000	2 300	2 100	2 400	870	800	950
AMR	943 019	21	18	24	330	250	420	260	240	280	37	34	40
EMR	608 628	99	61	150	1 000	660	1 500	660	590	740	8.7	7.6	9.9
EUR	899 500	45	44	46	500	370	650	380	350	400	23	20	25
SEAR	1 830 361	480	350	630	5 000	3 800	6 300	3 500	3 200	3 700	140	120	170
WPR	1 808 797	130	100	150	2 500	2 200	2 800	1 700	1 500	1 800	36	31	42
Global	**6 947 687**	**990**	**840**	**1 100**	**12 000**	**10 000**	**13 000**	**8 700**	**8 300**	**9 000**	**1 100**	**1 000**	**1 200**

[a] Numbers for mortality, prevalence and incidence shown to two significant figures. Totals (HBCs, regional and global) are computed prior to rounding.
[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.

TABLE 2.2 **Estimated burden of disease caused by TB, 2011.** Rates per 100 000 population except where indicated.[a]

	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	32 358	39	16	71	351	169	597	189	156	225	0.5	0.3	0.7
Bangladesh	150 494	45	19	82	411	199	698	225	185	268	0.2	0.1	0.3
Brazil	196 655	2.9	2.3	3.4	46	18	87	42	35	50	20	19	20
Cambodia	14 305	63	29	111	817	690	954	424	364	489	5.1	4.8	5.3
China	1 347 565	3.5	3.4	3.6	104	91	119	75	66	85	1.2	0.9	1.7
DR Congo	67 758	54	24	96	512	263	842	327	282	375	15	13	17
Ethiopia	84 734	18	14	24	237	191	288	258	191	335	17	17	18
India[c]	1 241 492	24	15	35	249	168	346	181	163	199	4.2	3.3	5.2
Indonesia	242 326	27	12	48	281	130	489	187	155	222	3.3	2.5	4.2
Kenya	41 610	22	11	36	291	152	475	288	276	300	39	39	40
Mozambique	23 930	47	17	91	490	235	837	548	380	747	63	63	64
Myanmar	48 337	48	22	84	506	390	637	381	326	439	9.9	8.8	11
Nigeria	162 471	17	3.7	40	171	44	382	118	56	204	26	25	26
Pakistan	176 745	33	15	60	350	158	618	231	190	276	0.4	0.3	0.5
Philippines	94 852	29	26	33	484	425	546	270	223	322	0.4	0.3	0.6
Russian Federation	142 836	16	15	16	124	50	229	97	82	114	6.7	5.7	7.7
South Africa	50 460	49	21	87	768	399	1 250	993	819	1 180	65	65	66
Thailand	69 519	14	6.1	25	161	73	282	124	102	147	15	14	15
Uganda	34 509	14	6.2	26	183	95	298	193	156	234	53	52	53
UR Tanzania	46 218	14	7.1	23	177	93	286	169	159	180	38	38	39
Viet Nam	88 792	33	14	62	323	148	563	199	153	250	8.0	7.8	8.2
Zimbabwe	12 754	47	19	88	547	287	889	603	466	757	60	59	60
High-burden countries	**4 370 719**	**19**	**15**	**22**	**222**	**190**	**255**	**163**	**155**	**171**	**13**	**11**	**14**
AFR	857 382	26	21	31	293	243	347	262	242	283	39	37	41
AMR	943 019	2.2	1.9	2.5	35	26	44	28	26	29	14	11	17
EMR	608 628	16	10	24	170	108	246	109	97	122	1.5	0.9	2.1
EUR	899 500	5.0	4.9	5.1	56	41	73	42	39	45	6.1	4.4	8.0
SEAR	1 830 361	26	19	34	271	206	344	189	176	203	4.1	3.3	5.0
WPR	1 808 797	6.9	5.7	8.3	138	123	154	92	84	100	2.2	1.4	3.1
Global	**6 947 687**	**14**	**12**	**17**	**170**	**150**	**192**	**125**	**120**	**130**	**13**	**12**	**14**

[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.

ed incident cases worldwide. Of the 8.7 million incident cases, an estimated 0.5 million were children (**Box 2.2**) and 2.9 million (range, 2.6–3.2 million) occurred among women.

The five countries with the largest number of incident cases in 2011 were India (2.0 million–2.5 million), China (0.9 million–1.1 million), South Africa (0.4 million–0.6 million), Indonesia (0.4 million–0.5 million) and Pakistan (0.3 million–0.5 million). India and China alone accounted for 26% and 12% of global cases, respectively.

Of the 8.7 million incident cases in 2011, 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 was highest in countries in the African Region (**Figure 2.6**); overall, 39% of TB cases were estimated to be coinfected with HIV in this region, which accounted for 79% of TB cases among people living with HIV worldwide.

Globally, incidence rates were relatively stable from 1990 up to around 2001, and then started to fall (**Figure 2.3**). Between 2010 and 2011, the rate of decline was 2.2%; if this trend is sustained, MDG Target 6.c will be achieved. The absolute number of incident cases is also falling, albeit slowly (**Figure 2.4**), as the decline in the incidence rate (per 100 000 population) exceeds the rate of growth in the world's population.

Incidence rates are declining in all of WHO's six regions (**Figure 2.7**). The rate of decline between 2010 and 2011 was 0.5% in the Eastern Mediterranean Region, 2.0% in the South-East Asia Region, 2.3% in the Western Pacific Region, 3.1% in the African Region, 3.8% in the Region of the Americas and 8.5% per year in the European

FIGURE 2.3 **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 1990–2011 and forecast TB prevalence and mortality rates 2012–2015. 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.

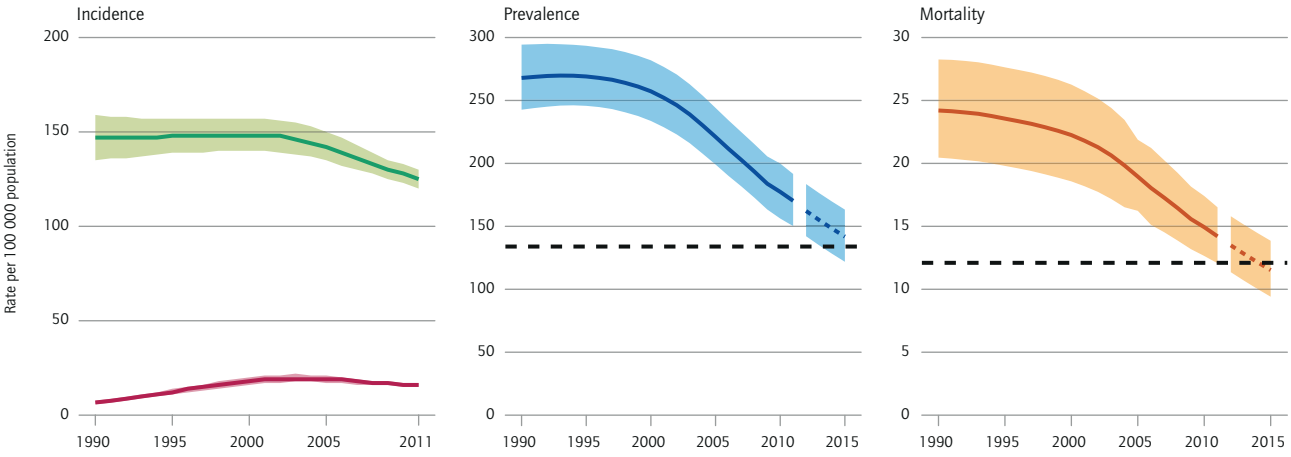
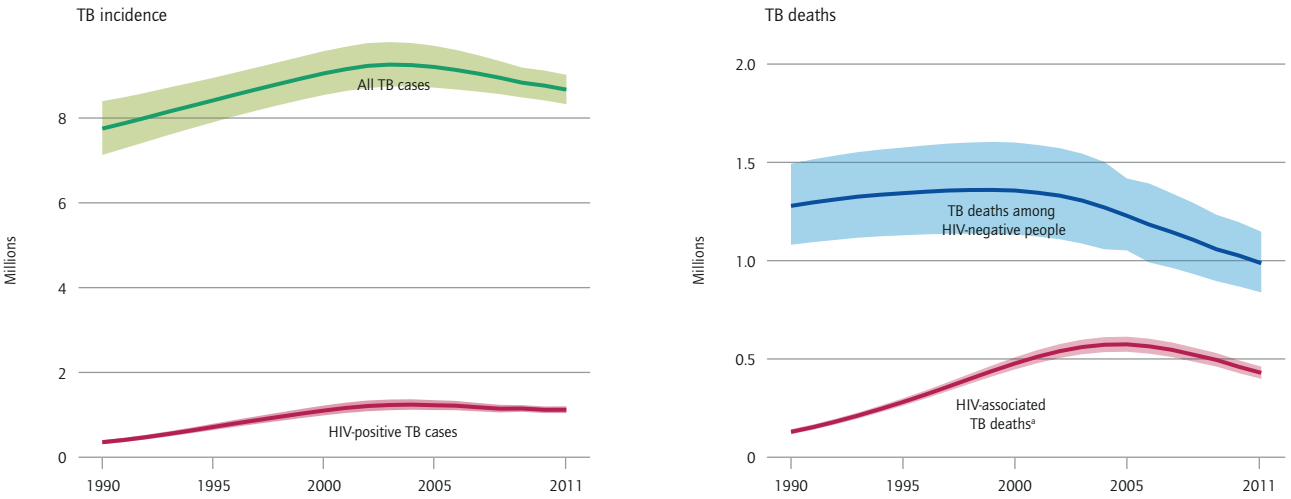


FIGURE 2.4 **Estimated absolute numbers of TB cases and deaths (in millions), 1990–2011**



[a] HIV-associated TB deaths are classified as HIV deaths according to ICD-10.

Region. Incidence rates have been falling since the mid-1990s in the Eastern Mediterranean Region and since around 2000 in South-East Asia; they peaked at the end of the 1990s in the European Region and around 2002 in Africa, and have been falling since 1990 in the Americas and the Western Pacific Region. The latest assessment for the 22 HBCs suggests that incidence rates are falling in most countries (Figure 2.8).

2.2 Prevalence

The prevalence of TB can be directly measured in nationwide population-based surveys, and comprehensive theoretical and practical guidance on how to design, implement, analyse and report such surveys is available.[1] When repeat surveys are conducted, trends in TB prevalence can be directly measured as well. The countries in which surveys have been implemented or are planned in the near future are shown in Figure 2.9.

If survey 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 Cambodia, China and the Philippines) and are becoming more widely avail-

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

FIGURE 2.5 **Estimated TB incidence rates, 2011**

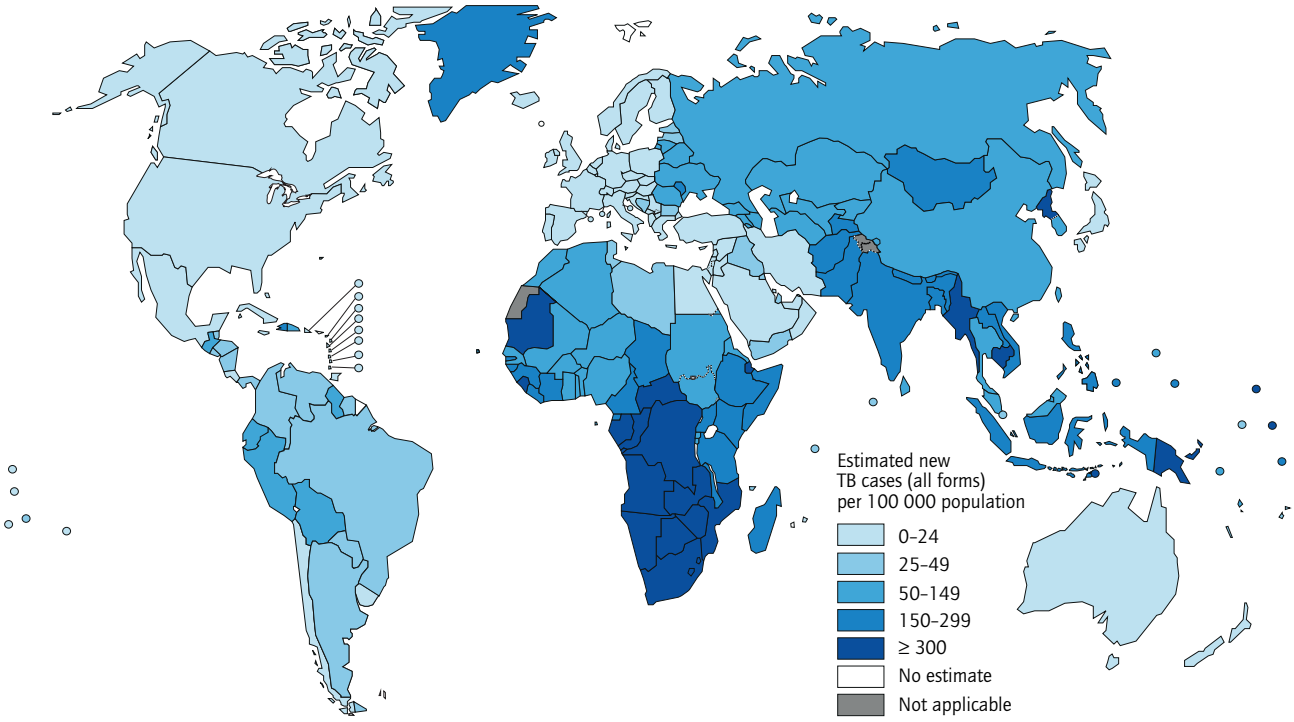
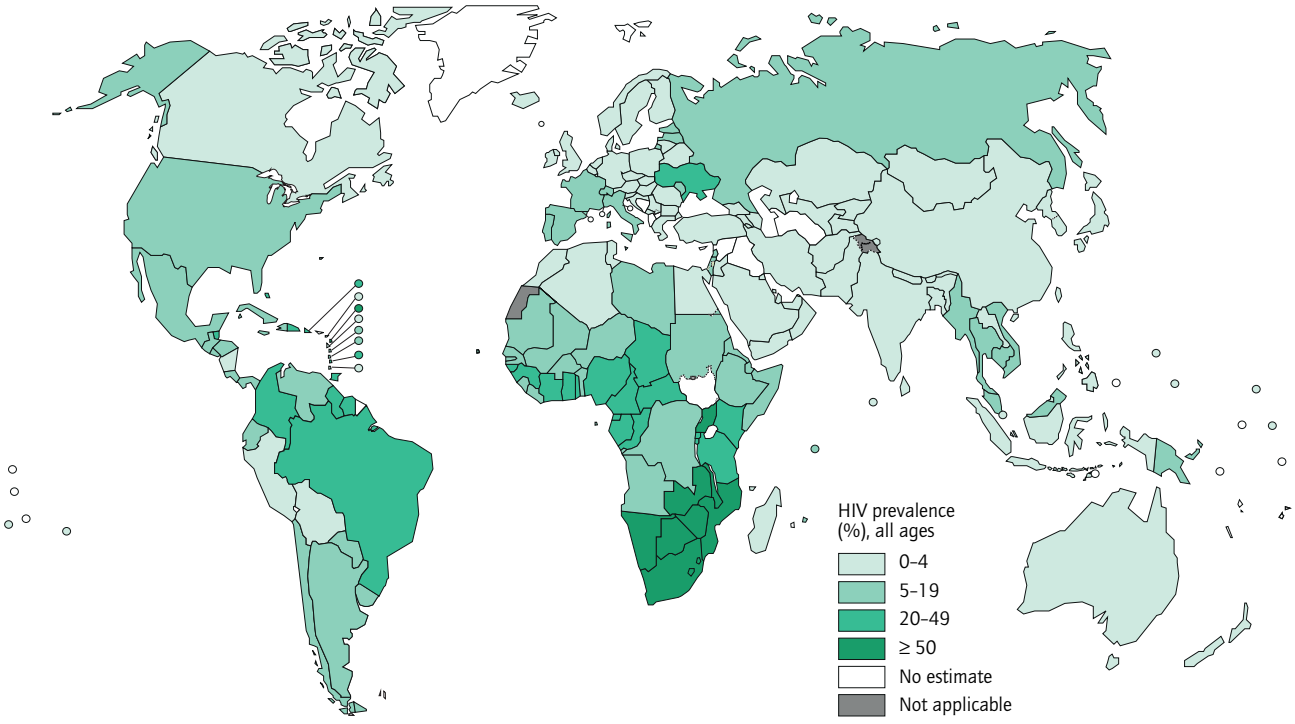


FIGURE 2.6 **Estimated HIV prevalence in new TB cases, 2011**



BOX 2.2

The burden of TB disease among children

For many years, the prevention, diagnosis and treatment of TB among children have been relatively neglected. Greatest attention has been given to the detection and treatment of infectious cases, most of which occur in adults. The Stop TB Strategy launched by WHO in 2006 includes case-finding in high-risk or vulnerable groups such as children and prevention of TB in children who live in the same household as newly detected TB cases. To help to address the burden of TB in children (defined as those aged <15 years) and monitor progress, robust data on childhood TB are necessary. This is the first WHO report on global TB care and control to include estimates of the burden of TB disease among children, with best estimates of 490 000 cases and 64 000 deaths per year.[1] The reasons why it remains difficult to estimate the burden of TB disease in children, the methods used to produce this first set of estimates and the next steps needed to improve them are discussed below.

Challenges in assessing the number of TB cases and deaths among children

There is no easy-to-use and accurate diagnostic test for TB in children. Most children have paucibacillary TB that is harder to diagnose with sputum smear microscopy and culture. Many children, especially younger children, are also not able to expectorate sputum. Diagnosis is usually made using a combination of clinical (as opposed to laboratory) criteria and a non-specific test for tuberculous infection, but there is no universally applied diagnostic algorithm. The definitive diagnosis of extrapulmonary TB requires specialised services that are usually available only in referral hospitals, and thus often not accessible to those in need. Besides diagnostic challenges, children diagnosed with TB are not always reported to national surveillance systems because of the lack of linkages among individual paediatricians, paediatric hospitals and national TB programmes, and data from national surveys including children are limited. Many countries lack VR systems in which deaths from TB are disaggregated and reported by age.

Estimates of TB notifications and TB incidence in children in 2011 – methods and results

The global number of new TB case notifications among children (aged <15 years) is estimated at 327 000 in 2011 (**Table B2.2.1**). This includes cases reported among children and an estimate of the number of cases among children in countries that did not report notifications disaggregated by age. For countries that did not report age-disaggregated data (**Figure B2.2.1**), it was assumed that the child:adult ratio among notified cases was the same (for each case type) as the ratio in countries that did report notifications disaggregated by age (an alternative method using the assumption that the child:adult ratio of notification rates was the same gave similar results). WHO does not request age-disaggregated data for relapse cases or those reported as of unknown treatment history; the number of children in these categories was assumed to be zero.

To estimate TB incidence among children, it was assumed that the ratio of notified to incident cases at the global level in 2011 (best estimate 66%, range 64%–69%) was the same for adults and children. On this basis, TB incidence among children was estimated at 490 000 (range, 470 000–510 000) in 2011, equivalent to about 6% of the total number of 8.7 million incident cases.

Limitations of the methods used include:

- The assumption that the ratio of notified to incident cases is the same for adults and children, in the absence of any data on levels of under-reporting of diagnosed cases for children and adults separately;
- The assumption that reported cases were true cases of TB. Misdiagnosis is possible, especially given the difficulties of diagnosing TB in children; and
- The proportion of cases among children may be different in countries for which age-disaggregated data are not available.

Estimates of TB mortality in children in 2011 – methods and results

Mortality data disaggregated by age from VR systems that have been reported to WHO were analysed. TB death rates per 100 000 population were calculated for children and adults, after adjustment for incomplete coverage and ill-defined causes (see **Annex 1** for further details). For countries without VR data, an ecological statistical model was used to predict the ratio of childhood to adult TB mortality rates. The model included a set of risk factors known to be associated with TB mortality (for example, GDP per capita, the percentage of new cases with MDR-TB, HIV prevalence in the general population and the treatment success rate). The total number of deaths from TB among HIV-negative children was estimated at 64 000 (range, 58 000–71 000) in 2011, equivalent to 6% of the 990 000 TB deaths among HIV-negative TB cases in 2011. The main limitation in the methods is that the countries reporting usable VR data were all middle or high-income countries. Predictions for low-income countries had to be extrapolated from these countries.

Besides the direct impact of TB on children themselves, parental deaths from TB have created large numbers of orphans. In 2009, there were almost 10 million children who were orphans as a consequence of losing at least one of their parents to TB.

Estimates of TB prevalence in children

Data on the prevalence of TB in children are limited to a few nationwide surveys conducted before 2001. Examples include a survey in India in 1956, and surveys in China in 1980, 1990, and 2000. The 2007 survey in the Philippines included children aged 10–14 years. These surveys consistently found a low burden of bacteriologically-confirmed TB in children compared with adults.

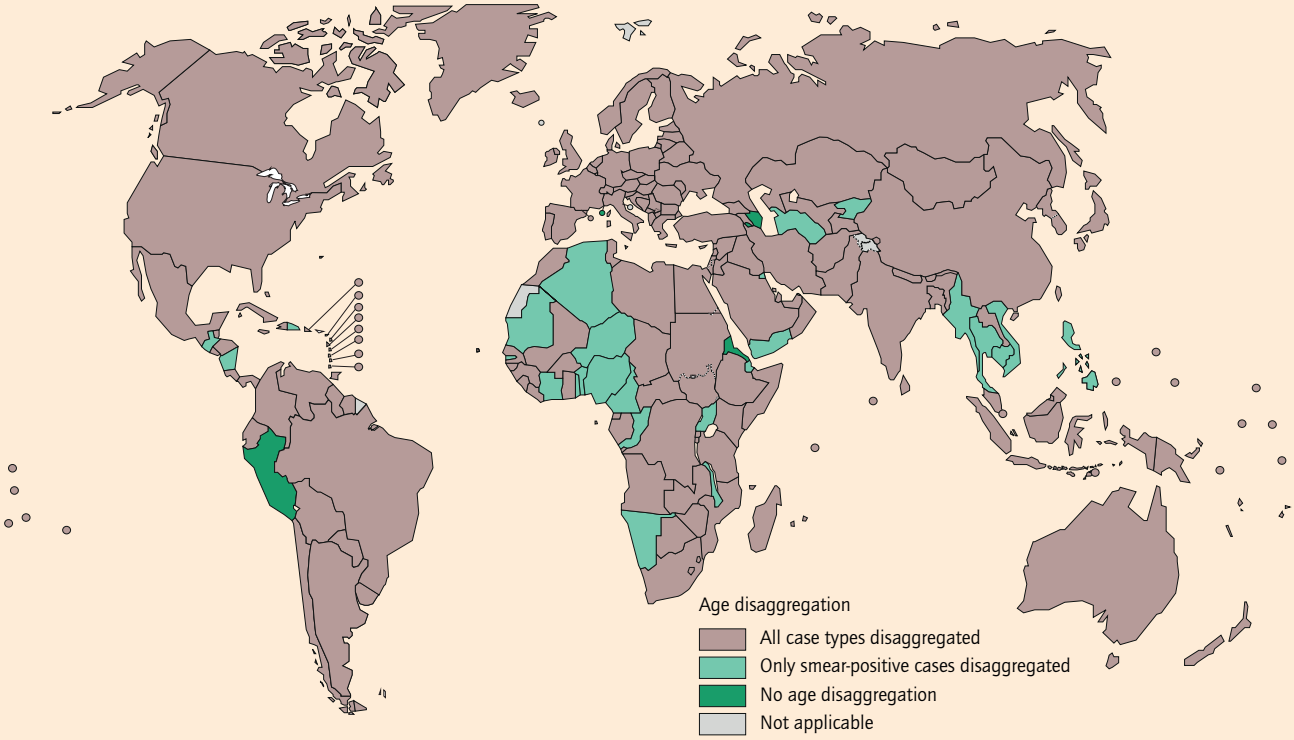
There has been impressive progress in the implementation of nationwide prevalence surveys to measure bacteriologically-confirmed TB since 2008 (see **Section 2.5.2**). These surveys are focusing on adults (aged ≥15 years) and the typical sample size is 50 000–

TABLE B2.2.1 **Reporting of TB case notifications disaggregated by age, 2011**

	SMEAR-POSITIVE	SMEAR-NEGATIVE[a]	EXTRAPULMONARY
Total notifications	2 621 049	1 872 745	813 636
Countries disaggregating by age	2 601 032	1 582 235	684 233
Countries not disaggregating by age	20 017	290 510	129 403
(% total notifications disaggregated)	(99%)	(84%)	(84%)
Number of countries that reported notifications disaggregated by age (number of HBCs)[b]	197 (22)	171 (15)	171 (15)
Total estimated childhood notifications			**327 000**

[a] This includes reported cases for whom smear results were unknown or smears were not done.
[b] An additional 9 countries reported zero TB cases in 2011 and two countries had not reported data to WHO by July 2012.

FIGURE B2.2.1
Reporting of notification data disaggregated by age, 2011



70 000 people. The screening strategy includes chest X-rays and a symptom-based questionnaire for the entire survey population, followed by collection of sputum samples from all those with TB signs and symptoms for subsequent smear and culture examination.

After careful weighing of the advantages and disadvantages by WHO's Global Task Force on TB Impact Measurement (see **Section 2.5**), the inclusion of children in national prevalence surveys has not been recommended. Major reasons are:

- Inclusion of children in a survey would not lead to a precise estimate of TB prevalence among children, since only a few bacteriologically-confirmed cases would be found. Even existing surveys of adults are not able to provide precise estimates for different age groups.
- There are ethical considerations associated with the mass screening of all children, most of whom are healthy. While evidence exists that chest X-ray screening is safe for adults, similar evidence does not exist for children. Furthermore, there is no simple and reliable tool that could be used to restrict the number of children screened by X-ray: for example, there is no reliable test for tuberculous infection.
- Among adults, use of broad criteria for considering an X-ray "abnormal" is encouraged to minimize the number of cases that are missed during screening. Among children, use of tests for tuberculous infection and broad criteria for considering an X-ray "abnormal" would lead to unnecessary efforts to obtain specimens, which among young children requires invasive and uncomfortable gastric aspiration.
- Referral hospitals are needed for the follow-up and diagnostic confirmation of TB in children. These are often not available in the rural areas that account for a large share of the clusters included in national prevalence surveys.
- Inclusion of children would approximately double the sample size and associated costs. The additional logistical complications of including children could also jeopardise the survey as a whole.

Next steps to improve existing estimates of TB cases and deaths among children

Next steps to improve the measurement and estimation of TB incidence among children include:

- Systematic literature reviews of existing data on incident childhood TB, under-reporting of TB in children and misdiagnosis;
- A global consultation to further develop analytical methods and to define and prioritize actions needed to obtain new data;
- Promotion of case-based electronic recording and reporting systems that would facilitate compilation and analysis of age-disaggregated data (among other advantages – see **Section 2.5.1**); and
- Nationwide inventory surveys to measure under-reporting of childhood TB.

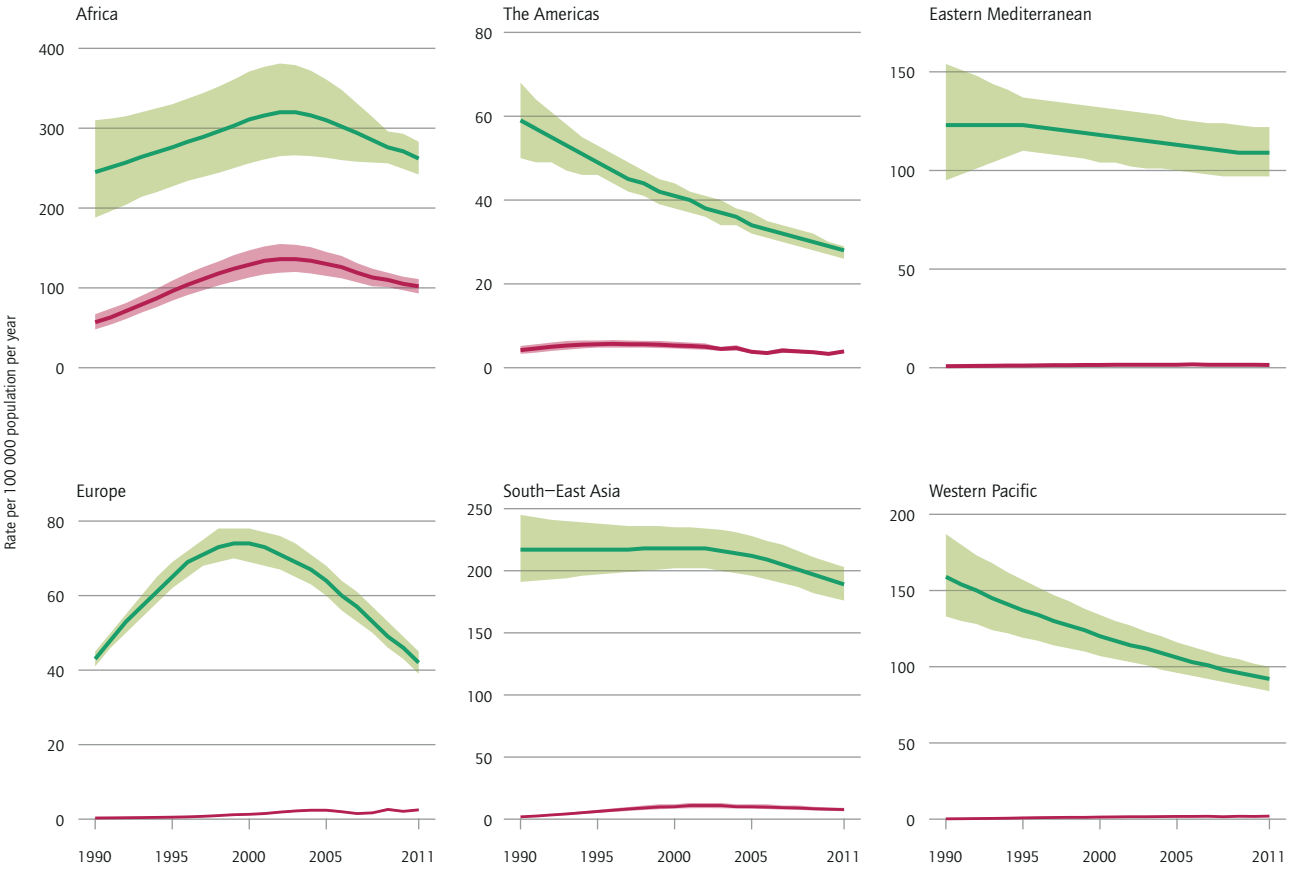
More contact-tracing and the integration of TB activities in maternal, newborn and child health services would also help to find children with TB that might otherwise not be diagnosed.

To improve estimates of TB mortality among children, the main actions required are:

- Collection of age-specific data from sample VR systems and mortality surveys in high-burden countries including China, India and Indonesia;
- Advocacy for further development of and continued investment in VR systems.

[1] This estimate is for TB deaths among HIV-negative children. TB deaths among HIV-positive children are classified as HIV deaths in ICD-10.

FIGURE 2.7 **Estimated TB incidence rates by WHO region, 1990–2011.** Regional trends in estimated TB incidence rates (green) and estimated incidence rates of HIV-positive TB (red). Shaded areas represent uncertainty bands.



able for countries with a high burden of TB (see Section 2.5.2), TB prevalence can be estimated only indirectly in most countries.

There were an estimated 12 million prevalent cases (range, 10 million–13 million) of TB in 2011 (Table 2.1), equivalent to 170 cases per 100 000 population (Table 2.2). The prevalence rate has fallen by 36% globally since 1990.

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 worldwide (Figure 2.3). Regionally, prevalence rates are declining in all of WHO's six regions (Figure 2.10). The Region of the Americas halved the 1990 level of TB prevalence by around 2005, well in advance of the target year of 2015, and the Western Pacific Region is close to doing so. Achieving the 50% reduction target by 2015 appears feasible in the European and South-East Asia regions, but not in the African and Eastern Mediterranean regions.

2.3 Mortality

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, or from ecological modelling based on mortality data from countries with VR systems.

Until 2008, WHO estimates of TB mortality used VR data for only three countries. This was substantially 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 enabled a further major improvement to estimates of TB mortal-

FIGURE 2.8 **Estimated TB incidence rates, 22 high-burden countries, 1990–2011.** 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.

ity, with direct measurements available for 91 countries in 2010. The estimates of TB mortality presented in this report are based on even more VR data. Use of VR data for 119 countries and survey data from India mean that direct measurements of TB mortality were used for 120 countries (shown in Figure 2.11) that collectively account for 46% of the estimated number of TB deaths globally. VR data are most limited in the African Region and parts of the South-East Asia Region. A current example of a country that is building a sample VR system is Indonesia (Box 2.3).

The best estimate of the number of TB deaths worldwide fell just below 1 million among HIV-negative people in 2011 (TB deaths among HIV-positive people are classified as AIDS deaths in ICD-10).[1] The best estimate for 2011 is 990 000 deaths (Table 2.1), with an uncertainty interval of 0.84 million–1.1 million. This was equivalent to 14 deaths per 100 000 population. There were also an additional 0.43 million HIV-associated deaths (range, 0.40 million–0.46 million) i.e. deaths from TB among people who were HIV-positive (data not shown). Thus a total of approximately 1.4 million people (range, 1.3 million–1.6 million) died of TB in 2011, of whom 0.5 million were women (Box 2.4).

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 in 2011.

Globally, mortality rates (excluding deaths among HIV-positive people)[2] have fallen by 41% since 1990; 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 2.3). Mortality rates are also declining in all of WHO's six regions (Figure 2.12). The 2015 target has already been surpassed in the Region of the Americas and the Western Pacific

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

[2] 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.

FIGURE 2.9 **Countries in which surveys of the prevalence of TB disease have been implemented since 1990 or are planned in the near future**

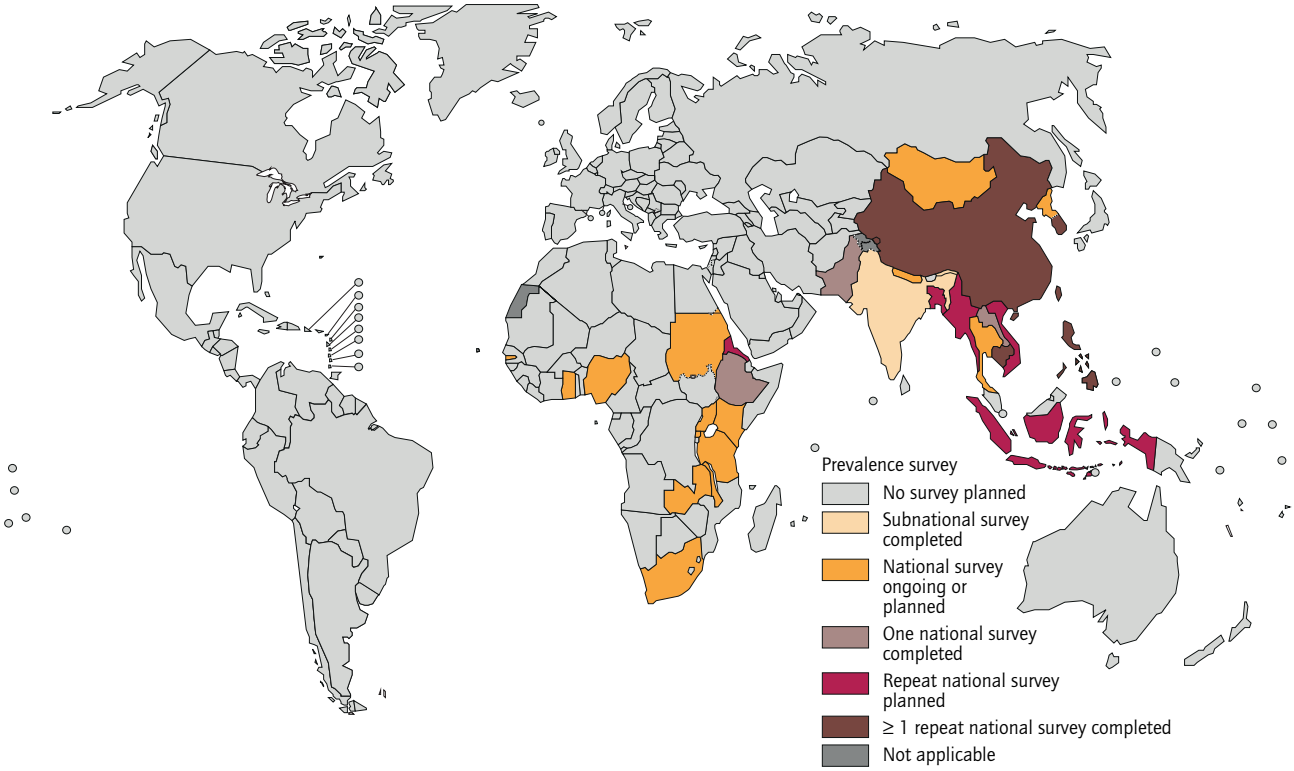


FIGURE 2.10 **Trends in estimated TB prevalence rates 1990–2011 and forecast TB prevalence rates 2012–2015, by WHO region.** Shaded areas represent uncertainty bands. The horizontal dashed lines represent the Stop TB Partnership target of a 50% reduction in the prevalence rate by 2015 compared with 1990. The other dashed lines show projections up to 2015.

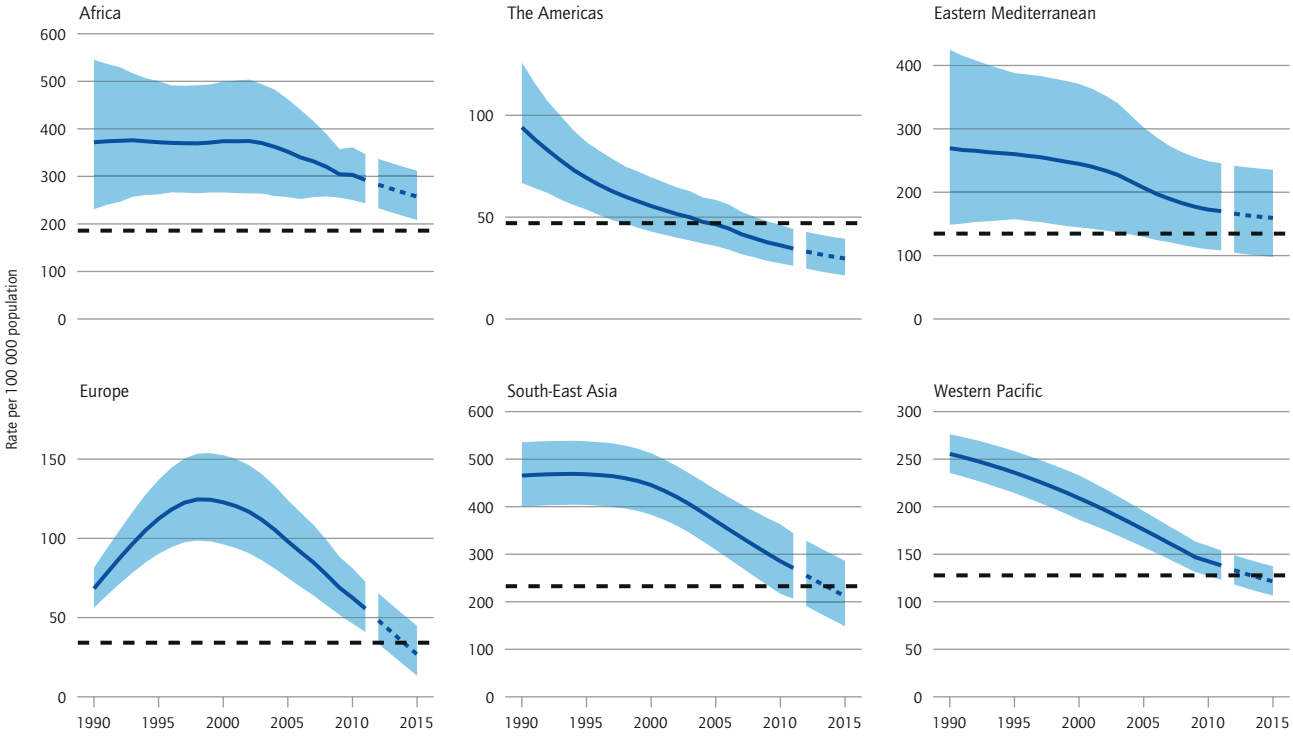
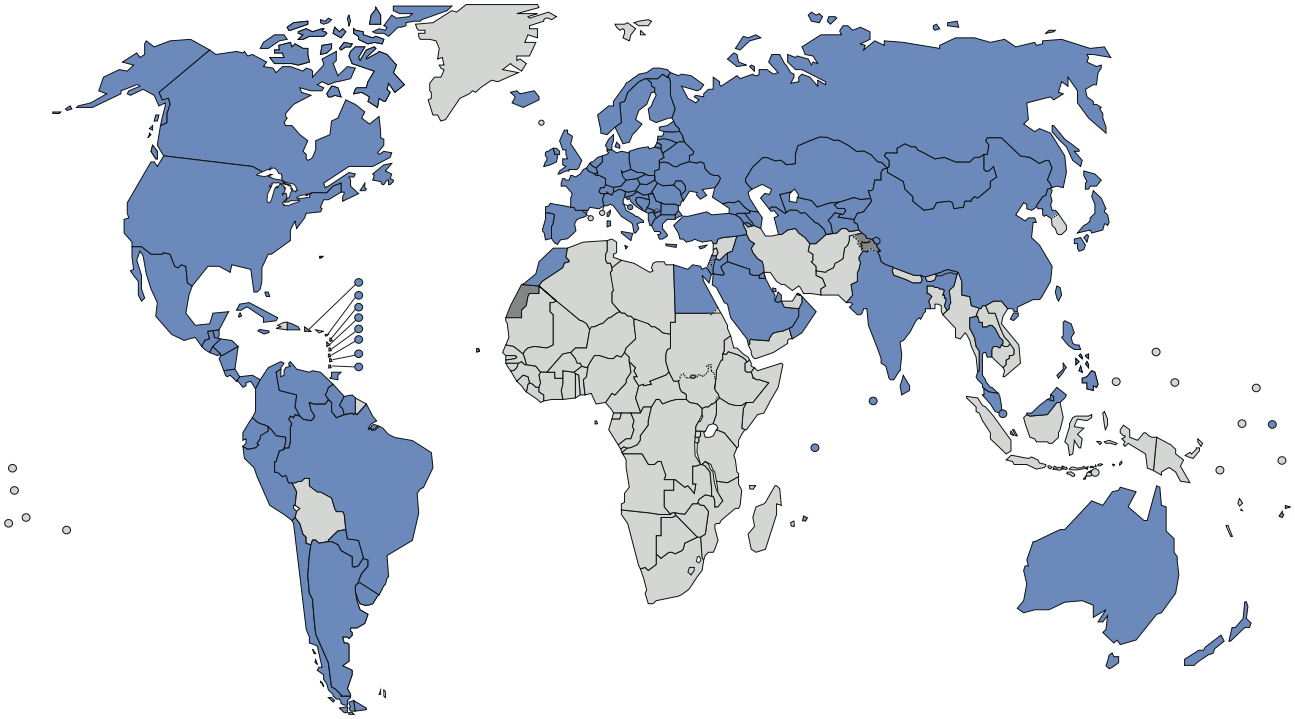


FIGURE 2.11 **Countries (in blue) for which TB mortality is estimated directly using measurements from vital registration systems and/or mortality surveys**



Region, and may have been reached in the Eastern Mediterranean Region. Among the other three regions, the South-East Asia Region appears best placed to achieve the target.

In 2012, considerably more VR data (dating back to 1990) became available to estimate TB mortality in European countries with a high burden of TB. The use of these data means that the regional trend for the European Region has been updated; it indicates a sharp rise until about 1998, followed by a sharp fall back to 1990 levels by 2011. This pattern is consistent across most individual countries (Figure 2.13), and corresponds to the economic, social and political disruption following the breakup of the former Soviet Union, and subsequent rebuilding and economic development. The striking relationship between TB mortality rates and national income per capita in Latvia is shown in Figure 2.14.

Among the 22 HBCs, mortality rates appear to be falling in most countries (Figure 2.15).

2.4 Multidrug-resistant tuberculosis

This report, as in 2011, focuses on estimates of the number of prevalent cases of MDR-TB. The reasons are that MDR-TB is a chronic disease and without appropriate diagnosis and treatment for most of these cases many more prevalent cases than incident cases are expected; calculations of the number of prevalent cases of MDR-TB are more readily understood compared with the complex

BOX 2.3

Building a sample vital registration system in Indonesia

With support from AusAID and technical assistance from University of Queensland, the Indonesian National Institute of Health Research and Development (NIHRD) piloted a sample vital registration system in selected sites (Central Java, Lampung, West Kalimantan, Gorontalo and Papua) covering 2.5 million population from 2006 to 2008. The pilot was named the Indonesian Mortality Registration System Strengthening Project (IMRSSP). The IMRSSP tested the verbal autopsy questionnaires, field implementation, and procedures and standards for calibration of causes of deaths. Results from the IMRSSP demonstrated that the measurement of cause-specific mortality is feasible by strengthening the death registration system in Indonesia. The cost was approximately US$ 0.5–1 per capita per year (in the areas covered by the system). After the pilot, the local Indonesian authorities continued to implement vital registration in the same sites with their own funding; data quality has yet to be assessed.

With support from a Global Fund round 10 grant on health system strengthening, a sample vital registration system is now being introduced. The NIHRD randomly selected 128 sub-districts across the country, covering a population of about 5 million (2% of the country's total). The 128 sub-districts do not include any of the IMRSSP pilot sites. By June 2013, all selected sub-districts will start to collect data on mortality, with preliminary results expected by December 2013. An analysis of the cost of implementing a sample vital registration system with resources that ensure data quality is planned.

BOX 2.4

TB mortality among women

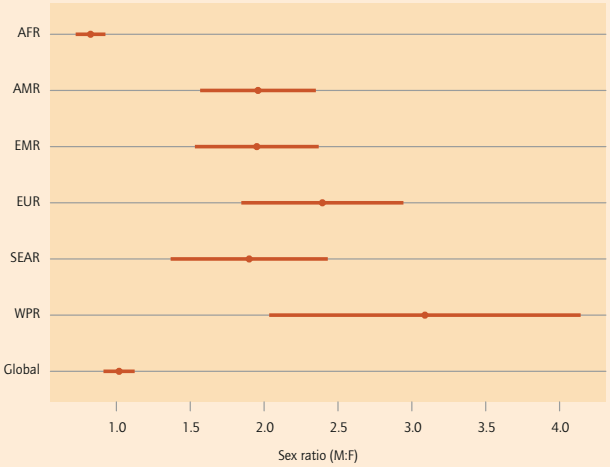
This is the first WHO report on global TB care and control to include estimates of the number of TB deaths among women[1] that include HIV-associated TB deaths (classified as HIV deaths in ICD-10) as well as TB deaths among HIV-negative people. In total, there were an estimated 0.5 million TB deaths among women. This includes 300 000 (range, 250 000–350 000) TB deaths among HIV-negative women (30% of all TB deaths among HIV-negative people) and 200 000 (range, 185 000–215 000) HIV-associated TB deaths (Table 2.4.1). TB is one of the top killers of women worldwide.

Although globally the numbers of HIV-associated TB deaths were similar among men and women, there were regional variations (Figure B2.4.1). In the African Region, more deaths occurred among women than men, while in other regions more deaths were estimated to occur among men. The male:female ratio of HIV-associated TB deaths ranged from 0.83 in the African Region to 3.1 in the Western Pacific Region.

TABLE B2.4.1
Number of HIV-associated TB deaths among women in 2011, by WHO region

	ESTIMATED NUMBER OF DEATHS	
WHO REGION	BEST ESTIMATE	UNCERTAINTY INTERVAL
AFR	169 000	155 000–184 000
AMR	3 130	2 710–3 580
EMR	1 290	1 100–1 500
EUR	2 960	2 490–3 460
SEAR	19 800	16 000–24 000
WPR	3 680	2 810–4 660
Global	200 000	185 000–215 000

FIGURE B2.4.1
The male:female ratio for HIV-associated TB deaths among adults (aged ≥15 years), globally and for WHO regions



[1] Defined as females aged ≥15 years.

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 number of prevalent cases of MDR-TB can be estimated as the product of the estimated number of prevalent cases of TB and the best estimate of the proportion of notified TB patients[1] with MDR-TB (and in China a direct measurement is available from the 2010 national TB prevalence survey). Globally in 2011, there were an estimated 630 000 cases of MDR-TB (range, 460 000–790 000) among the world's 12 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[2] or data from periodic surveys of drug resistance that are designed, implemented and analysed according to WHO guidelines.[3] There has been substantial progress in the coverage of continuous surveillance and surveys of drug resistance (Figure 2.16). Unfortunately, progress is not yet sufficient to provide a definitive assessment of trends in MDR-TB globally or regionally.[4]

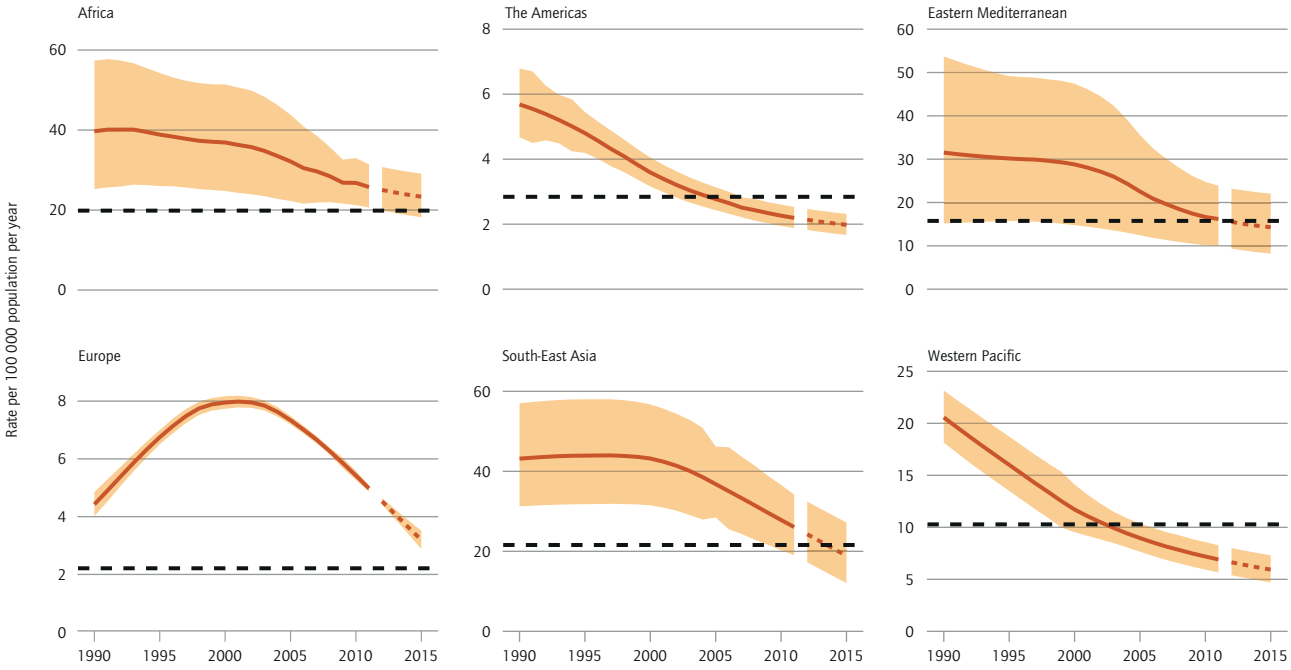
[1] This includes new and retreatment cases (see Chapter 3 for definitions).

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

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

[4] For further details, see Box 2.6 in the 2011 WHO report on global TB control.

FIGURE 2.12 **Trends in estimated TB mortality rates 1990–2011 and forecast TB mortality rates 2012–2015, 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 an uncertainty band narrows as the proportion of regional mortality estimated using vital registration data increases or the quality and completeness of the vital registration data improves.

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 revised, and since April 2009 consultations have been held with 96 countries accounting for 89% of the world's TB cases. Nonetheless, there is considerable scope for further improvement. This final section of the chapter describes 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.

Established in mid-2006, the mandate of the WHO Global Task Force on TB Impact Measurement is to ensure the best possible assessment of whether the 2015 global targets for reductions in the burden of disease caused by TB are achieved, to report on progress in the years leading up to 2015 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]

At its second meeting in December 2007, the Task Force defined three strategic areas of work:[2]

- 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 revision of the methods used to translate surveillance and survey data into estimates of TB incidence, prevalence and mortality.

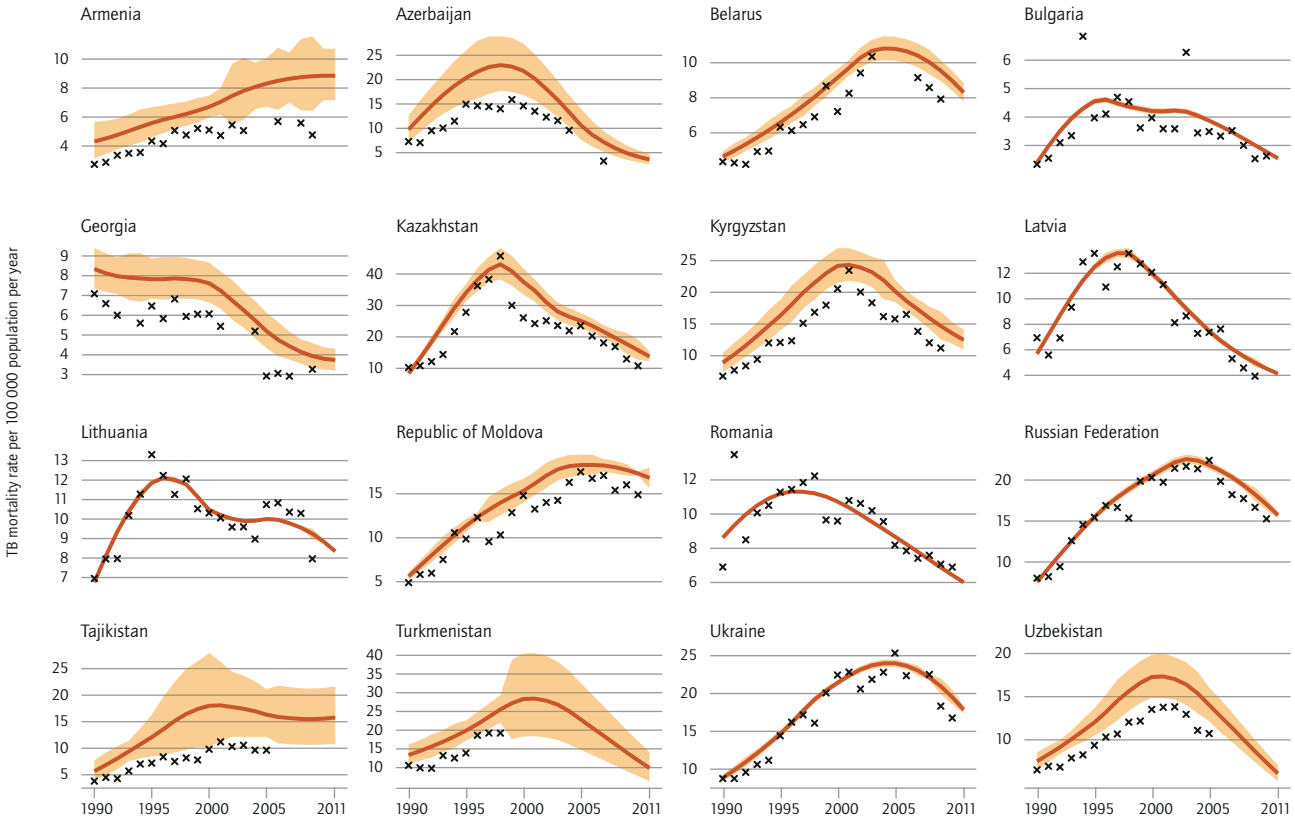
The third area of work is discussed in more detail in Annex 1. The following sections focus on the first two strategic areas of work. Full details of the Task Force's work are available on its web site.[3]

[1] Partners that are actively participating in the work of the Task Force include the Centers for Disease Control and Prevention in the USA, 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.

[2] *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).

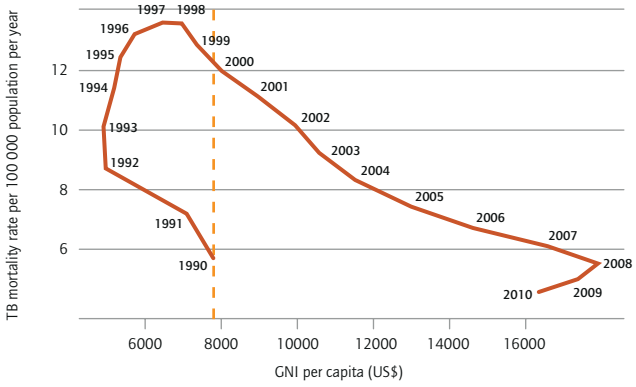
[3] www.who.int/tb/advisory_bodies/impact_measurement_taskforce

FIGURE 2.13 **Trends in TB mortality rates in Eastern European countries, 1990–2011.** The solid orange line shows the best estimate of the TB mortality rate and the orange band represents the uncertainty related to this estimate.[a] Uncertainty is due to adjustments made to the mortality data from vital registration systems that were reported by countries (the reported data are represented by the "x" symbol). Reported data were adjusted to account for incomplete coverage (deaths with no reported cause) and ill-defined causes, and the uncertainty range does not account for miscoding of causes of deaths (such as HIV deaths miscoded as TB deaths); further explanation of methods is provided in **Annex 1**.



[a] The width of an uncertainty band narrows as the quality and completeness of the vital registration data improves.

FIGURE 2.14 **Changes in TB mortality and gross national income (GNI) per capita in Latvia, 1990–2011.** The vertical dashed line shows the GNI per capita in 1990, prior to the economic crisis. The economy shrank during the early 1990s and the level of 1990 was only recovered in 1999.



2.5.1 Strengthening surveillance

In 2008, the Task Force defined a conceptual framework to assess 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 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 the framework were also developed, and used in the 96 country consultations illustrated in **Figure 2.1**. Major challenges in current estimates of TB incidence include reliance on expert opinion about the number of cases that are diagnosed but not reported to national surveillance systems and the number of cases that are not diagnosed at all. Major challenges in estimating TB mortality include the lack of VR systems of sufficient coverage and quality in many countries, notably in Africa and parts of Asia (**Figure 2.11**).

Since 2011, the Task Force's three priorities have been:

- developing and applying standards and benchmarks for TB surveillance;
- preparing a guide on inventory studies to measure TB under-reporting;

- producing and widely disseminating a guide on electronic recording and reporting (ERR) for TB care and control.

These are discussed in more detail below.

Standards and benchmarks for TB surveillance

The long-term goal is direct measurement of the burden of disease caused by TB from routine surveillance data, using notification data to measure TB incidence and VR data to measure TB mortality. Achieving this goal requires strengthened surveillance in most countries.

While the need to "strengthen surveillance" is difficult to dispute in many countries, putting it into practice requires a clear understanding of what a "model" surveillance system should look like and a method for assessing the current performance of TB surveillance. An assessment of the performance of TB surveillance could then be used to identify which countries have surveillance systems that already provide an accurate measure of the number of TB cases and deaths that occur each year, and to define the actions necessary to strengthen surveillance in countries in which gaps are identified. Countries in the former category could be "certified" or "accredited" as having TB surveillance data that provide a direct measure of TB incidence and/or mortality.

In 2011, the Task Force's subgroup on TB surveillance began work on a TB surveillance checklist of standards and benchmarks, the purpose of which is to:

- assess a national surveillance system's ability to accurately measure TB cases and deaths; and
- identify gaps in national surveillance systems that need to be addressed.

The *standards* are general statements about the characteristics that define a high-performance TB surveillance system. For each standard, *benchmarks* define (in quantitative terms wherever possible) the level of performance that is considered good enough to meet the standard.

A prototype checklist was developed in the first half of 2011. Progress in piloting and refinement of the checklist accelerated after June 2011 mainly due to intensified collaboration between WHO and the Centers for Disease Control and Prevention in the United States of America (USA). By mid-2012, three rounds of testing had been completed with the checklist applied in Brazil, China, Egypt, Estonia, Japan, Kenya, the Netherlands, Thailand, Uganda, the United Kingdom (UK) and the USA; two global meetings to discuss findings and refine the checklist had been held; and a close-to-final version of the checklist was available. The pre-final version contains 9 standards related to measurement of TB cases and one standard related to measurement of TB deaths. For standards related to measurement of TB cases, one is specific to paper-based systems with aggregated data and one is specific to electronic case-based systems. For a coun-

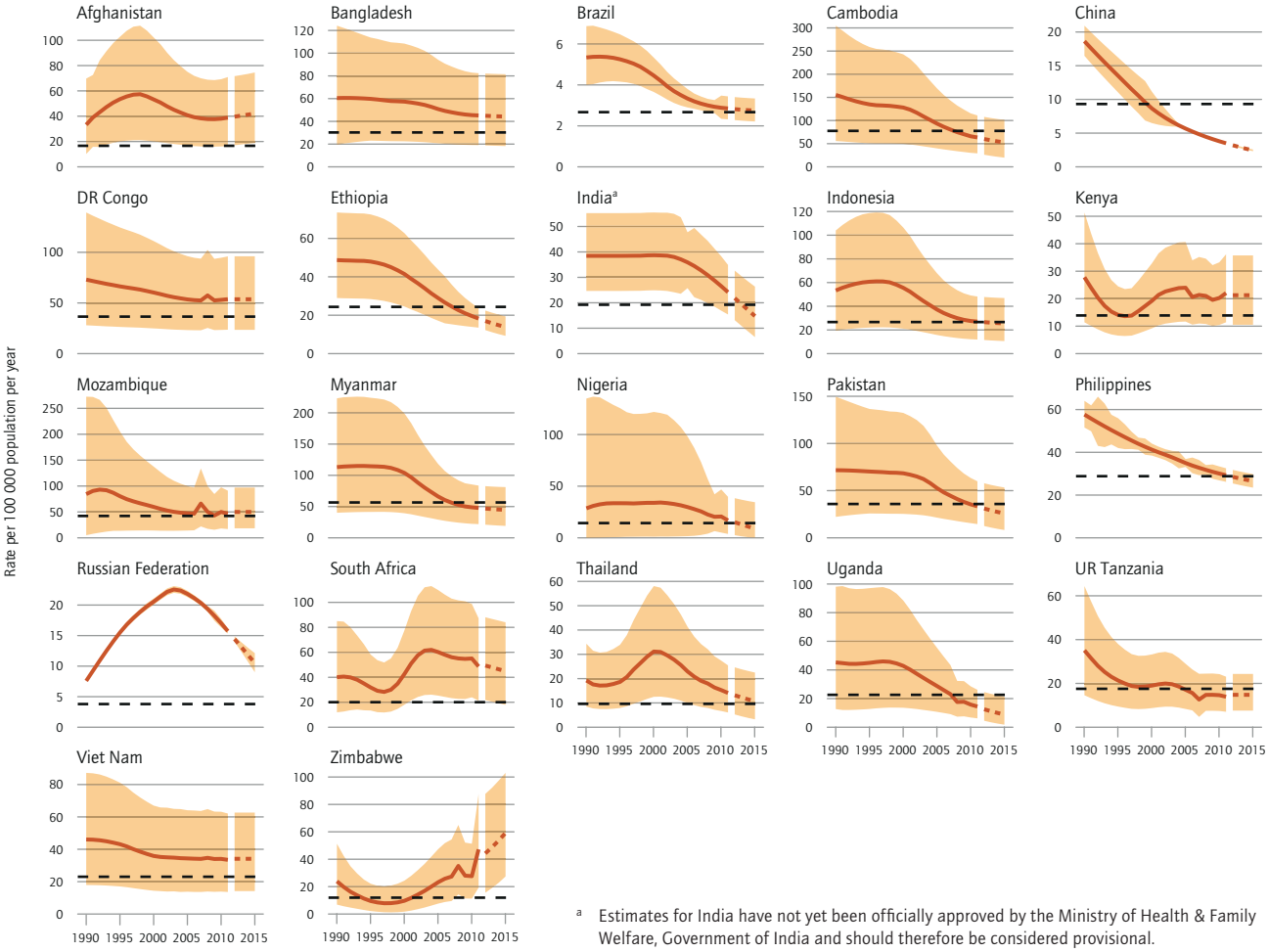
TABLE 2.3 Estimated proportion of TB cases that have MDR-TB, 27 high MDR-TB burden countries and WHO regions

	ESTIMATED % OF NEW TB CASES WITH MDR-TB[a]	CONFIDENCE INTERVAL	ESTIMATED % OF PREVIOUSLY TREATED TB CASES WITH MDR-TB[a]	CONFIDENCE INTERVAL
Armenia	9.4	7.1–12	43	38–49
Azerbaijan	22	19–26	55	52–60
Bangladesh	1.4	0.7–2.5	29	24–34
Belarus	32	30–35	76	72–79
Bulgaria	2.0	1.1–3.2	26	19–33
China	5.7	4.6–7.1	26	22–30
DR Congo	*3.1*	*0.1–7.1*	*10*	*2.1–18*
Estonia	23	17–29	58	43–71
Ethiopia	1.6	0.9–2.7	12	5.6–21
Georgia	11	9.6–12	32	28–35
India	2.1	1.5–2.7	15	13–17
Indonesia	1.9	1.4–2.5	12	8.1–17
Kazakhstan	30	29–32	51	50–53
Kyrgyzstan	26	23–31	52	45–58
Latvia	13	10–16	29	20–40
Lithuania	11	9.2–13	49	44–54
Myanmar	4.2	3.1–5.6	10	6.9–14
Nigeria[b]	*3.1*	*0.1–7.1*	*10*	*2.1–18*
Pakistan	*3.4*	*0.1–11*	*29*	*2.6–56*
Philippines	4.0	2.9–5.5	21	14–29
Republic of Moldova	19	17–22	64	60–67
Russian Federation	20	18–22	46	41–52
South Africa	1.8	1.4–2.3	6.7	5.5–8.1
Tajikistan	13	9.8–16	54	48–59
Ukraine	16	14–18	44	40–49
Uzbekistan	23	18–30	62	53–71
Viet Nam	2.7	2–3.6	19	14–25
High MDR-TB burden countries	**4.3**	**2.1–6.4**	**21**	**12–30**
AFR	2.9	0.1–6.2	11	3.4–18
AMR	2.0	0.8–3.3	11	4.5–18
EMR	3.4	0.1–10	30	6.9–53
EUR	15.1	10–20	44	40–49
SEAR	2.1	1.8–2.5	16	12–19
WPR	4.8	3.4–6.1	22	18–26
Global	**3.7**	**2.1–5.2**	**20**	**13–26**

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

[b] Direct measurements will be available shortly and are expected to be consistent with the estimates provided in the table.

FIGURE 2.15 **Trends in estimated TB mortality rates 1990–2011 and forecast TB mortality rates 2012–2015, 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.

try's TB surveillance system to be certified as providing a direct measurement of TB cases, all of the standards need to be met. For a country's surveillance system to provide a direct measure of TB deaths, both of the two benchmarks (which are related to geographical coverage and data quality) must be met.

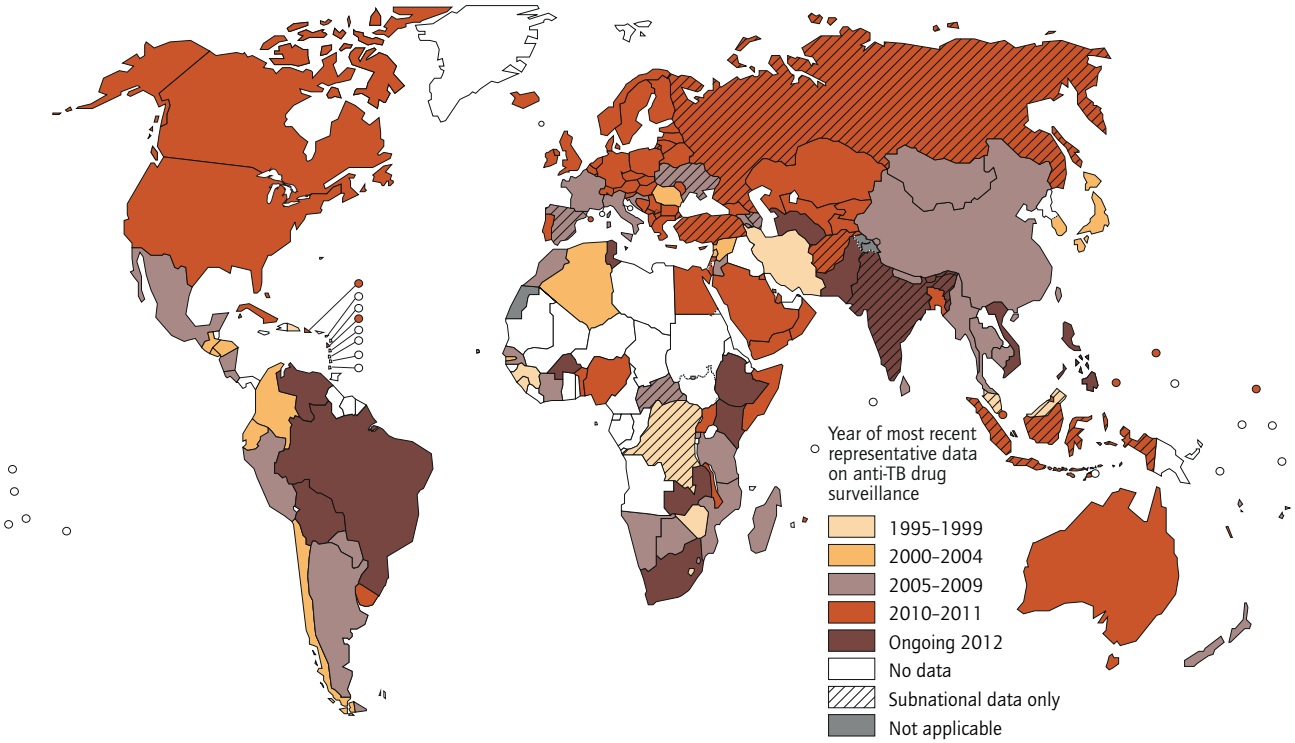
The checklist also includes a supplementary list of three standards and associated benchmarks that can be used to assess whether TB surveillance data provide a direct measure of the number of cases of MDR-TB, the number of HIV-positive cases of TB and TB in children specifically.

The TB surveillance checklist was discussed at meetings of the Technical Evaluation Reference Group (TERG) of the Global Fund and the WHO Global Task Force on TB Impact Measurement held in May 2012. There was consensus that use of the checklist should be integrated within the grant processes of the Global Fund, with results from the systematic assessments of existing TB surveillance using the checklist then used to develop an "investment plan" to strengthen surveillance. With more than 100 low-income and middle-income countries receiving grants for TB care and control from the Global Fund, this approach has great potential to make a real difference to TB surveillance worldwide. As of July 2012, the aim was to apply the checklist in three countries before the end of 2012, and in approximately 15 countries by mid-2014.

Inventory studies to measure TB under-reporting

Inventory studies with record-linkage are used to quantify the number of TB cases that are diagnosed but not recorded in surveillance (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). One of the standards in the TB surveillance checklist is that underreporting of diagnosed TB cases is minimal, with a benchmark that in a national investigation less than 10% of diagnosed cases are missed by TB surveillance. Inventory studies are needed to provide evidence of the level of under-reporting; if reporting is below acceptable levels,

FIGURE 2.16 **Progress in global coverage of data on drug resistance, 1994–2011**



corrective actions need to be identified and implemented.

Inventory studies have been implemented in very few countries to date. Examples include the UK, the Netherlands and several countries in the Eastern Mediterranean Region (Egypt, Iraq, Yemen and, most recently, Pakistan). To facilitate and encourage inventory studies in more countries, WHO and its partners (notably the Centers for Disease Control and Prevention in the USA and the UK's Health Protection Agency) initiated the development of a guide on how to design, implement, analyse and report on inventory studies in 2011. As this report went to press, the guide was due to be published before the end of 2012.

Electronic recording and reporting of data

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**) and several of the standards in the TB surveillance checklist are about data quality. In all of the regional and country workshops held between 2009 and 2012, it was evident that it is much easier to assess the quality of TB surveillance data in countries with case-based electronic recording and reporting. In 2011, WHO and its partners produced a guide on electronic recording and reporting for TB care and control, which was widely disseminated in April 2012 (**Box 2.5**).

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.

Before 2007, few countries had implemented prevalence surveys (**Figure 2.9**, **Figure 2.17**). In the 1990s, national surveys were confined 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. From 2002 to 2008, there was typically one survey per year. 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.

Following five years of substantial efforts by countries, supported by the Task Force (**Box 2.6**), enormous progress has been achieved (**Figure 2.17**). If surveys are implemented according to schedule, around 20 surveys will be implemented during 2011–2013, with a major peak in activity in 2012 and 2013. The number of surveys being implemented at the same time in 2012, at five,

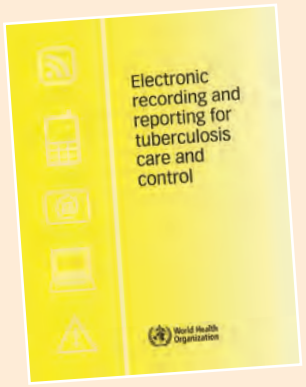
BOX 2.5

New guidance on electronic recording and reporting for TB care and control

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).

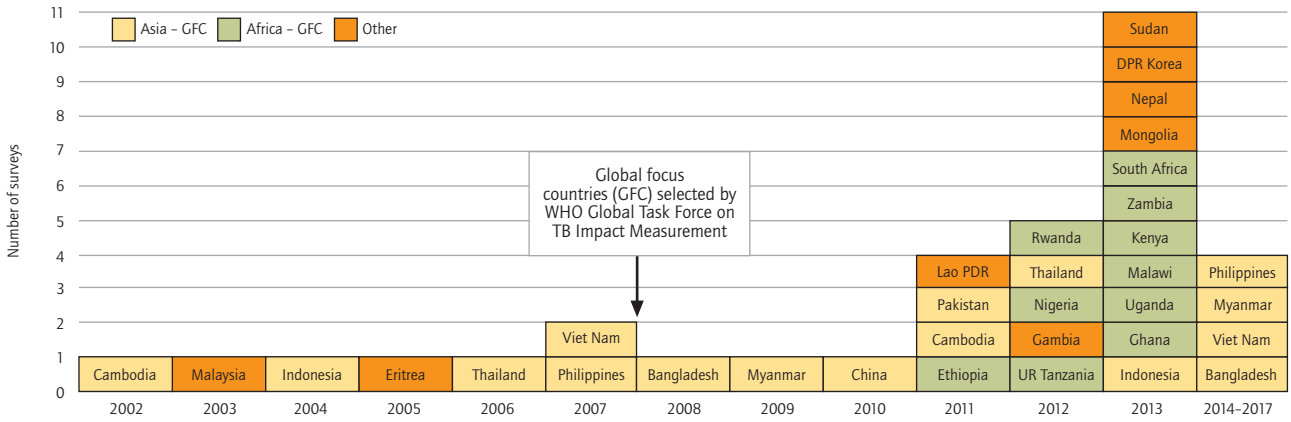
Advantages of ERR include:

- 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 coordinated the development of a guide on how to design and implement ERR according to best-practice standards in 2011. The guide was widely disseminated in April 2012 and is available at www.who.int/tb/publications/electronic_recording_reporting

FIGURE 2.17 **Global progress in implementing national surveys of the prevalence of TB disease, actual (2002–2012) and expected (2013–2017)**



BOX 2.6

Efforts by the Task Force to support TB prevalence surveys and build "AA" collaboration

The WHO Global Task Force on TB Impact Measurement has strongly recommended national TB prevalence surveys in 22 global focus countries: 13 in Africa and 9 in Asia. The African countries are Ethiopia, Ghana, Kenya, Malawi, Mali, Mozambique, Nigeria, Rwanda, Sierra Leone, South Africa, Uganda, the United Republic of Tanzania and Zambia. The Asian countries are Bangladesh, Cambodia, China, Indonesia, Myanmar, Pakistan, the Philippines, Thailand and Viet Nam.

Since 2008, the Task Force has made substantial efforts to support countries to design, implement, analyse and report on surveys. The Task Force subgroup on TB prevalence surveys, led by WHO, has been very active and activities have included:

- 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 and expert reviews of protocols by at least two Task Force partners not directly involved in the survey;
- production of a second edition of a WHO 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;
- training courses for survey coordinators without prior experience of survey implementation, including opportunities to observe field operations in ongoing surveys;
- 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, mostly funded by the US government through the TB-TEAM mechanism (see **Box 5.2** in **Chapter 5**).

The concept of Asia–Asia, Asia–Africa and Africa–Africa ("AA") collaboration has been strongly promoted. This involves building collaboration among countries implementing surveys such that survey coordinators and other staff can learn from and help each other, with the result that capacity to implement prevalence surveys is built at country, regional and global levels. Examples of AA collaboration are survey coordinators from Asian countries providing guidance and support to those leading surveys in African countries where no recent experience exists; survey staff from Ethiopia providing support to African countries planning surveys in 2012 and 2013; exchange visits and study tours; workshops to observe central and field operations hosted by Cambodia and Thailand; and mid-term reviews in which survey coordinators visit other countries where survey operations are underway.

Besides WHO, technical partners that are actively engaged in prevalence surveys include the Centers for Disease Control and Prevention, USA; the KNCV Tuberculosis Foundation in the Netherlands; the London School of Hygiene and Tropical Medicine, UK; and the Research Institute for Tuberculosis, Japan.

[1] *TB prevalence surveys: a handbook*. Geneva, World Health Organization, 2011 (WHO/HTM/TB/2010.17).
www.who.int/tb/advisory_bodies/impact_measurement_taskforce/resources_documents/thelimebook

is already unprecedented. As this report went to press, surveys were nearing completion in the Gambia, Nigeria, Rwanda, Thailand and the United Republic of Tanzania, with results expected in the first half of 2013.

In late 2011 and early 2012, results from surveys completed in Ethiopia (June 2011) and Cambodia (September 2011) were disseminated. The Ethiopian survey found a lower prevalence of TB than was previously estimated, with most cases in young adults. As this report went to press, dissemination of results from surveys in the Lao People's Democratic Republic and Pakistan was expected by early 2013.

Cambodia is only the third high-burden country to implement a repeat national prevalence survey in the past 20 years (following China and the Philippines). The results provide an excellent example of the value of national TB prevalence surveys for measuring disease burden, evaluating the impact of TB control and identifying ways to improve TB care and control in future (**Box 2.7**).

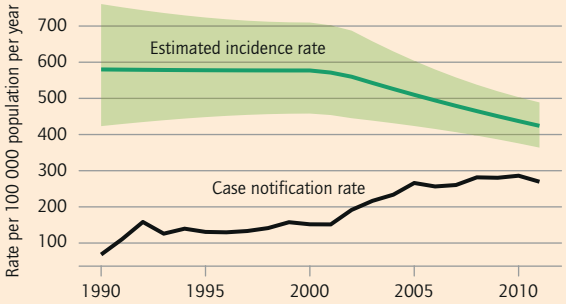
BOX 2.7

Reducing the burden of TB disease: a success story from Cambodia

For the last two decades, Cambodia has been known to have one of the highest levels of TB burden (in terms of rates per 100 000 population) in the world. TB control in Cambodia was reinstated in 1994 following decades of civil conflict and economic hardship. TB services were first limited to provincial and district hospitals. Decentralization of TB control services to the health centre level was initiated in the early 2000s, with nationwide expansion achieved in 2005, contributing to rapidly increasing case notifications (depicted with a solid black line in **Figure B2.7.1**).

At the early stage of DOTS expansion to health centres, the National TB Programme decided to directly measure the burden of TB through a nationwide prevalence survey, completed in 2002. A total of 22 160 people aged ≥15 years participated in the survey, grouped in 42 geographically determined clusters. The survey identified 81 smear-positive TB cases (63% were symptomatic) and 190 smear-negative culture-positive cases. After adjustment for unconfirmed TB and for childhood TB, the prevalence rate for all forms of TB was estimated at 1511 (range 1244–1803) per 100 000 population, one of the highest prevalence rates observed in the world in recent history.

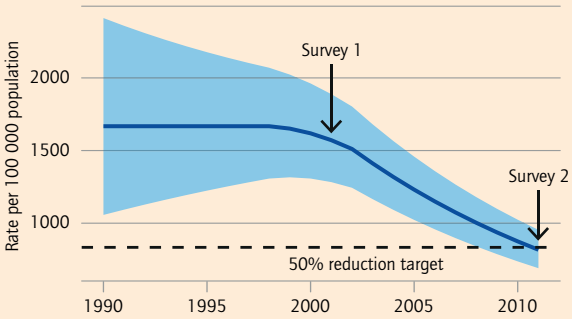
FIGURE B2.7.1
Case notification and estimated incidence rates in Cambodia, 1990–2011



A second nationally representative survey was conducted in 2011. In total, 39 680 people aged ≥15 years were sampled from 62 clusters. 95 smear-positive TB cases (46% were symptomatic) and 218 smear-negative culture-positive TB cases were identified. After adjustment for unconfirmed TB and for childhood TB, the prevalence rate for all forms of TB was estimated at 817 (range 690–954) per 100 000 population, showing a statistically significant reduction since the first survey.

Most bacteriologically-confirmed prevalent cases did not report symptoms listed in the screening criteria. The proportion of people reporting TB symptoms listed in the screening criteria among bacteriologically-confirmed cases declined from 30% in 2002 to 22% in 2011. This highlights the need to revise criteria for TB screening in self-reporting patients, in favour of more sensitive criteria than the traditional but insensitive criteria of a cough of ≥2weeks. There was a significant decline in prevalence rates for all age groups but the biggest reduction was observed in younger age groups. The 2011 survey also highlighted the need for more sensitive diagnostics than sputum smear microscopy.

FIGURE B2.7.2
Estimated TB prevalence (all forms) in Cambodia, 1990–2011



The repeat survey provides robust evidence of a decline in TB burden in Cambodia, following DOTS expansion in 2002 (**Figure B2.7.2**). Results indicate a 45% reduction in the prevalence of bacteriologically-confirmed cases since the first national prevalence survey conducted in 2002, that is, over a period of only 9 years.

The Cambodia results provide a major success story for TB control.

CHAPTER 3

TB case notifications and treatment outcomes

KEY FACTS AND MESSAGES

- In 2011, 6.2 million cases of TB were notified by national TB control programmes and reported to WHO: 5.8 million were individuals newly diagnosed in 2011 and 0.4 million were previously diagnosed TB patients whose treatment regimen was changed. India and China accounted for 39% of notified cases of TB worldwide in 2011, Africa for 24% and the 22 HBCs for 81%.
- In 2010, the treatment success rate was 85% among all new TB cases and 87% among new cases of sputum smear-positive pulmonary TB (the most infectious cases). Improvement in treatment outcomes is needed in the European Region, where the treatment success rate in 2010 was 74% and 67% for new cases and new smear-positive cases respectively.
- The provision of diagnosis and treatment according to the DOTS/Stop TB Strategy has resulted in major achievements in TB care and control. Between 1995 and 2011, 51 million people were successfully treated for TB in countries that had adopted the DOTS/Stop TB Strategy, saving 20 million lives.
- Notifications of TB cases have stabilized in recent years, and in 2011 represented 66% (range, 64–69%) of estimated incident cases. Major efforts are needed to ensure that all cases are detected, notified to national surveillance systems and treated according to international standards, for example through PPM initiatives.
- In most of the 21 countries that reported data, PPM initiatives contributed about 10-40% of total notifications.
- In countries reporting age-disaggregated data, most cases (88%) were aged 15–64 years. Children (aged <15 years) accounted for 6% of notified cases. The male:female ratio was 1.7 globally, ranging from 1.1 to 2.2 among WHO's six regions.
- Reporting of cases and treatment outcomes disaggregated by age and sex needs to be improved in some parts of the world, including several HBCs.

The total number of TB cases that occur each year can be estimated globally and for regions and individual countries, but with uncertainty (as explained in Chapter 2). This uncertainty reflects the fact that national surveillance systems do not capture all cases in most countries. 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 the outcomes of treatment is one of the core elements of the Stop TB Strategy (Chapter 1). The number of people diagnosed and treated for TB and associated treatment outcomes are routinely reported by NTPs in almost all countries; these data are reported in turn 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 with readily accessible and high-quality health care.

This chapter has four parts. Section 3.1 summarizes the total number of people diagnosed with TB and notified by NTPs in 2011, including disaggregations by case type, age and sex. Section 3.2 highlights the contribution to total case notifications of public–public and public–private mix (PPM) initiatives. Section 3.3 presents trends in notifications between 1990 and 2011 and compares these with trends in estimated TB incidence. Estimates of the ratio of notified:incident cases (an indicator known as the case detection rate) are provided for selected years. Section 3.4 describes the latest data on treatment outcomes (for cases registered for treatment in 2010) as well as treatment outcomes achieved in each year since 1995.

3.1 Case notifications in 2011 by type of disease, age and sex

In 2011, 6.2 million people with TB were notified to NTPs and reported to WHO. Of these, 5.8 million had a new episode of TB (shown as the total of new and relapse cases in Table 3.1). Of these 5.8 million cases, 5.5 million had

TABLE 3.1 **TB case notifications, 2011**

	TOTAL NOTIFIED	NEW					RETREATMENT		NEW AND RELAPSE(A)	HISTORY UNKNOWN	PERCENT NEW PULMONARY CASES SMEAR-POSITIVE
		SMEAR-POSITIVE	SMEAR-NEGATIVE	SMEAR NOT DONE	EXTRA-PULMONARY	CASE TYPE UNKNOWN	RELAPSE	RETREATMENT EXCL. RELAPSE			
Afghanistan	28 167	13 789	4 166	1 989	6 286	623	1 130	184	27 983		69
Bangladesh	159 023	98 948	21 921	0	27 329	0	2 701	4 665	150 899	3 459	82
Brazil	84 137	40 294	12 683	8 278	10 067	15	3 555	6 490	74 892	2 755	66
Cambodia	39 670	15 812	7 686	0	14 690	0	367	1 115	38 555	0	67
China	911 884	377 005	479 486	2 028	6 540	0	34 610	12 215	899 669	0	44
DR Congo	114 290	71 321	13 471		21 579		3 761	4 158	110 132		84
Ethiopia	159 017	49 594	52 967	2 530	49 305	0	2 143	2 478	156 539	0	47
India	1 515 872	642 321	340 203		226 965	1 952	112 508	191 923	1 323 949		65
Indonesia	321 308	197 797	101 750		14 054		5 348	2 359	318 949		66
Kenya	103 981	37 085	30 394	9 416	17 069	0	3 356	6 661	97 320	0	48
Mozambique	47 452	19 537	18 159	0	5 504	0	1 427	2 825	44 627	0	52
Myanmar	143 140	42 324	62 038		27 769		4 606	6 403	136 737		41
Nigeria	93 050	47 436	33 034	0	3 793	0	2 515	6 272	86 778	0	59
Pakistan	270 394	105 733	103 824	0	45 537	0	5 947	5 460	261 041	3 893	50
Philippines	202 033	90 876	95 297		2 202	0	3 190	10 468	191 565	0	49
Russian Federation	159 479	29 191	63 917	1 189	10 023		8 590	46 569	112 910		31
South Africa	389 974	129 770	70 341	77 925	47 285	0	18 394	27 521	343 715	18 738	47
Thailand	67 676	33 169	20 726		10 014	0	1 915	1 852	65 824	0	62
Uganda	49 016	25 614	12 830	1 559	5 001		1 302	2 710	46 306		64
UR Tanzania	61 148	24 115	20 438	0	13 725	0	1 079	1 791	59 357	0	54
Viet Nam	100 176	50 719	20 205		17 934	2 679	6 925	1 714	98 462		72
Zimbabwe	41 305	12 596	15 303	3 869	5 192	0	1 444	2 901	38 404	0	40
High-burden countries	**5 062 192**	**2 155 046**	**1 600 839**	**108 783**	**587 863**	**5 269**	**226 813**	**348 734**	**4 684 613**	**28 845**	**56**
AFR	1 460 766	605 929	357 811	109 258	240 843	1 069	52 283	74 622	1 367 193	18 951	56
AMR	231 880	121 130	36 371	14 254	33 757	1 315	10 004	11 613	216 831	3 436	71
EMR	425 821	170 748	128 182	7 206	93 605	623	11 223	10 102	411 587	4 132	56
EUR	356 670	79 831	121 362	6 896	42 489	3 191	22 838	73 296	275 872	7 502	38
SEAR	2 358 127	1 067 367	598 800	0	333 993	2 878	135 650	215 554	2 138 688	3 885	64
WPR	1 383 249	576 044	630 219	17 435	68 949	2 708	50 841	33 257	1 346 196	3 796	47
Global	**6 216 513**	**2 621 049**	**1 872 745**	**155 049**	**813 636**	**11 784**	**282 839**	**418 444**	**5 756 367**	**41 702**	**56**

Blank cells indicate data not reported.

TB for the first time and 0.3 million were people who had a recurrent episode of TB after being previously cured of the disease. 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 their treatment was changed to a retreatment regimen (for definitions of each type of case, see Box 3.1).

Among people who were diagnosed with TB for the first time (new cases), 2.6 million had sputum smear-positive pulmonary TB, 1.9 million had sputum smear-negative pulmonary TB, 0.2 million did not have a sputum smear done and 0.8 million had extrapulmonary TB (Table 3.1). Of the new cases of pulmonary TB, 56% were sputum smear-positive.

India and China accounted for 39% of the 5.8 million new and relapse cases of TB that were notified in 2011 (23% and 16%, respectively); the South-East Asia and Western Pacific regions of which these countries are a part accounted for 60% of cases globally. African countries accounted for 24% (one quarter of these cases were from one country – South Africa). The WHO Eastern Mediterranean and European regions and the Region of the Americas accounted for 16% of new and relapse cases notified in 2011 (7%, 5% and 4%, respectively). The 22 HBCs accounted for 81%.

Among the 22 HBCs, the percentage of new cases of pulmonary TB that were sputum smear-positive was relatively low in the Russian Federation (31%), Zimbabwe (40%), Myanmar (41%), South Africa (47%), Ethiopia (47%) and Kenya (48%). A comparatively high proportion of new cases of pulmonary TB were sputum smear-positive in Bangladesh (82%), the Democratic Republic of the Congo (84%) and Viet Nam (72%).

Almost all (98%) of the notifications of new cases of

BOX 3.1[1]

Definitions of TB cases

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 *M. 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 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 anti-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-positive plus 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 who does not meet the above criteria for smear-positive disease. Diagnostic criteria should include: at least two AFB-negative sputum smear examinations; 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 most patients diagnosed with MDR-TB, WHO recommends treatment for 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).

BOX 3.2

Achievements in global TB care and control, 1995–2011

WHO began systematic monitoring of progress in TB control in 1995. Data compiled on an annual basis since then allow achievements in TB care and control to be assessed.

Between 1995 and 2011, 51 million people were successfully treated for TB in countries that had adopted the DOTS/Stop TB Strategy (out of a total of 60 million treated). This saved approximately 20 million lives.[1]

The number of lives saved is based on the estimate that in the absence of treatment, approximately 40% of people with TB would die of the disease. This estimate allows for differences in the mortality rates for smear-positive compared with other types of TB disease (see Chapter 1), and for differences in mortality rates between HIV-negative and HIV-positive people.

[1] For estimates of the incremental number of lives saved by improvements in TB care associated with implementation of the DOTS and Stop TB Strategy compared with pre-1995 standards of care, see 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.

TABLE 3.2 **Notifications of new cases of smear-positive pulmonary TB by age and sex, 2011**

	0–14 YEARS	15–44 YEARS	45–64 YEARS	≥65 YEARS	% AGED < 15 YEARS	MALE/FEMALE RATIO
Afghanistan	669	8 574	3 319	1 227	5	0.51
Bangladesh	932	53 585	30 877	13 554	< 1	1.9
Brazil	692	25 270	11 080	3 211	2	2.2
Cambodia	73	6 810	6 412	2 581	< 1	1.2
China	1 378	173 523	128 585	73 519	< 1	2.6
DR Congo	3 379	47 529	17 207	3 206	5	1.2
Ethiopia	3 830	38 518	6 272	1 074	8	1.2
India	12 985	388 447	187 705	53 174	2	2.2
Indonesia	1 714	115 631	67 378	13 074	< 1	1.5
Kenya	985	29 884	5 207	1 009	3	1.6
Mozambique					–	–
Myanmar	307	23 902	14 198	3 907	< 1	1.9
Nigeria	1 107	34 559	9 604	2 167	2	1.6
Pakistan	3 895	64 309	27 495	10 034	4	1.1
Philippines	953	51 919	31 069	6 935	1	2.4
Russian Federation	51	18 066	9 477	1 597	< 1	2.7
South Africa	3 404	94 427	27 552	4 387	3	1.2
Thailand	114	14 980	11 862	6 213	< 1	2.4
Uganda	695	18 486	4 842	917	3	1.8
UR Tanzania	411	17 149	5 047	1 508	2	1.8
Viet Nam	95	23 404	18 271	8 949	< 1	3.0
Zimbabwe	326	9 953	1 879	438	3	1.2
High-burden countries	**37 995**	**1 258 925**	**625 338**	**212 681**	**2**	**1.9**
AFR	19 183	427 731	114 303	23 574	3	1.4
AMR	2 337	62 127	27 495	11 311	2	1.8
EMR	5 763	105 833	42 736	16 303	3	1.2
EUR	391	46 807	24 197	6 962	< 1	2.3
SEAR	17 144	626 659	329 687	93 857	2	2.0
WPR	2 880	272 434	196 490	104 444	< 1	2.4
Global	**47 698**	**1 541 591**	**734 908**	**256 451**	**2**	**1.9**

Blank cells indicate data not reported.
– indicates values that cannot be calculated.

smear-positive pulmonary TB were disaggregated by age and sex (Table 3.2); 85% were aged 15–64 years and 2% were children (aged <15 years). The global male:female sex ratio was 1.9, but among HBCs this varied from 0.5 in Afghanistan to 3.0 in Viet Nam. Variation among countries may reflect real differences in epidemiology as well as differential access to or use of health-care services linked to the NTP.

Reporting of cases disaggregated by age and sex was much less complete for new smear-negative pulmonary and extrapulmonary cases. For example, data disaggregated by age and sex according to the categories shown in Table 3.2 were not available for 12 HBCs. When the available data for all new cases were combined, most cases (88%) were aged 15–64 years and 6% were among children (<15 years); the male:female ratio was 1.7, ranging from 1.1 to 2.2 among WHO's six regions. Further efforts are needed to improve reporting of all cases disaggregated by age and sex.

3.2 Contribution of public–public and public–private mix (PPM) initiatives to TB case notifications in 2011

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 given 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 health-care providers 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 locally, and reporting and analysis of aggre-

TABLE 3.3 **Contribution of public–private and public–public mix (PPM) to notifications of TB cases in 21 countries, 2011**

WHO REGION AND COUNTRY	TYPES OF NON-NTP CARE PROVIDERS ENGAGED	NUMBER OF NEW TB CASES NOTIFIED IN 2011	CONTRIBUTION TO TOTAL NOTIFICATIONS OF NEW TB CASES IN 2011
AFRICAN REGION			
Angola	Diverse private and public providers	13 989	28%
Ethiopia	Diverse private providers	15 052	9.5%
Ghana	Diverse private and public providers	1 781	11%
Kenya	Private clinics and hospitals and prisons	10 076	9.6%
Nigeria	Private clinics and hospitals	21 562	23%
UR Tanzania	Private facilities and faith-based organizations	13 067	21%
REGION OF THE AMERICAS			
El Salvador	Diverse private and public providers	581	30%
Haiti	Private practitioners, NGOs and prison services	5 170	36%
EASTERN MEDITERRANEAN REGION			
Iran (Islamic Republic of)	Diverse private and public providers	3 563	31%
Iraq	Diverse private and public providers	5 624	61%
Pakistan[a]	Private clinics and hospitals	21 117	20%
Egypt	Health insurance organizations, NGOs and other public providers	2 234	24%
Sudan	Diverse private and public providers	2 277	11%
Syrian Arab Republic	Diverse private and public providers	2 694	73%
SOUTH-EAST ASIA REGION			
Bangladesh	Diverse private, public and NGO providers	19 668	12%
India[b]	Diverse private, public and NGO providers	13 991	2.1%
Indonesia	Public and private hospitals	71 454	22%
Myanmar	Diverse private, public and NGO providers	31 838	22%
WESTERN PACIFIC REGION			
China	General public hospitals	389 112	43%
Philippines	Private clinics and hospitals	24 031	12%
Republic of Korea	Diverse private providers	44 684	89%

[a] Data are for smear-positive cases of pulmonary TB only.
[b] Data are for smear-positive cases of pulmonary TB in 14 cities where PPM surveillance is in place.

gated data nationally.[1] Nonetheless, a growing number of countries are systematically recording and reporting data on the contribution of PPM initiatives to TB notifications (**Table 3.3**). In most of the 21 countries (including 11 HBCs) for which data were reported, PPM initiatives contributed about 10% to 40% of total notifications.

Approaches to engage non-NTP care providers vary according to the local context. For example, in the Philippines, the national health insurance organization has designed a special TB package for providers that collaborate with the NTP. India has incentive-based schemes for individual and institutional providers. China uses an Internet-based system for mandatory reporting of TB cases by all providers. 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 and the Republic of Korea), medical colleges (in India) and health insurance organizations that also provide health services (in Egypt). Social security organizations and prison health services are the main non-NTP providers in the Region of the Americas and in Eastern Europe, respectively.

Comparisons with data reported by countries in previous years show that the contribution of PPM to case notifications has grown in some countries, including China, Indonesia, Myanmar and the Republic of Korea. The unexplained variations in the data from other countries indicate that their PPM initiatives, and the recording and reporting aspects in particular, need to be strengthened.

In most countries, only a small proportion of targeted care providers collaborate actively with NTPs and contribute to TB case notifications. Achieving early TB case detection to minimize disease transmission will require greater involvement of front-line health workers such as community-based informal providers, general practitioners and pharmacists – who are often the first point of contact for people with symptoms of TB. The need for

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

BOX 3.3

Engaging private providers in countries with a large private sector

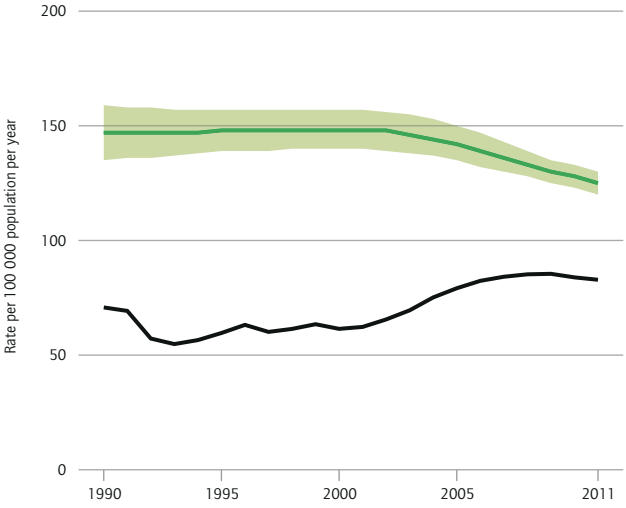
Data reported by countries indicate that NTPs mostly engage non-profit and institutional care providers as part of their PPM programmes. Establishing collaborative links with these providers is relatively less demanding than engaging for-profit private providers and, for a given amount of effort, may yield a higher number of TB case notifications. However, engaging more seriously with for-profit practitioners, especially in countries with a large private sector, is necessary to increase the number of people with TB who are diagnosed early, treated according to international standards and reported to national TB control programmes. It is also required to reduce costs to TB patients, prevent the emergence and spread of drug-resistant TB and protect soon-to-be-available new anti-TB drugs.

The extent of the sale and use of anti-TB drugs in the private sector in 10 countries that account for about 60% of estimated TB cases globally was assessed in 2011.[1] The private markets in four Asian countries (India, Indonesia, Pakistan and the Philippines) had the largest volumes of sales relative to estimated numbers of TB cases. Annual sales ranged from 65% to 117% of the drugs needed to treat the estimated number of incident cases occurring each year with a standard 6–8 month regimen in these countries. The study authors concluded that expansion of PPM programmes was needed.

Efforts to engage public and private health-care providers in TB care and control have been implemented for several years in India, Indonesia, Pakistan and the Philippines. Nonetheless, the reported data indicate that there is substantial scope for greater engagement of the private sector in these and other countries with a large private sector. Disaggregated data on the contribution of providers in the private sector to TB case notifications is not reported by most countries; among those that do report, the contribution of the large for-profit private sector is too small to be of any significance. The recent decision by the Government of India to make notification of TB cases mandatory by law is a welcome step in the right direction.

[1] Wells WA et al. Size and usage patterns of private TB drug markets in the high burden countries. *PLoS One*, 2011, 6(5):e18964.

FIGURE 3.1 **Global trends in case notification (black) and estimated TB incidence (green) rates, 1990–2011**



greater attention to collaboration with for-profit private providers, especially in countries where there is a large private medical sector and anti-TB drugs are readily available in private pharmacies, is highlighted in Box 3.3.

A new initiative to engage nongovernmental organizations in TB care and control, named ENGAGE-TB, is described in Box 3.4.

3.3 Trends in case notifications since 1990 and estimates of the case detection rate

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]

The case detection rate (CDR)[2] for TB is an indicator that is included within the Millennium Development Goals (Chapter 1). For a given country and year, the CDR is calculated as the number of new and relapse TB cases (see Box 3.1 for definitions) that were notified by NTPs (Table 3.1), divided by the estimated number of incident

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

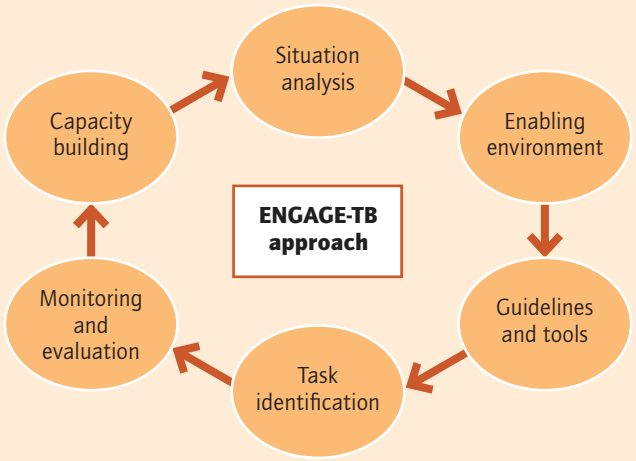
[2] The CDR is actually a ratio rather than a rate, but the term "rate" has become standard terminology in the context of this indicator.

BOX 3.4

Integrating community-based TB activities – ENGAGE-TB

During the past five years, the percentage of estimated cases of incident TB detected and reported to NTPs has stagnated at around 60–70%. The "missing" cases are either diagnosed and treated by providers not reporting to the public health system or are not reached by the current network of providers of TB care at all. Among notified cases, diagnosis may be delayed. To reach the unreached and to find people with TB earlier in the course of their illness, a wider range of stakeholders already involved in community-based activities needs to be engaged. These include non-governmental organizations (NGOs) and other civil society organizations that are active in community-based development, particularly in primary health care, maternal and child health and HIV prevention, treatment and care, but which have not yet included TB in their activities.

The ENGAGE-TB initiative seeks to integrate community-based activities to control TB in the ongoing work of such NGOs, aligned with national strategies and plans and supported by new operational guidance developed by WHO.[1] The guidance recommends the creation or strengthening of NGO coalitions for TB care and control, regular meetings between the leadership of such coalitions and NTP staff at various levels, and streamlining monitoring and evaluation through a single recording and reporting system. The guidance supports more explicit measurement of community-based contributions to case notifications and treatment outcomes. The six components through which integration can be more systematically undertaken are shown in the figure opposite.



Community-based activities are conducted outside the premises of formal health facilities (hospitals, health centres and clinics) using community-based structures (such as schools, places of worship and congregate settings) and homesteads. Examples include:

- creating awareness about TB, communication for behavioural change and community mobilization;
- efforts to reduce stigma and discrimination;
- screening and testing for TB and other TB related co-morbidities (e.g. through HIV counselling and testing, and screening for diabetes), including through home visits;
- facilitating access to diagnostic services, for example by providing transportation to health-care facilities;
- initiating and providing interventions to prevent TB, including isoniazid preventive therapy and TB infection control;
- referring community members for diagnosis of TB and other co-morbidities;
- initiating, providing and observing treatment for TB and other co-morbidities;
- supporting adherence to treatment through peer support, education and individual follow-up;
- supporting social and livelihood schemes, such as food supplementation and income generation;
- providing home-based palliative care for TB and other co-morbidities; and
- supporting community-led advocacy.

[1] ENGAGE-TB: Integrating community-based TB activities into the work of NGOs and other CSOs (in press).

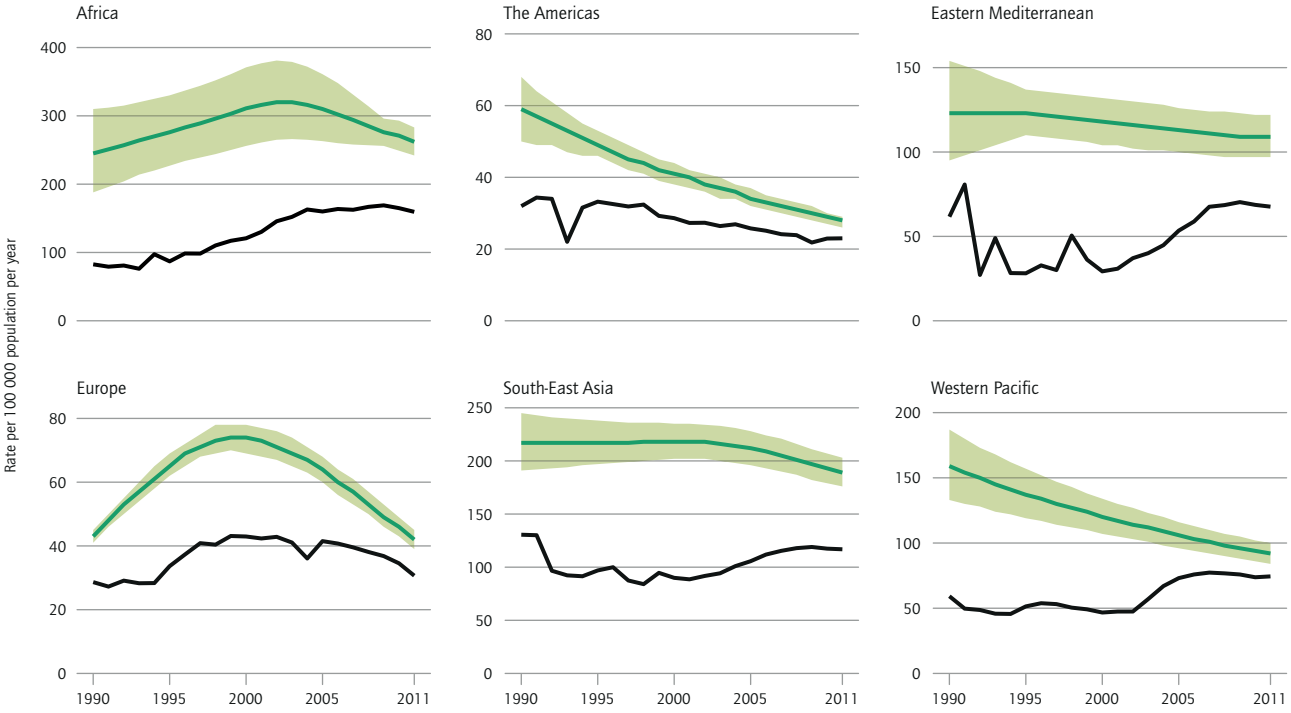
cases of TB that year. The CDR is expressed as a percentage; it gives an approximate[1] indication of the proportion of all incident TB cases that are actually diagnosed, reported to NTPs and started on treatment.

The best estimate of the CDR for all forms of TB globally in 2011 was 66% (range, 64–69%), up from 53–59% in 2005 and 38–43% in 1995 – the year in which the DOTS strategy began to be introduced and expanded (Table 3.4). The highest CDRs in 2011 were estimated to be in the Region of the Americas (best estimate 84%; range, 79–89%), the Western Pacific Region (best estimate 81%; range, 75–89%) and the European Region (best estimate 73%; range, 69–78%). The other regions had estimated CDRs in the range 55–70%, 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 2011 were estimated to be in Brazil, China, Kenya, the Russian Federation and the United Republic of Tanzania; the lowest rates were in Afghanistan, Bangladesh, Mozambique and Nigeria.

To close the gap between notified cases and estimated

[1] 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.

FIGURE 3.2 **Case notification and estimated TB incidence rates by WHO region, 1990–2011.** Regional trends in case notification rates (new and relapse cases, all forms) (**black**) and estimated TB incidence rates (green). Shaded areas represent uncertainty bands.



TB incidence, action is needed in three broad areas:

- **strengthening surveillance**, 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 (see Section 2.5.1 in Chapter 2 for further details) can be used to help quantify the extent to which diagnosed cases are unreported (the "surveillance gap").
- **improving diagnostic capacity**, 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. Details about current progress in strengthening laboratories and introducing new rapid diagnostics are provided in Chapter 6.
- **increasing access to health care** (in financial and/or geographical terms), for people with TB who do not seek care, and improved awareness of how to recognize the signs and symptoms of TB.

3.4 Treatment outcomes

3.4.1 New cases of smear-positive pulmonary TB

Data on treatment outcomes for sputum smear-positive cases of pulmonary TB are shown in Table 3.5 (definitions of the categories used to report treatment outcomes are provided in Box 3.5). Globally, the rate of treatment success for the 2.7 million new cases of sputum smear-positive pulmonary TB who were treated in the 2010 cohort was 87%. This was the fourth successive year that the target of 85% (first set by the World Health Assembly in 1991) was met or exceeded globally. It is also impressive that as the size of the global treatment cohort grew from 1.0 million in 1995 to 2.7 million in 2010, the treatment success rate progressively improved.

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 82% in the African Region (where there has been steady improvement since 1999), 77% in the Region of the Americas (where the rate has been relatively stable since 2002) and 67% in the European Region (where major efforts to increase treatment success rates are needed).

Of the 22 HBCs, 15 reached or exceeded the 85% target in 2010. The seven HBCs that reported lower rates of treatment success were Brazil (74%), Ethiopia (83%), Nigeria (84%), the Russian Federation (53%), South Africa (79%), Uganda (71%) and Zimbabwe (81%); all except Ethiopia and the Russian Federation made prog-

TABLE 3.4 **Estimates of the case detection rate for new and relapse cases (%), 1995–2011[a]**

	1995			2000			2005			2010			2011		
	BEST[b]	LOW	HIGH	BEST	LOW	HIGH	BEST	LOW	HIGH	BEST	LOW	HIGH	BEST	LOW	HIGH
Afghanistan	–	–	–	16	14	20	42	35	51	47	40	57	46	38	55
Bangladesh	21	18	26	26	22	32	39	32	48	46	39	56	45	37	54
Brazil	79	66	97	74	62	91	84	71	100	88	75	110	91	77	110
Cambodia	23	18	29	26	21	33	52	44	63	65	57	76	64	55	74
China	33	28	40	33	28	39	74	65	85	87	77	99	89	79	100
DR Congo	30	25	36	38	32	45	52	45	61	53	46	61	50	43	58
Ethiopia	11	7.2	18	33	22	55	49	32	82	69	52	97	72	55	96
India	58	51	67	49	44	54	49	44	54	59	54	65	59	54	65
Indonesia	8.7	7.0	11	19	16	24	56	46	70	66	56	80	70	59	85
Kenya	61	56	66	72	67	77	80	76	85	82	79	86	81	78	85
Mozambique	23	11	73	23	13	51	31	20	54	34	25	49	34	25	49
Myanmar	11	8.6	14	17	14	21	57	49	68	71	62	83	74	64	87
Nigeria	8.8	2.7	160	12	3.9	170	26	9.4	190	40	24	83	45	26	96
Pakistan	4.5	3.7	5.5	3.3	2.8	4.0	39	32	47	65	55	79	64	54	78
Philippines	48	40	59	47	39	58	53	44	65	65	54	79	75	63	91
Russian Federation	60	51	70	75	65	89	66	56	78	79	67	93	81	70	96
South Africa	56	47	69	59	49	72	61	51	75	72	61	87	69	58	83
Thailand	59	49	71	32	27	38	56	47	68	75	63	91	76	64	93
Uganda	22	14	41	29	20	48	47	36	66	61	51	76	69	57	86
UR Tanzania	59	51	69	68	60	77	74	69	80	77	72	82	76	71	81
Viet Nam	37	29	49	56	44	73	56	44	74	54	43	70	56	44	73
Zimbabwe	55	40	79	56	45	71	50	41	63	56	44	72	50	40	65
High-burden countries	**39**	**36**	**42**	**39**	**36**	**42**	**54**	**51**	**58**	**65**	**62**	**69**	**66**	**63**	**69**
AFR	31	26	38	39	33	47	52	44	61	61	56	66	61	56	66
AMR	68	63	73	70	65	75	75	70	80	80	75	86	84	79	89
EMR	23	21	26	25	22	28	47	42	54	63	56	71	62	55	70
EUR	52	49	54	58	55	62	65	61	70	76	71	81	73	69	78
SEAR	45	41	49	41	38	44	50	46	54	61	57	66	62	58	66
WPR	37	33	43	39	35	43	69	63	76	79	72	86	81	75	89
Global	**40**	**38**	**43**	**41**	**39**	**44**	**56**	**53**	**59**	**66**	**63**	**68**	**66**	**64**	**69**

– indicates values that cannot be calculated.

[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.

ress compared with 2010. In Brazil and Uganda, low rates reflect a relatively high proportion of patients for whom the outcome of treatment was not evaluated (10% and 13%, respectively) and high default rates (11% in both countries). In the Russian Federation, treatment failure rates are high, possibly linked to MDR-TB.

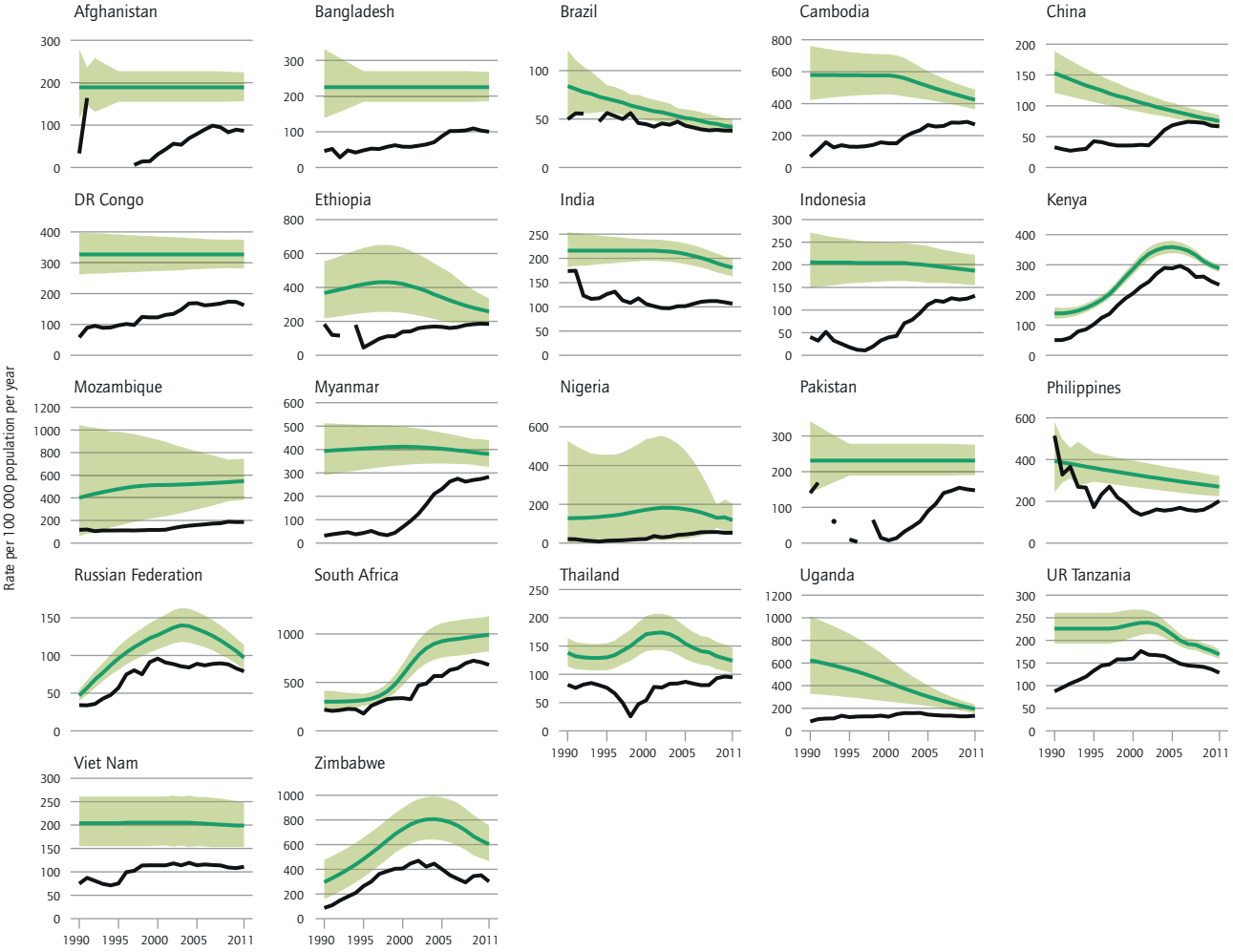
3.4.2 All new cases

Data on treatment outcomes for all new cases of TB are shown in Table 3.6. Globally, the rate of treatment success was 85% in 2010. Among WHO's six regions, the highest rates were in the Eastern Mediterranean (88%), South-East Asia (89%) and Western Pacific (92%) regions. The treatment success rate was 73% in the African Region, 74% in the Region of the Americas and 74% in the European Region. The data for the African Region were affected by missing data for South Africa. Once these are available and reported, the treatment success rate will be higher.

Of the 22 HBCs, 14 reached or exceeded a treatment success rate of 85% among all new cases in 2010. The eight countries that reported lower rates of treatment success were Brazil (72%), Ethiopia (77%), Nigeria (81%), the Russian Federation (66%), South Africa (53%),[1] Thailand (83%), Uganda (68%) and Zimbabwe (76%).

[1] The NTP in South Africa noted that data reported to WHO were incomplete; the figure of 53% is thus an underestimate.

FIGURE 3.3 **Case notification and estimated TB incidence rates, 22 high-burden countries, 1990–2011.** Trends in case notification rates (new and relapse cases, all forms) (**black**) and estimated TB incidence rates (green). Shaded areas represent uncertainty bands.



BOX 3.5

Definitions of treatment outcomes for drug-susceptible TB

Cured A patient who was initially sputum smear-positive and who was sputum 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 sputum smear-positive and sputum smear-negative patients with pulmonary TB and to patients with extrapulmonary disease.

Died A patient who died from any cause during treatment.

Failed A patient who was initially sputum smear-positive and who remained sputum 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 sputum smear-positive cases registered in the calendar year 2010). 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) and "transferred out" cases should equal the number of cases registered. Some countries monitor outcomes among cohorts defined by sputum smear and/or culture, and define cure and failure according to the best laboratory evidence available for each patient.

TABLE 3.5 Treatment success for new smear-positive cases (%) and cohort size (thousands), 1995–2010

a. Treatment success (%)

	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Afghanistan	–	–	45	33	86	85	84	87	86	89	90	84	87	88	86	90
Bangladesh	71	63	73	77	79	81	83	84	85	90	91	92	92	91	92	92
Brazil	17	20	27	40	78	71	55	80	77	76	76	73	72	71	72	74
Cambodia	91	94	91	95	93	91	92	92	93	91	93	93	94	95	95	94
China	93	94	95	95	95	93	95	92	93	94	94	94	94	94	95	96
DR Congo	74	48	64	70	69	78	77	78	83	85	85	86	87	87	88	90
Ethiopia	61	71	72	74	74	80	76	76	70	79	78	84	84	84	84	83
India	25	21	18	27	21	34	54	60	76	82	86	86	87	87	88	88
Indonesia	91	81	54	58	50	87	86	86	87	90	91	91	91	91	91	90
Kenya	75	77	65	77	79	80	80	79	80	80	82	85	85	85	86	87
Mozambique	39	55	65	–	71	75	78	78	76	77	79	83	79	84	85	85
Myanmar	67	79	82	82	81	82	81	81	81	84	84	84	85	85	85	86
Nigeria	49	32	73	73	75	79	79	79	78	73	75	76	82	78	83	84
Pakistan	70	–	67	23	70	74	77	78	79	82	83	88	91	90	91	91
Philippines	60	35	78	71	87	88	88	88	88	87	89	88	89	88	89	91
Russian Federation	65	57	67	68	65	68	67	67	61	60	58	58	58	57	55	53
South Africa	58	61	68	72	57	63	61	68	67	69	71	74	74	76	73	79
Thailand	64	78	58	68	77	69	75	74	73	74	75	77	83	82	86	85
Uganda	44	33	40	62	61	63	56	60	68	70	73	70	75	70	67	71
UR Tanzania	73	76	77	76	78	78	81	80	81	81	82	85	88	88	88	90
Viet Nam	89	89	85	92	92	92	93	92	92	93	92	93	92	92	92	92
Zimbabwe	53	32	69	70	73	69	71	67	66	54	68	60	78	74	78	81
High-burden countries	**53**	**50**	**56**	**62**	**60**	**67**	**72**	**75**	**81**	**84**	**86**	**87**	**87**	**87**	**88**	**88**
AFR	60	56	64	70	68	71	70	73	73	74	76	75	80	80	80	82
AMR	50	51	58	67	79	76	69	81	80	79	79	76	79	77	76	77
EMR	79	66	73	57	79	81	82	84	82	83	83	86	88	88	88	88
EUR	67	58	72	63	75	75	74	74	75	70	72	70	71	70	69	67
SEAR	33	31	29	40	34	50	63	68	79	84	87	87	88	88	89	88
WPR	80	72	91	92	91	90	91	90	91	91	92	92	92	92	93	93
Global	**57**	**54**	**60**	**64**	**64**	**69**	**73**	**76**	**80**	**83**	**85**	**84**	**86**	**86**	**86**	**87**

b. Cohort size (thousands)

	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Afghanistan			2.0	2.9	2.0	3.1	6.3	7.8	6.8	10	10	12	13	13	12	13
Bangladesh	11	30	34	38	38	38	41	47	54	63	85	102	104	106	109	106
Brazil	46	45	43	30	27	34	41	29	38	43	42	48	38	41	41	42
Cambodia	4.4	9.1	12	13	16	15	14	17	19	19	21	19	19	20	18	17
China	131	175	189	210	208	214	190	194	267	385	473	470	466	464	449	430
DR Congo	16	25	26	33	35	36	41	45	54	62	65	63	66	66	72	73
Ethiopia	5.1	11	12	15	21	30	32	37	40	41	39	37	38	41	45	47
India	265	291	293	284	345	349	384	396	420	489	507	553	592	616	625	630
Indonesia	3.0	12	21	40	46	52	54	76	93	129	159	175	161	166	169	183
Kenya	6.5	13	19	22	27	28	31	31	34	41	40	39	38	37	37	36
Mozambique	11	13	11		12	13	14	15	16	17	18	18	18	19	20	20
Myanmar	7.9	9.7	9.2	10	12	17	21	24	27	31	37	40	43	41	42	42
Nigeria	9.5	24	11	13	15	16	17	21	28	34	35	40	44	46	45	45
Pakistan	0.8		2.8	29	3.0	4.1	6.3	15	20	32	48	66	89	100	102	104
Philippines	90	126	27	21	37	50	55	59	68	78	81	86	87	85	89	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	30
South Africa	28	45	55	37	81	86	101	99	114	127	135	140	143	144	139	134
Thailand	20	0.1	3.7	8.0	14	23	20	27	28	28	30	29	30	33	28	30
Uganda	15	15	18	13	14	14	17	19	20	21	21	20	21	23	23	23
UR Tanzania	20	21	22	24	24	24	24	24	25	26	25	25	25	24	25	24
Viet Nam	38	48	54	55	53	53	54	57	56	58	55	56	54	53	51	52
Zimbabwe	9.7	12	12	13	13	14	17	16	14	15	13	16	11	10	10	12
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**	**2 184**	**2 185**
AFR	178	233	268	235	323	365	409	452	491	552	564	566	577	591	606	635
AMR	129	134	125	111	110	111	102	105	110	121	119	132	116	109	123	123
EMR	46	51	60	89	66	64	52	76	81	98	114	132	156	167	167	170
EUR	34	94	24	48	22	41	50	54	60	75	81	98	108	114	105	84
SEAR	318	360	376	399	473	512	550	604	661	780	856	938	974	1 011	1 022	1 045
WPR	296	372	294	313	353	360	346	357	439	575	663	663	661	657	641	622
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**	**2 665**	**2 680**

Blank cells indicate data not reported.
– indicates values that cannot be calculated.

TABLE 3.6 Treatment success for all new cases (%) and cohort size (thousands), 1995–2010

a. Treatment success (%)

	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Afghanistan	–	–	45	33	86	85	84	87	86	89	90	84	87	88	86	86
Bangladesh	71	63	73	77	79	81	83	84	85	90	90	91	90	91	91	91
Brazil	17	20	27	40	78	71	55	80	77	72	72	69	72	69	70	72
Cambodia	91	94	91	95	93	91	92	92	93	91	91	92	93	94	94	89
China	93	94	95	95	95	93	95	92	93	92	92	92	93	93	94	95
DR Congo	74	48	64	70	69	78	77	78	83	85	85	60	86	86	88	89
Ethiopia	61	71	72	74	74	80	76	76	70	79	78	84	84	80	81	77
India	25	21	18	27	21	34	54	60	76	81	87	87	88	88	89	89
Indonesia	91	81	54	58	50	87	86	86	87	87	89	90	90	90	89	89
Kenya	75	77	65	77	79	80	80	79	80	77	81	83	83	84	84	86
Mozambique	39	55	65	–	71	75	78	78	76	77	79	83	79	84	85	85
Myanmar	67	79	82	82	81	82	81	81	81	82	83	83	84	84	84	88
Nigeria	49	32	73	73	75	79	79	79	78	73	75	76	82	78	84	81
Pakistan	70	–	67	23	70	74	77	78	79	80	82	86	90	89	91	90
Philippines	60	35	78	71	87	88	88	88	88	78	89	88	88	84	85	90
Russian Federation	65	57	67	68	65	68	67	67	61	65	67	69	69	69	68	66
South Africa	58	61	68	72	57	63	61	68	67	65	69	70	71	73	68	53
Thailand	64	78	58	68	77	69	75	74	73	71	71	75	81	80	84	83
Uganda	44	33	40	62	61	63	56	60	68	70	73	68	72	67	64	68
UR Tanzania	73	76	77	76	78	78	81	80	81	82	83	85	88	88	88	89
Viet Nam	89	89	85	92	92	92	93	92	92	92	92	92	91	92	92	92
Zimbabwe	53	32	69	70	73	69	71	67	66	48	66	67	78	70	75	76
High-burden countries	**53**	**50**	**56**	**62**	**60**	**67**	**72**	**75**	**81**	**82**	**85**	**85**	**87**	**87**	**86**	**86**
AFR	60	56	64	70	68	71	70	73	73	70	74	72	77	77	76	73
AMR	50	51	58	67	79	76	69	81	80	76	75	73	78	73	73	74
EMR	79	66	73	57	79	81	82	84	82	82	82	86	87	87	87	88
EUR	67	58	72	63	75	75	74	74	75	75	77	75	76	76	75	74
SEAR	33	31	29	40	34	50	63	68	79	83	87	87	88	88	89	89
WPR	80	72	91	92	91	90	91	90	91	88	90	90	91	91	91	92
Global	**57**	**54**	**60**	**64**	**64**	**69**	**73**	**76**	**80**	**81**	**84**	**84**	**85**	**85**	**85**	**85**

b. Cohort size (thousands)

	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010
Afghanistan			2.0	2.9	2.0	3.1	6.3	7.8	6.8	10	10	12	13	13	12	26
Bangladesh	11	30	34	38	38	38	41	47	54	63	119	141	144	106	156	150
Brazil	46	45	43	30	27	34	41	29	38	81	78	81	47	73	75	78
Cambodia	4.4	9.1	12	13	16	15	14	17	19	30	34	34	35	38	39	40
China	131	175	189	210	208	214	190	194	267	644	788	847	889	932	923	877
DR Congo	16	25	26	33	35	36	41	45	54	62	65	92	89	93	106	109
Ethiopia	5.1	11	12	15	21	30	32	37	40	41	39	37	38	139	139	152
India	265	291	293	284	345	349	384	396	420	1 066	1 071	1 137	1 199	1 226	1 244	1 229
Indonesia	3.0	12	21	40	46	52	54	76	93	206	244	266	263	293	289	296
Kenya	6.5	13	19	22	27	28	31	31	34	97	98	101	99	99	99	90
Mozambique	11	13	11		12	13	14	15	16	17	18	18	18	19	20	20
Myanmar	7.9	9.7	9.2	10	12	17	21	24	27	66	73	84	85	90	91	127
Nigeria	9.5	24	11	13	15	16	17	21	28	34	35	40	44	46	86	78
Pakistan	0.8		2.8	29	3.0	4.1	6.3	15	20	84	117	149	191	206	212	256
Philippines	90	126	27	21	37	50	55	59	68	126	81	123	136	140	141	162
Russian Federation	0.05	43	0.7	0.7	1.5	3.6	4.1	5.2	6.3	39	74	97	99	103	101	94
South Africa	28	45	55	37	81	86	101	99	114	243	259	271	247	236	367	338
Thailand	20	0.1	3.7	8.0	14	23	20	27	28	47	49	47	47	54	43	48
Uganda	15	15	18	13	14	14	17	19	20	21	21	31	37	39	38	40
UR Tanzania	20	21	22	24	24	24	24	24	25	61	59	58	25	59	60	59
Viet Nam	38	48	54	55	53	53	54	57	56	92	55	91	91	91	88	88
Zimbabwe	9.7	12	12	13	13	14	17	16	14	54	43	43	39	40	45	46
High-burden countries	**739**	**967**	**879**	**912**	**1 044**	**1 119**	**1 186**	**1 260**	**1 450**	**3 183**	**3 430**	**3 799**	**3 872**	**4 134**	**4 374**	**4 403**
AFR	178	233	268	235	323	365	409	452	491	846	886	940	930	1 087	1 297	1 251
AMR	129	134	125	111	110	111	102	105	110	191	187	197	157	168	191	196
EMR	46	51	60	89	66	64	52	76	81	178	226	259	307	320	331	391
EUR	34	94	24	48	22	42	50	55	60	171	221	274	276	279	248	220
SEAR	318	360	376	399	473	512	550	604	661	1 530	1 639	1 758	1 835	1 880	1 940	1 980
WPR	296	372	294	313	353	360	346	357	439	963	1 030	1 163	1 216	1 261	1 259	1 240
Global	**1 001**	**1 245**	**1 147**	**1 195**	**1 347**	**1 453**	**1 511**	**1 649**	**1 843**	**3 879**	**4 188**	**4 592**	**4 720**	**4 995**	**5 267**	**5 278**

Blank cells indicate data not reported.
– indicates values that cannot be calculated.

CHAPTER 4

Drug-resistant TB

KEY FACTS AND MESSAGES

- By the end of 2012, representative surveillance data on levels of MDR-TB will be available from all 27 high MDR-TB and 22 high TB burden countries, and from 135 of 194 Member States. Globally, 3.7% (2.1–5.2%) of new cases and 20% (13–26%) of previously treated cases are estimated to have MDR-TB.
- There were an estimated 310 000 (range, 220 000–400 000) MDR-TB cases among notified TB patients with pulmonary TB in 2011. Almost 60% of these cases were in India, China and the Russian Federation.
- Extensively drug-resistant TB, or XDR-TB, has been identified in 84 countries; the average proportion of MDR-TB cases with XDR-TB is 9.0% (6.7–11.2%).
- Levels of MDR-TB remain worryingly high in some parts of the world, notably countries in eastern Europe and central Asia. In several of these countries, 9–32% of new cases have MDR-TB and more than 50% of previously treated cases have MDR-TB.
- There has been progress in the detection and treatment of MDR-TB in the last two years. Globally, almost 60 000 cases of MDR-TB were notified to WHO in 2011, mostly by European countries and South Africa. The number of cases reported by the 27 high MDR-TB burden countries almost doubled between 2009 and 2011.
- Despite progress, the number of MDR-TB cases notified in 2011 represented only 19% of the estimated 310 000 cases of MDR-TB among reported TB patients with pulmonary TB, and less than 10% in the two countries with the largest number of cases, China and India. Achieving universal access to treatment requires a bold and concerted drive on many fronts of TB care, and increased financing.
- Major efforts are needed to improve treatment success rates among patients with MDR-TB. The Global Plan target of ≥75% by 2015 was reached by only 30 of 107 countries that reported treatment outcome data for patients with MDR-TB.

Drug-resistant TB (DR-TB) threatens global TB control and is a major public health concern in several countries. The first part of this chapter summarizes the latest status of progress in global surveillance of anti-TB drug resistance, using the most recent data on multidrug-resistant TB (MDR-TB), extensively drug-resistant TB (XDR-TB) and resistance to fluoroquinolones gathered from special surveys and continuous surveillance (**Section 4.1**). The second part of the chapter (**Section 4.2**) assesses national progress in diagnosing and treating MDR-TB, using data on diagnostic testing for DR-TB, enrolment on treatment with second-line drugs for those found to have MDR-TB and treatment outcomes.

4.1 Surveillance of drug-resistant TB

4.1.1 Progress in the coverage of drug resistance surveillance

Since the launch of the Global Project on Anti-tuberculosis Drug Resistance Surveillance in 1994, data on drug resistance have been systematically collected and analysed from 135 countries worldwide (70% of WHO's 194 Member States). This includes 63 countries that have continuous surveillance systems based on routine diagnostic drug susceptibility testing (DST) of all TB patients and 72 countries that rely on special surveys of representative samples of patients.

During the past 4 years, most of the 27 high MDR-TB and 22 high TB burden countries (a total of 36 countries) have expanded coverage of surveillance of drug resistance to obtain more accurate estimates of the burden of MDR-TB (**Figure 4.1**). In 2008, 16 of these 36 countries had no nationally representative drug resistance surveillance data (including 8 countries with data only from subnational areas) and only 3 countries (the Baltic States) had a nationwide routine surveillance system for monitoring drug resistance. By the end of 2012 when the survey concludes in Pakistan, baseline representative information about the burden of drug resistance will be available from all 27 high MDR-TB and 22 high TB burden countries.

Countries such as Afghanistan (Central region), Bangladesh, Belarus, Bulgaria, Nigeria, Uganda and the central Asian republics of Kyrgyzstan, Tajikistan and Uzbekistan, which previously had no or very limited information on drug resistance, concluded surveys in 2010–2011. Data for Afghanistan could not be disaggregated by history of treatment (% of MDR among all forms

FIGURE 4.1 **Progress in implementing surveys for anti-TB drug-resistance in the 27 high MDR-TB and 22 high-TB burden countries**

	2008	2012
Afghanistan	No data	Completed in 2010
Bangladesh	No data	Completed in 2011
Belarus	No data	Completed in 2011
Bulgaria	No data	Completed in 2010
Kyrgyzstan	No data	Completed in 2011
Nigeria	No data	Completed in 2011
Pakistan	No data	Ongoing
Tajikistan	No data	Completed in 2011
DR Congo	1999	No more recent data
India	9 States	1 additional State
Indonesia	2 Provinces	1 additional Province in 2010
Russian Federation	4 Oblasts	17 additional Oblasts
Azerbaijan	2007	Planned for 2013
Uganda	1997	Completed in 2011
Ukraine	2006	Planned for 2013
Uzbekistan	2005	Completed in 2011
Brazil	1996	Ongoing
Cambodia	2007	No more recent data
China	2007	Planned for 2013
Ethiopia	2005	Ongoing
Kenya	1995	Ongoing
Mozambique	2007	No more recent data
Myanmar	2007	Planned for 2013
Philippines	2004	Ongoing
South Africa	2002	Ongoing
Thailand	2006	No more recent data
UR Tanzania	2007	No more recent data
Viet Nam	2006	Ongoing
Zimbabwe	1995	Planned for 2013
Armenia	2007	Moving towards routine surveillance
Georgia	2007	Routine surveillance
Kazakhstan	2001	Routine surveillance
Republic of Moldova	2006	Routine surveillance
Estonia	Routine surveillance	Routine surveillance
Latvia	Routine surveillance	Routine surveillance
Lithuania	Routine surveillance	Routine surveillance

Survey/surveillance at subnational level
Nationwide survey
Nationwide routine surveillance

of TB: 6.3%; range 3.7–10.0). Six countries (Azerbaijan, the Democratic Republic of the Congo, India, Indonesia, the Russian Federation and Ukraine) still rely on drug resistance surveillance data gathered from limited subnational areas. In the Democratic Republic of the Congo, logistic issues have prevented the implementation of a nationwide survey. In Indonesia, after two surveys at provincial level, the national TB control programme (NTP) has opted to work towards establishing a nationwide sentinel system to monitor drug resistance. Concrete plans exist in Azerbaijan and Ukraine to start nationwide surveys in 2012. Drug resistance surveys are ongoing in Brazil, Ethiopia, Kenya, Pakistan, the Philippines, South Africa and Viet Nam.

By the end of 2011, India and the Russian Federation, which combined with China contribute to almost 60% of the estimated global burden of MDR-TB, had produced reliable data only at subnational level. These countries should consider conducting nationwide drug resistance surveys in the short term to better understand the burden of MDR-TB and properly plan diagnostic and treatment services.

Routine surveillance represents the best approach for measuring drug resistance and monitoring trends. Among the 27 high MDR-TB and 22 high TB burden countries, Georgia, Kazakhstan, the Republic of Moldova and the Baltic States now have proper routine surveillance systems to monitor drug resistance.

A group of countries – Benin, Bolivia, Chile, Colombia, El Salvador, Lebanon, Sri Lanka, Mongolia, Nicaragua and Rwanda – that relied on special surveys to monitor drug resistance have established a routine surveillance system for all previously treated cases. This is the first step towards routine drug susceptibility testing for all TB patients.

Central and Francophone Africa remain the regions where drug resistance surveillance data are most lacking, largely as a result of the scarce laboratory infrastructure.

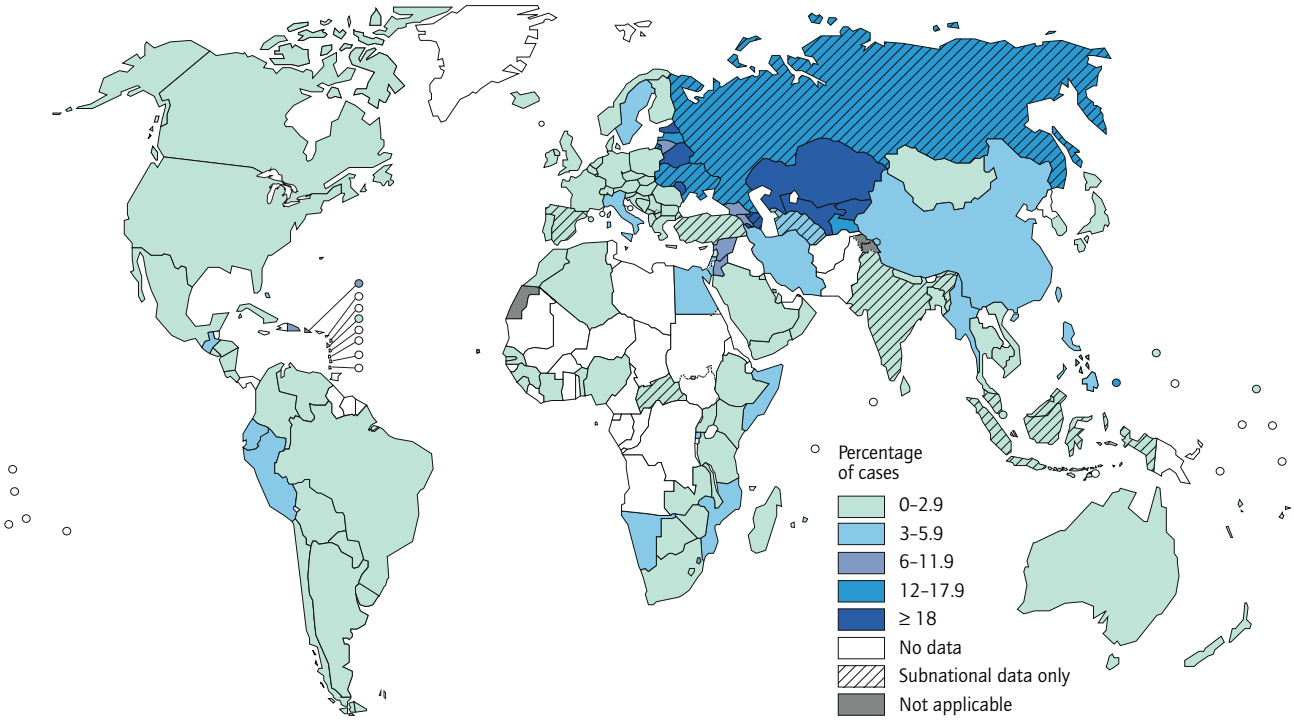
4.1.2 Percentage of new and previously treated TB cases that have MDR-TB

Globally, 3.7% (2.1–5.2%) of new cases and 20% (13–26%) of previously treated cases are estimated to have MDR-TB (Chapter 2).

The proportions of new TB cases with MDR-TB at country level are shown in Figure 4.2. Proportions ranged from 0% to 32.3% and were highest in Belarus (32.3%), Estonia (22.9%), Kazakhstan (30.3%), Kyrgyzstan (26.4%; preliminary results), the Republic of Moldova (19.4%) and Uzbekistan (23.2%). Although the average proportion of patients with MDR-TB in the Russian Federation is lower than in these countries, the proportion is high in several oblasts (with Arkhangelsk Oblast at the highest level: 35.1% in 2010).

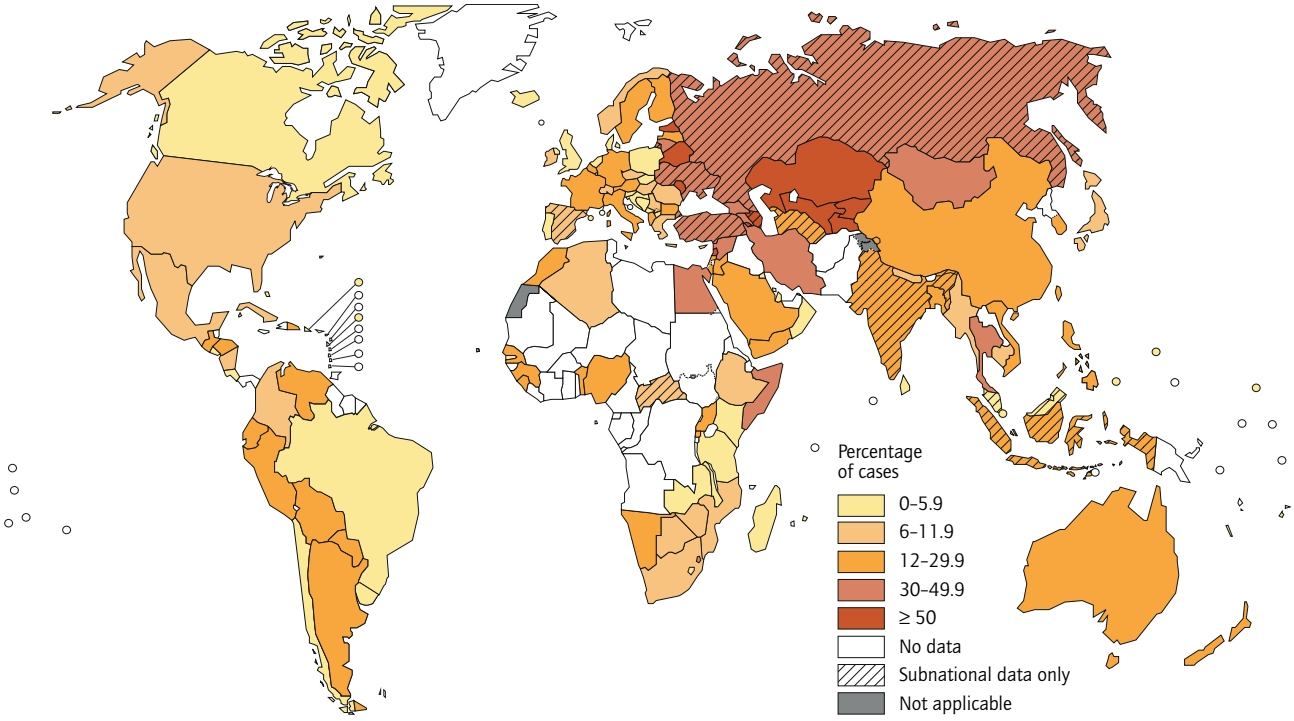
The proportion of previously treated TB cases with

FIGURE 4.2 **Percentage of new TB cases with MDR-TB[a]**



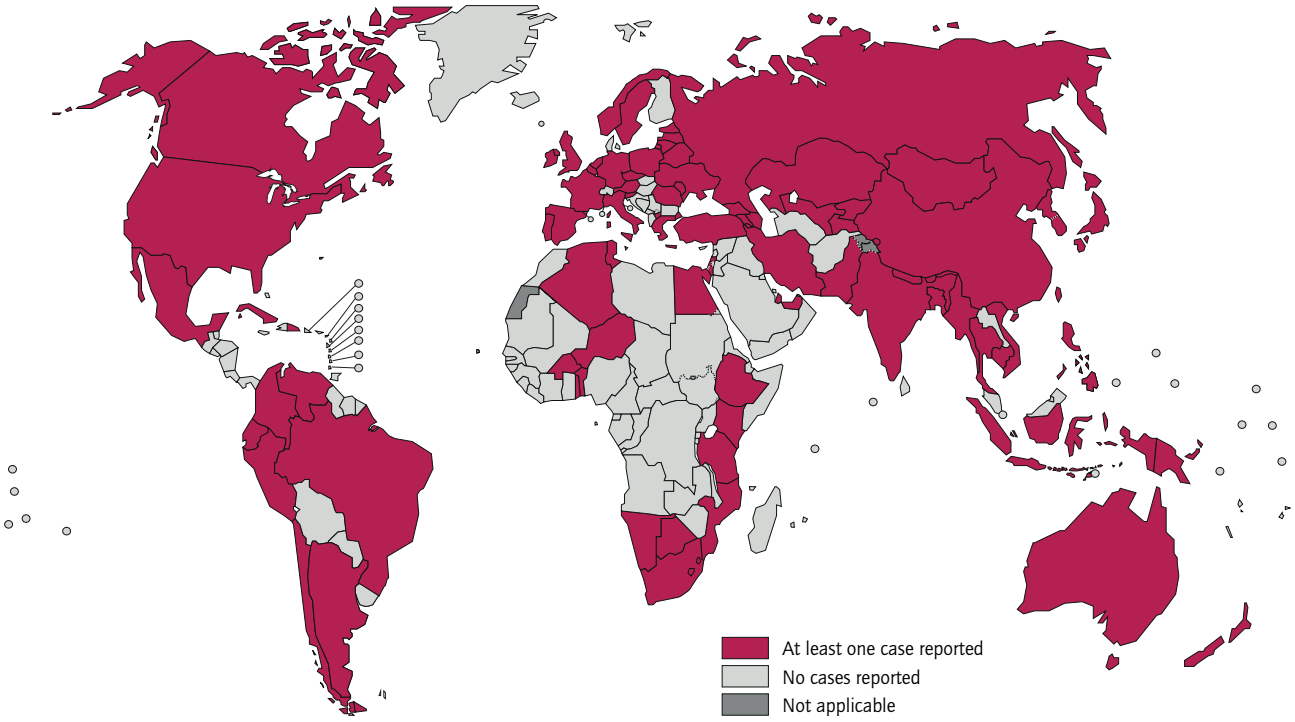
[a] Figures are based on the most recent year for which data have been reported, which varies among countries.

FIGURE 4.3 **Percentage of previously treated TB cases with MDR-TB[a]**



[a] Figures are based on the most recent year for which data have been reported, which varies among countries.

FIGURE 4.4 **Countries that had notified at least one case of XDR-TB by the end of 2011**



MDR-TB at country level ranged from 0% to 65.1% (Figure 4.3). Countries or subnational areas with the highest reported proportions were Azerbaijan (Baku city, 55.8% in 2007), Belarus (75.6% in 2011), Estonia (57.7% in 2011), Kazakhstan (51.3% in 2011), Kyrgyzstan (51.6% in 2011; preliminary results), the Republic of Moldova (63.5% in 2011), Tajikistan (53.6% in 2011; preliminary results) and Uzbekistan (62.0% in 2011). In the Russian Federation, even if the average proportion of cases with MDR-TB does not exceed 50%, the proportion is above 50% in several oblasts (with Arkhangelsk Oblast at the highest level: 58.8% in 2008).

These data confirm that eastern European and central Asian countries continue to represent hot spots for MDR-TB, with nearly one third of new and two thirds of previously treated TB cases affected by MDR-TB in some settings.

4.1.3 XDR-TB and resistance to second-line anti-TB drugs

Extensively drug-resistant TB (XDR-TB) has been identified in 84 countries globally (Figure 4.4). A total of 65 countries and 3 territories reported representative data from continuous surveillance or special surveys on the proportion of XDR-TB among MDR-TB cases. Combining their data, the proportion of MDR-TB cases with XDR-TB was 9.0% (95% confidence interval, 6.7%–11.2%). Since 2007, only 13 out of 68 (19.1%) countries and territories have reported more than 10 XDR-TB cases in a single year. Among them, the proportion of MDR-TB cases with XDR-TB was highest in Azerbaijan (Baku city, 12.7%), Belarus (11.9%), Estonia (18.7%), Latvia (12.6%), Lithuania (16.5%) and Tajikistan (Dushanbe city and Rudaki district, 21.0%).

The levels of resistance to fluoroquinolones in patients with MDR-TB are described in Box 4.1.

4.2 Management of drug-resistant TB

4.2.1 Coverage of drug susceptibility testing (DST)

The diagnosis of DR-TB requires that TB patients are tested for susceptibility to drugs. The Global Plan to Stop TB 2011–2015 (Chapter 1) includes targets that by 2015 all new cases of TB considered at high risk of MDR-TB (estimated at about 20% of all new bacteriologically-positive cases globally) and all previously treated cases should undergo DST. Likewise, all patients with MDR-TB need to be tested for XDR-TB.

With the exception of the European Region, DST for first-line drugs was done for a small proportion of cases in 2011 (Table 4.1); just over 50% of countries reported data. Coverage of DST in new cases has remained stable in recent years and is below that envisaged by the Global Plan for 2011 (Figure 4.5). Globally, less than 4% of new bacteriologically-positive cases and 6% of previously treated cases were tested for MDR-TB in 2011, with particularly low levels of testing in the African and South-East Asia regions. In the European Region, 56% of new cases and 27% of previously treated cases were tested for MDR-TB. Among the 27 high MDR-TB burden countries – which account for 86% of estimated MDR-TB cases in

BOX 4.1

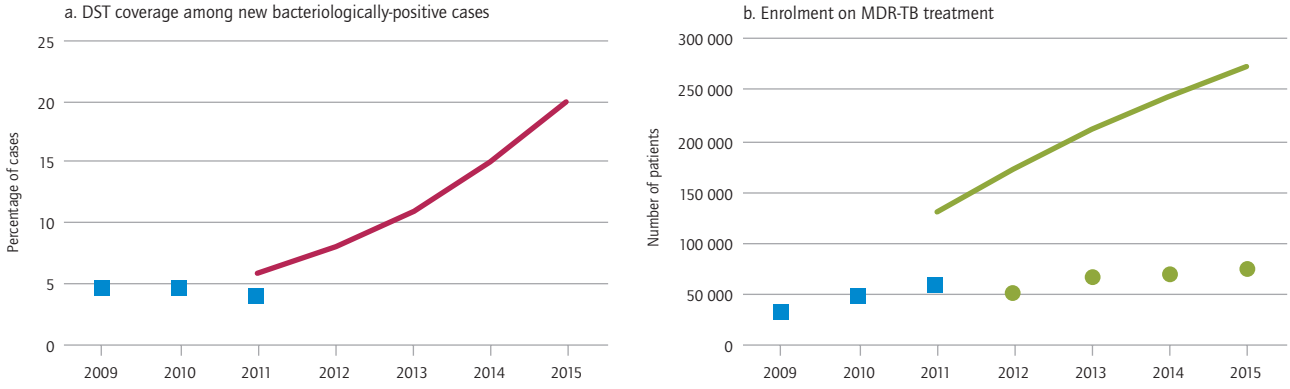
Frequencies of resistance to fluoroquinolones among MDR-TB cases

Fluoroquinolones represent the most powerful class of bactericidal second-line drugs for the treatment of MDR-TB. Patients with MDR-TB and additional resistance to fluoroquinolones have a more serious form of disease compared with those with MDR-TB alone. Their disease is more difficult to treat, and risks evolving into XDR-TB and acquiring resistance to any of the second-line injectable agents.

Monitoring resistance to fluoroquinolones in MDR-TB patients is critical to predict the efficacy of second-line treatment and possibly modify the composition of the treatment regimen. Since 2007, WHO has collected surveillance data on cases of MDR-TB with additional resistance to fluoroquinolones. In most cases, only the compound most commonly used in the country is tested for susceptibility, usually ofloxacin, moxifloxacin or levofloxacin.

A total of 62 countries and 3 territories reported representative data on the proportion of MDR-TB cases that had additional resistance to fluoroquinolones. Combining their data, the proportion of MDR-TB cases with additional resistance to fluoroquinolones was 14.5% (95% confidence interval 11.6–17.4%), inclusive of cases with XDR-TB.

FIGURE 4.5 **DST coverage among new cases and enrolment on MDR-TB treatment, compared with the targets in the Global Plan to Stop TB, 2011–2015.** Lines indicate the planned targets, blue squares show the situation in 2009–2011 and green circles the projected enrolments 2012–2015.



the world – the proportion of cases tested was higher than 20% among new cases in 10 of the 12 European countries reporting data, and exceeded 50% among previously treated cases in six European countries. While data on DST were not available for new and previously treated cases separately, overall 13% of TB cases were tested for drug resistance in South Africa. Among non-European high MDR-TB burden countries, testing for MDR-TB among new cases was highest in China (2.6%); among previously treated cases testing coverage was higher and reached 17% in the Philippines. India, the country estimated to have the highest number of MDR-TB cases among notified TB patients (Figure 4.6), reported no data.

Among TB patients who were notified and confirmed to have MDR-TB in 2011, 23% were reported to have second-line DST for both fluoroquinolones and second-line injectable drugs, and coverage exceeded 90% in Armenia, Estonia, Georgia, Lithuania and Pakistan. South Africa accounted for most of the cases with second-line DST data reported globally, as well as the high level observed in the African Region, which drops from 67% to 9% when excluding this country. Otherwise, second-line DST reports were available for 51% of cases in the Eastern Mediterranean Region, 40% in the Region of the Americas and 8–10% in the other regions.

Progressive acquisition of drug resistance is a considerable risk if TB patients are inadequately tested and treated (see Box 4.2). Increasing the coverage of diagnostic DST is urgently needed to improve the diagnosis of MDR-TB and XDR-TB, and requires strengthening laboratory capacity and the introduction of new rapid diagnostics (for further details, see Chapter 6).

4.2.2 Notification of MDR-TB cases and enrolment on treatment

The suboptimal levels of coverage of DST in many countries are one of the main reasons why the number of people who are diagnosed with MDR-TB remains low. Globally, just under 60 000 cases of MDR-TB were notified to WHO in 2011, mostly by European countries and South Africa (Table 4.2). This represented 19% of the 310 000 (range, 220 000–400 000) cases of MDR-TB estimated to exist among patients with pulmonary TB who were notified in 2011. An additional 4500 rifampicin-

TABLE 4.1 **DST coverage among TB and MDR–TB cases, 27 high MDR-TB burden countries and WHO regions, 2011**

	NEW BACTERIOLOGICALLY POSITIVE CASES		PREVIOUSLY TREATED CASES		CONFIRMED MDR-TB CASES	
	NUMBER WITH DST[a] RESULT	% OF CASES WITH DST RESULT	NUMBER WITH DST[a] RESULT	% OF CASES WITH DST RESULT	NUMBER WITH DST[b] RESULT	% OF CASES WITH DST RESULT
Armenia	439	96	90	23	79	100
Azerbaijan		–		–	0	0
Bangladesh	71	0.1	761	10	0	0
Belarus		–		–	0	–
Bulgaria	588	62	145	41	46	84
China	9 940	2.6		–	46	2.9
DR Congo	22	<0.1	160	2.0	0	0
Estonia	210	100	52	68	75	96
Ethiopia	73	0.1	139	3.0	0	0
Georgia	2 197	83	675	52	440	93
India		–		–	0	0
Indonesia	5	<0.1	695	9.0	88	23
Kazakhstan	5 293	83	4 790	55	0	0
Kyrgyzstan	451	29	232	22	357	44
Latvia	562	96	82	85	95	90
Lithuania	1 031	100	369	100	295	100
Myanmar		–		–	0	0
Nigeria	12	<0.1	76	0.9	14	15
Pakistan		–		–	344	100
Philippines	25	<0.1	2 325	17	0	0
Republic of Moldova	1 379	74	1 006	68	0	0
Russian Federation	34 007	78	13 620	25	0	0
South Africa		–		–	8 072	80
Tajikistan	161	7.4	415	45	122	20
Ukraine		–		–	0	0
Uzbekistan	484	11	123	6.4	834	60
Viet Nam		–		–	0	0
High MDR–TB burden countries	**56 950**	**2.6**	**25 755**	**4.5**	**10 907**	**21**
AFR	1 311	0.2	3 707	2.9	8 272	67
AMR	13 334	10	4 234	20	1 183	40
EMR	2 264	1.2	1 466	6.9	431	51
EUR	69 467	56	25 561	27	2 757	8.5
SEAR	1 200	0.1	1 925	0.5	642	9.7
WPR	25 284	4.2	5 131	6.1	336	7.7
Global	**112 860**	**3.8**	**42 024**	**6.0**	**13 621**	**23**

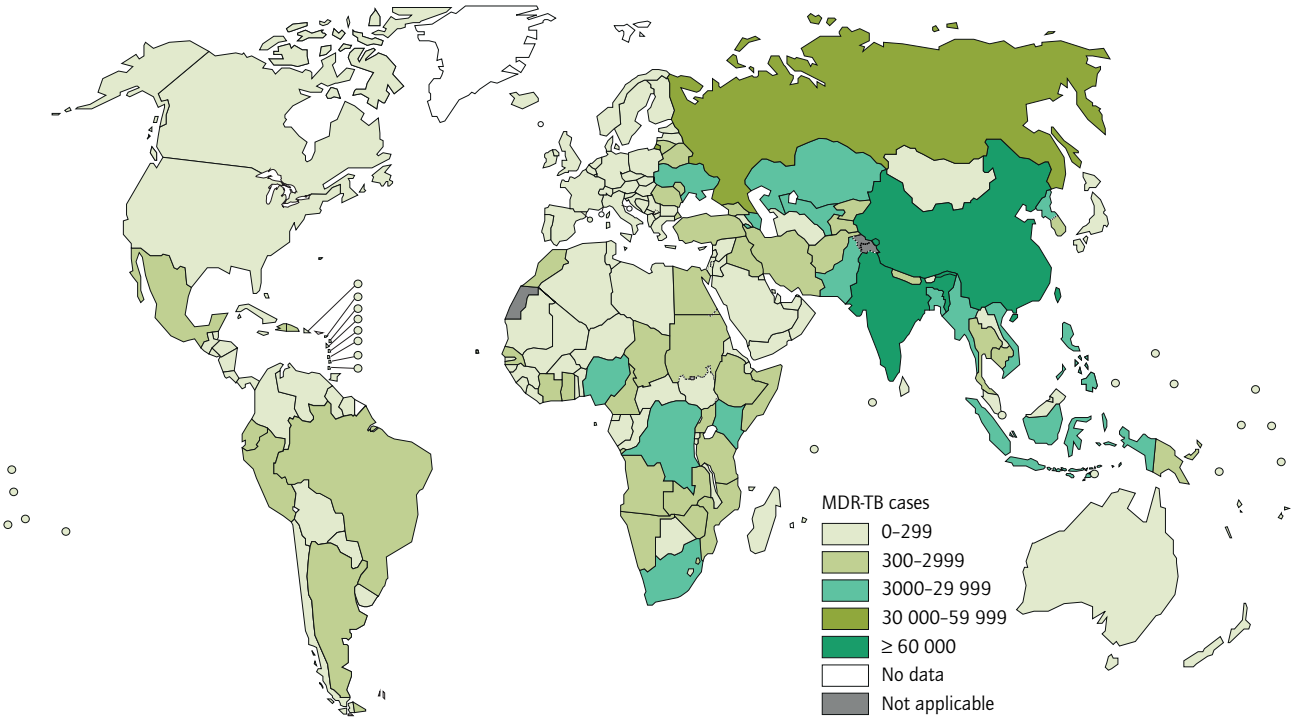
Blank cells indicate data not reported.
– indicates values that cannot be calculated.
[a] DST is for isoniazid and rifampicin.
[b] DST is for a fluoroquinolone and a second-line injectable drug.

resistant cases were reported to have been detected using Xpert MTB/RIF; 80% of these were accounted for by the Philippines and South Africa.[1]

The proportion of TB patients estimated to have MDR-TB that were actually diagnosed was under 20% in almost all of the high MDR-TB countries outside the European Region – including India (6%) and China (3%). The notable exception was South Africa where the numbers reported exceeded the estimated number of cases (**Figure 4.7**). In the Russian Federation, which ranks third in terms of estimated numbers of cases of MDR-TB globally, the proportion of estimated cases that were diagnosed was 31%. Overall, 52/174 countries estimated to have at least one MDR-TB case among notified TB patients reported more than 50% of their expected MDR-TB caseload (2015 target: 100%). Nonetheless, there has been an increase

[1] These are separate from other rifampicin-resistant cases detected by Xpert MTB/RIF, which were included under MDR-TB notifications following subsequent laboratory testing.

FIGURE 4.6 **Number of MDR-TB cases estimated to occur among notified pulmonary TB cases, 2011**



BOX 4.2

"Totally drug-resistant TB" and developments in India in 2012

In December 2011, clinicians in Mumbai, India reported TB patients with what was termed "total drug resistance".[1] As a result of the intense public interest generated by this episode, in March 2012 WHO convened 40 experts to discuss its implications, whether current evidence makes it possible to define patterns of drug resistance beyond extensively drug resistance TB (XDR-TB) and if better guidance on appropriate treatment options for these patients was possible. While the group acknowledged that patients such as those described in Mumbai pose a formidable challenge to clinicians and public health authorities, no reliable definition beyond XDR-TB could be proposed. Without having a better evidence base, no changes to the current guidelines on how to design treatment regimens for patients with broad patterns of resistance could be recommended. Improvements in the accuracy of drug susceptibility testing to certain drugs and the release of innovative new drugs will, however, change this position in future.

Since December 2011, several important measures have been taken by the Indian government. In Mumbai, laboratory and hospital facilities were improved, contact-tracing stepped up and efforts made to train staff on drug-resistant TB and infection control. Medical staff and funding were increased substantially. Access to second-line drugs was provided to eligible patients. National regulations governing private sales of anti-TB medication were strengthened. By the end of 2012, all 35 states in the country are expected to provide programmatic management of drug-resistant TB. In May 2012, India made TB a notifiable disease and data collection on TB using a web-based system was initiated.[2]

[1] Udwadia ZF et al. Totally drug-resistant tuberculosis in India. *Clinical Infectious Diseases*, 2012, 54(4):579–581.

[2] Press Information Bureau English Releases (available from: http://pib.nic.in/newsite/erelease.aspx?relid=83486).

in the total number of MDR-TB cases notified between 2010 and 2011 in 19 of the high MDR-TB countries and in all WHO regions except the Eastern Mediterranean and European regions.

The ratio of notified MDR-TB cases to numbers of patients starting treatment with second-line drug regimens for MDR-TB was almost 1:1 globally, but lower in the African and South-East Asia regions in 2011, possibly reflecting the empiric treatment of TB patients at risk of MDR-TB without a laboratory confirmation or enrolment on treatment of MDR-TB patients detected before 2011 (Table 4.2). Enrolments in the high MDR-TB burden countries nearly doubled between 2009 and 2011 as a result of steady annual increases in 12 of the countries, including India, the Philippines, the Russian Federation, South Africa and Ukraine, each of which reported enrolling more than 2000 patients in 2011. Among 120 countries reporting sex-disaggregated data, the median male:female ratio was 2. Most countries providing MDR-TB enrolment data did not report the inclusion of any

TABLE 4.2 **Notified cases of MDR-TB and enrolments on MDR-TB treatment 2009–2011, projected enrolments 2012–2015 and treatment outcome reporting for 2009 cohort, 27 high MDR-TB burden countries and WHO regions**

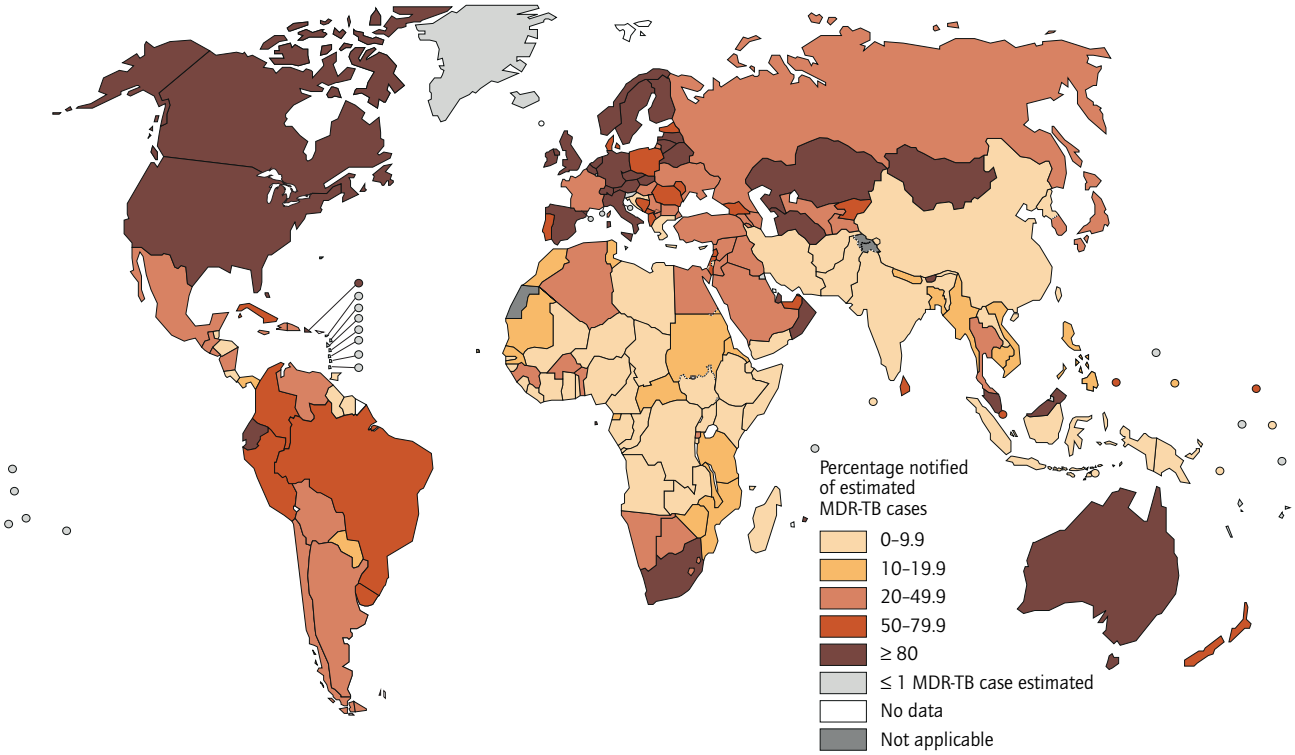
	NOTIFIED CASES			CASES ENROLLED ON MDR-TB TREATMENT			CASES EXPECTED TO BE ENROLLED ON MDR-TB TREATMENT				MDR-TB CASES REPORTED WITH TREATMENT OUTCOME DATA, 2009 COHORT	
	2009	2010	2011	2009	2010	2011	2012	2013	2014	2015	N	%[a]
Armenia	156	177	79	134	154	88	240	200	200		134	86
Azerbaijan		552	722		286	572						–
Bangladesh		339	509	352	339	390	2 597	1 050	1 300	2 000	167	–
Belarus	1 342	1 576			200							–
Bulgaria	43	56	55	43	56	42	60	70	70	70	43	100
China	474	2 792	1 601	458	1 222	1 155	7 237	3 495			260	55
DR Congo	91	87	121	176	191	128	700	800	900	1 000	177	195
Estonia	86	63	78	86	63	75	80	70	65	65	85	99
Ethiopia	233	140	212	88	120	199	1 071	1 714	2 143	2 571	73	31
Georgia	369	359	475	266	618	737	550	540	540	530	503	136
India	1 660	2 967	4 237	1 136	2 967	3 384	15 000	25 000	30 000	32 000	715	43
Indonesia		182	383	20	142	260	900	1 800	1 700		19	–
Kazakhstan	3 644	7 387	7 408	3 209	5 705	5 261		6 280	7 000	7 000	7 579	208
Kyrgyzstan	785	566	806	545	566	492		1 100	1 000		545	69
Latvia	131	87	105	124	87	103	125	125	125	125	131	100
Lithuania	322	310	296	322	310	296					322	100
Myanmar	815	192	690	64	192	163	400	400	400	400	64	7.9
Nigeria	28	21	95	0	23	38	220	400	450	550		–
Pakistan	49	444	344	368	424	344	1 115	2 900	5 300	6 360	74	151
Philippines	1 073	522	1 148	501	548	2 397	2 372	2 372	2 237	2 237	394	37
Republic of Moldova	1 069	1 082	1 001	334	791	765						–
Russian Federation	14 686	13 692	13 785	8 143	13 692	18 902						–
South Africa	9 070	7 386	10 085	4 143	5 402	5 643					4 654	51
Tajikistan	319	333	604	52	245	380	230	800	800	800	52	16
Ukraine	3 482	5 336	4 298	3 186	3 870	4 950					3 238	93
Uzbekistan	654	1 023	1 385	464	628	855	1 865	2 155			464	71
Viet Nam	217	101	601	307	101	578	950	1 100	1 300	1 500	101	47
High MDR-TB burden countries	**40 798**	**47 772**	**51 123**	**24 521**	**38 942**	**48 197**	**35 712**	**52 371**	**55 530**	**57 208**	**19 794**	**49**
AFR	10 741	9 340	12 384	5 994	7 209	7 467	4 409	5 735	6 645	7 539	6 143	57
AMR	2 884	2 661	2 969	3 153	3 249	3 087	3 435	3 684	3 404	5 551	2 340	81
EMR	496	886	841	707	976	756	3 293	3 937	6 499	7 770	511	103
EUR	28 157	33 863	32 348	17 169	28 336	34 769	4 023	12 262	10 073	8 863	14 158	50
SEAR	2 560	3 937	6 615	2 040	3 901	4 572	20 856	30 217	35 374	36 373	1 140	45
WPR	2 059	4 295	4 392	1 422	2 210	4 946	11 102	7 553	4 167	4 440	1 027	50
Global	**46 897**	**54 982**	**59 549**	**30 485**	**45 881**	**55 597**	**47 118**	**63 388**	**66 162**	**70 536**	**25 319**	**54**

Blank cells indicate data not reported.

– indicates values that cannot be calculated.

[a] The percentage of MDR-TB cases originally notified in 2009 with outcomes reported. Percentage may exceed 100% as a result of updated information about MDR-TB cases in 2009, absence of linkage between notification systems for TB and MDR-TB, and the inclusion in the treatment cohort of cases of MDR-TB cases from a year prior to 2009.

FIGURE 4.7 **Notified cases of MDR-TB as a percentage of MDR-TB cases estimated to occur among notified pulmonary TB cases, 2011[a]**



[a] MDR-TB notifications from 2010 are used for 18 countries with missing 2011 data.

children; in the 37 that did, children represented 1–13% of total enrolments.

While the absolute numbers of TB cases notified with MDR-TB and started on second-line treatment remain low compared with the Global Plan's targets, enrolments increased by 21% globally between 2010 and 2011 (**Figure 4.5**). Country plans envisage increased enrolments between 2012 and 2015, although numbers remain well below targets, partly as a result of incomplete information on forecasts in countries with large burdens, such as China, the Russian Federation and South Africa. To reach the targets set out in the Global Plan and advance towards universal access to treatment, a bold and concerted drive will be needed on many fronts of TB care, particularly in the countries where the highest burden is located.

4.2.3 Treatment outcomes for MDR-TB and XDR-TB

Standardized monitoring methods and indicators have allowed countries to report MDR-TB treatment outcomes in a comparable manner for several years.[1] In most cases, treatment of MDR-TB lasts 20 months or longer, and requires daily administration of drugs that are more toxic and less effective than those used to treat drug-susceptible forms of TB. In a few countries, shorter treatment regimens are being used to treat patients with MDR-TB (**Box 4.3**).

A total of 107 countries reported outcomes for more than 25 000 MDR-TB cases started on treatment in 2009 (**Table 4.2**; **Figure 4.8**). This is equivalent to 54% of the number of MDR-TB cases notified by countries in the same year. The Global Plan envisages that by 2015, all countries will report outcomes for all notified MDR-TB cases. In contrast, among 117 countries reporting at least one case of MDR-TB in 2009, 60 overall – including 10 high MDR-TB burden countries – reported outcomes for a cohort whose size exceeded 80% of original notifications.

The proportion of MDR-TB patients who successfully completed treatment varied from 44% (Eastern Mediterranean Region) to 58% (South-East Asia Region). Deaths were highest in the African Region (19%) and the proportion of patients whose treatment failed was highest in the European Region (12%). Overall, treatment success was 48%, while 28% of cases were reported as lost to follow-up or had no outcome information. Among a subset of 200 XDR-TB patients in 14 countries, treatment success was 33% overall and 26% died. The Global Plan's target for 2015 of achieving at least 75% treatment success in MDR-TB patients was only reached by 30/107 countries. Moving towards the target for treatment success requires enhancing and scaling up the currently available drug

[1] These methods and indicators are defined in *Guidelines for the programmatic management of drug-resistant tuberculosis, Emergency update 2008*. Geneva, World Health Organization, 2008 (WHO/HTM/TB/2008.402). It is anticipated that revised definitions of treatment outcomes will be released in 2013 following piloting in several countries.

BOX 4.3

Treatment regimens for MDR-TB lasting up to 12 months

WHO's guidelines on treatment of MDR-TB recommend an intensive phase of 8 months and a total duration of 20 months in most patients.[1] While these recommendations are conditional, they are based on >9000 cases treated in observational studies.[2] There is much less evidence on the effectiveness and safety of regimens of substantially reduced duration and different drug composition, which have been termed short-regimens. One observational study from Bangladesh using shorter regimens yielded much higher treatment success than is usually achieved with the longer regimens, and for this reason has generated much interest in the scientific community.[3]

WHO's position is that regimens which are markedly different from those that make up the current norm should be used only within the context of research and under close monitoring of the clinical and bacteriological response to treatment for a period of at least 12 months after treatment is completed. One of the major concerns is that patients who do well after 9–12 months of treatment with less drugs in the continuation phase than in the longer regimen may have a higher risk of acquiring resistance in the process and relapsing. Proper attention to regulatory and ethical issues will be needed to facilitate gathering evidence for use in future updates of policy and standards. Until sufficient evidence is available to inform a change in policy, WHO is advising countries on a case-by-case basis to introduce short MDR-TB regimens in projects where:

- treatment is delivered under operational research conditions following international standards (including Good Clinical Practice and safety monitoring), with the objective of assessing the effectiveness and safety of these regimens;
- the project is approved by a national ethics review committee, ahead of any patient enrolment; and
- the programmatic management of DR-TB and the corresponding research project are monitored by an independent monitoring board set up by, and reporting to, WHO.

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1 *Guidelines for the programmatic management of drug-resistant tuberculosis*, 2011 update. (WHO/HTM/TB/2011.6). Geneva, World Health Organization, 2011.

2 Ahuja SD et al. Multidrug Resistant Pulmonary Tuberculosis Treatment Regimens and Patient Outcomes: An Individual Patient Data Meta-analysis of 9,153 Patients. *PLoS Med*. 2012, 9(8):e1001300.

3 Van Deun A et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *American Journal of Respiratory and Critical Care Medicine*, 2010, 182(5): 684–692.

BOX 4.4

MDR-TB and mortality

The national surveillance data included in this report show that in all WHO regions a much larger proportion of patients in the MDR-TB cohorts die compared with the overall TB patient cohorts (**Figure 4.8**; see also **Table 3.5** and **Table 3.6** in **Chapter 3**). MDR-TB has been described as an independent risk factor for dying even after adjustment for potential confounders.[1,2]

Data on TB mortality for 2011 from vital registration systems (which exclude deaths attributed to HIV) and data from drug resistance surveillance on the proportion of TB patients with MDR-TB (among those not previously treated for TB) were analysed to explore the relationship between these variables. There was no association between TB mortality rates and the proportion of TB patients with MDR-TB level in high-income countries ($p=0.3$) but there was a positive and significant association in low and lower middle-income countries ($p<0.001$). The positive association remained after adjusting for differences in the age-structure of the population and the prevalence of HIV-related TB.

Variations in the mortality to total TB notification (M:N) ratio observed in the European region, with high levels in the Russian Federation (M:N ratio of 20%), lower levels in Estonia, Latvia and Lithuania (11%) and even lower levels in the high-income western European countries, may reflect the impact of differences in the burden of drug-resistant TB and in the effectiveness of efforts to treat MDR-TB.

Analysis of TB mortality data, despite inherent limitations, may help to improve understanding of the different determinants of death in TB patients, such as MDR-TB. Further exploration of these data is warranted.

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1 Low S et al. Mortality among tuberculosis patients on treatment in Singapore. *Int J Tuberc Lung Dis*, 2009, 13(3):328-34.

2 Mathew TA et al. Causes of death during tuberculosis treatment in Tomsk Oblast, Russia. *Int J Tuberc Lung Dis*, 2006, 10(8):857-63.

regimens globally, providing more support that helps patients adhere to treatment and improving data collection, including TB mortality statistics (Box 4.4).

4.2.4 Other aspects of MDR-TB programme management

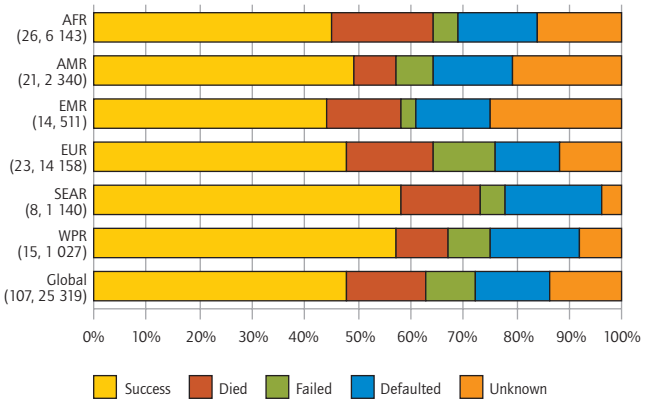
In the course of their illness, patients with MDR-TB may be cared for as outpatients or in hospitals, usually secondary or tertiary facilities. WHO recommends that where possible patients with MDR-TB are treated using ambulatory care rather than models of care based principally on hospitalization. National policies differ in the predominant model of care that is employed. Among the high MDR-TB burden countries, those in Eastern Europe hospitalize 75–100% of patients except for the central Asian countries (Kazakhstan, Tajikistan and Uzbekistan; 30–71%). In the African Region, there is very wide variation in hospitalization, from 10% of patients (Democratic Republic of the Congo) to much higher levels of 70% (South Africa) and >95% (Ethiopia and Nigeria). The average duration of hospital stay ranged from 7 to 240 days (median: 90 days). The number of visits to a health facility after diagnosis of MDR-TB also differed markedly among countries from less than 25 (Bangladesh, Estonia, Georgia, Pakistan, South Africa and Viet Nam) to over 600 (Bulgaria, Indonesia and Latvia).

Palliative and end-of-life care delivered through home-based or institutional services is important for patients with advanced disease that is not responding to treatment. Nine of the European high MDR-TB burden countries plus South Africa reported providing such care within the scope of the TB control programme.

Among 14 high MDR-TB burden countries providing information on the quality of second-line drugs in the public sector, most reported conformity to international standards in all or some supplies of kanamycin (12/14), capreomycin (9/11, with 3 other countries not using it), levofloxacin (10/12, with 2 others not using it), ethionamide/prothionamide (12/14) and *p*-aminosalicylic acid (9/11, with 3 others not using it). Two countries reported that all their drugs conformed only to national regulatory norms.

The information needed to adequately monitor TB patients, and in particular those on MDR-TB treatment, is substantial. The use of electronic systems as a tool to manage data is therefore strongly encouraged (see also Box 2.5). One of the Global Plan's targets is that all 27 high MDR-TB countries manage their data on treatment of MDR-TB patients electronically by 2015. By 2011, 20 reported that national databases were in place for MDR-TB patients, but none were available in Bangladesh, India (see also Box 4.2), Myanmar, Nigeria, the Russian Federation, Ukraine and Viet Nam.

FIGURE 4.8 Treatment outcomes for patients diagnosed with MDR-TB by WHO region, 2009 cohorts.
The number of countries reporting outcomes for at least one case, followed by total cases with outcome data, shown beside each bar.



CHAPTER 5

Financing TB care and control

KEY FACTS AND MESSAGES

- The Global Plan to Stop TB 2011–2015 sets out the funding needed for implementation of TB care and control in low and middle-income countries. From 2013 to 2015, up to US$ 8 billion per year is required. In 2015, about US$ 5 billion is needed for the diagnosis and treatment of drug-susceptible TB, US$ 2 billion for diagnosis and treatment of MDR-TB and almost US$ 1 billion for TB/HIV interventions.
- In 2013 funding is expected to reach US$ 4.8 billion in 104 low- and middle-income countries (94% of global cases) that reported data to WHO. These amounts generally exclude funding for TB/HIV interventions, notably ART, that are funded via HIV programmes. Thus, an extra US$ 2–3 billion per year is needed from national and international sources by 2015.
- There is capacity to mobilize increased funding from domestic sources in low and middle-income countries, especially in Brazil, the Russian Federation, India, China and South Africa (BRICS) that already rely entirely or mostly on national contributions. Increased domestic funding in BRICS will be especially critical for scaling up the diagnosis and treatment of MDR-TB.
- International donor funding of up to US$ 1 billion per year is needed for low and middle-income countries 2013–2015 to close funding gaps. This is double the amount of US$ 0.5 billion expected in 2013 but still much less than the amounts being mobilized for malaria (US$ 2.0 billion in 2010) and HIV (US$ 6.9 billion in 2010).
- International donor funding is especially critical to safeguard recent gains in TB care and control and enable further progress in low-income countries and in the group of 17 HBCs outside BRICS. In these country groups, it provides >60% and about one third of total funding, respectively.
- Of the international donor funding expected by national TB control programmes in 2013, 88% is from the Global Fund. In the absence of any other major streams of international donor funding for TB, the Global Fund has a crucial role in sustaining and ensuring further progress in TB care and control worldwide.
- The cost per person successfully treated for TB with first-line drugs is in the range US$ 100 to US$ 500 in almost all countries with a high burden of TB.

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 2013. This chapter focuses on the years 2006–2013, during which trends can be assessed for 104 low- and middle-income countries that collectively account for 94% of the world's TB cases.

Trends in total funding are broken down by country group (**Section 5.1**), category of expenditure (**Section 5.2**) and sources of funding (**Section 5.3**), highlighting striking variations in countries' reliance on donor funding. **Section 5.4** compares funding for TB care and control with total government expenditures on health care. **Section 5.5** presents estimates of the cost per patient successfully treated with first-line drugs, as well as the total reported funding and unit cost per person for first-line and second-line anti-TB drugs. **Section 5.6** describes the funding gaps reported by countries. The final part of the chapter (**Section 5.7**) assesses the gap between projections of potential funding from domestic sources and the funding requirements specified in the Global Plan.

Further details for each of the 104 countries and a few additional countries for which trends could not be assessed for the entire period 2006–2013 are provided in country finance profiles that are available online.[1]

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

5.1 Funding for TB care and control by country group, 2006–2013

In the 104 countries for which trends in TB funding since 2006 can be assessed and that report 94% of the world's TB cases (listed in Table 5.1), funding is expected to reach US$ 4.8 billion in 2013 (Figure 5.1). This is an increase in real terms from US$ 3.4 billion in 2006 and a small increase from US$ 4.6 billion in 2012.

Brazil, the Russian Federation, India, China and South Africa (BRICS), which report 48% of the world's TB cases (Chapter 3), account for US$ 3 billion (63%) of the expected total of US$ 4.8 billion in 2013 (Figure 5.1). The other 17 high TB burden countries (HBCs) outside BRICS (listed in Table 5.2), which report 34% of the world's TB cases, account for US$ 0.6 billion. A group of 10 European countries other than the Russian Federation accounts for a further US$ 0.5 billion (80% of which is accounted for by three countries: Romania, Turkey and Uzbekistan).

Patterns of funding for multidrug-resistant TB (MDR-TB) specifically are different, as described in Box 5.1.

5.2 Funding for TB care and control by category of expenditure, 2006–2013

In each year 2006–2013, the largest share of funding has been used for the diagnosis of TB and treatment with first-line drugs (all categories of expenditure except those labelled MDR-TB in Figure 5.2 and Figure 5.4). However, funding for the diagnosis and treatment of MDR-TB has been increasing and is expected to exceed US$ 0.7 billion in 2013 (Figure 5.2). Much of the increase is accounted for by BRICS, but allocations are increasing in other HBCs and the rest of the world as well (Figure 5.4).

The relatively small amounts of funding reported for collaborative TB/HIV activities (see Chapter 7 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).

5.3 Funding for TB care and control by source of funding, 2006–2013

Domestic funding from national governments is the single largest source of funding for TB care and control (Figure 5.3), accounting for 90% of total expected funding in 2013.[1] Of the remaining 10% that is expected from donor sources in 2013, most (88%) is accounted for by

[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).

FIGURE 5.1 **Funding for TB care and control in 104 countries reporting 94% of global cases, by country group, 2006–2013**

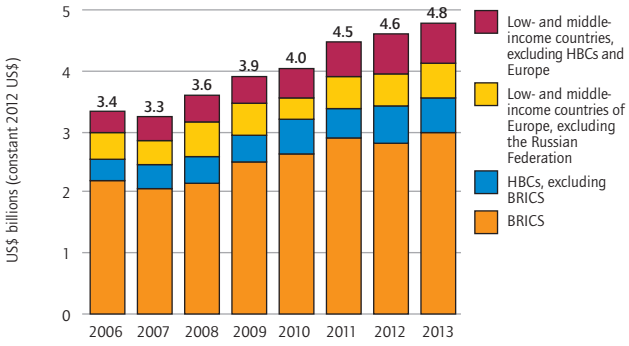
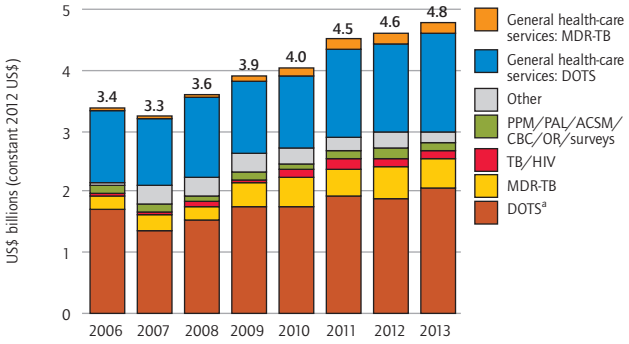


FIGURE 5.2 **Funding for TB care and control in 104 countries reporting 94% of global cases, by line item, 2006–2013**



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

FIGURE 5.3 **Funding for TB care and control in 104 countries reporting 94% of global cases, by source, 2006–2013**

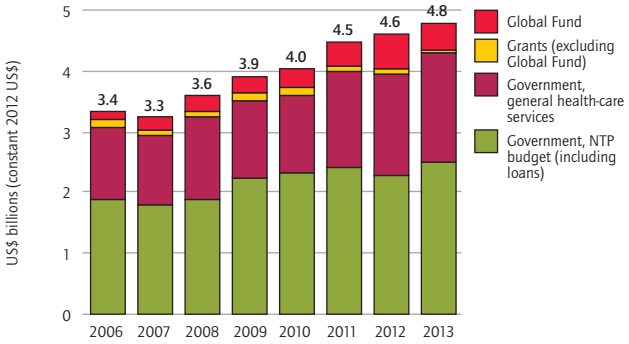
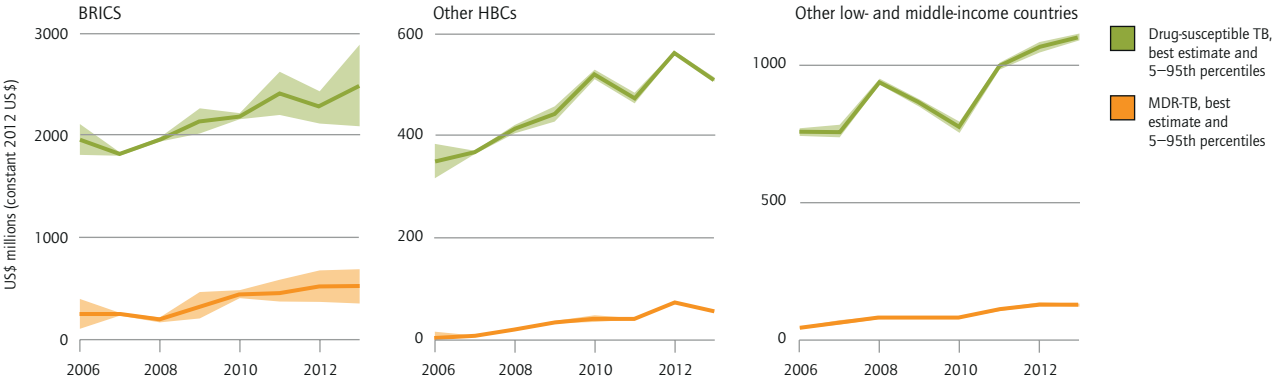


TABLE 5.1 104 countries for which trends in TB funding could be assessed, by income group and WHO region, 2006–2013[a]

WHO REGION	LOW-INCOME (GNI PER CAPITA US$ 1025 IN 2011)	LOWER MIDDLE-INCOME (GNI PER CAPITA US$ 1026–4035 IN 2011)	UPPER MIDDLE-INCOME (GNI PER CAPITA US$ 4036–12 475 IN 2011)
African	Benin, Burkina Faso, Burundi, Central African Republic, Chad, Democratic Republic of the Congo, Eritrea, Ethiopia, Gambia, Guinea-Bissau, Kenya, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique, Niger, Rwanda, Sierra Leone, Togo, Uganda, United Republic of Tanzania, Zimbabwe	Cameroon, Cape Verde, Congo, Côte d'Ivoire, Ghana, Lesotho, Nigeria, Sao Tome and Principe, Senegal, Swaziland, Zambia	Botswana, Gabon, Namibia, South Africa
Americas	Haiti	Bolivia (Plurinational State of), El Salvador, Guatemala, Guyana, Honduras, Nicaragua, Paraguay	Argentina, Brazil, Colombia, Dominican Republic, Ecuador, Jamaica, Mexico, Panama, Suriname, Venezuela (Bolivarian Republic of)
Eastern Mediterranean	Afghanistan, Somalia	Djibouti, Egypt, Morocco, Pakistan, Sudan, Yemen	Iran (Islamic Republic of), Jordan, Lebanon, Tunisia
European		Armenia, Georgia, Republic of Moldova, Uzbekistan	Bulgaria, Latvia, Montenegro, Romania, Russian Federation, Serbia, Turkey
South-East Asia	Bangladesh, Myanmar, Nepal	Bhutan, India, Indonesia, Sri Lanka, Timor-Leste	Maldives, Thailand
Western Pacific	Cambodia	Kiribati, Lao People's Democratic Republic, Micronesia (Federated States of), Mongolia, Papua New Guinea, Philippines, Solomon Islands, Tonga, Vanuatu, Viet Nam	China, Malaysia, Tuvalu

[a] Another 11 low- and lower middle-income countries with data available for the years 2011–2013 were included in the analyses of Figure 5.12: **low-income, African**: Guinea; **low-income, European**: Kyrgyzstan, Tajikistan; **low-income, South-East Asia**: Democratic People's Republic of Korea; **lower middle-income, Americas**: Belize; **lower middle-income, Eastern Mediterranean**: Iraq, Syrian Arab Republic, West Bank and Gaza Strip; **lower middle-income, European**: Ukraine; **lower middle-income, Western Pacific**: Fiji, Marshall Islands.

FIGURE 5.4 Funding for drug-susceptible TB[a] and MDR-TB,[b] 2006–2013, by country group



[a] Costs include first-line drugs, NTP staff, programme management and supervision, laboratory equipment and supplies, hospital stays and clinic visits.
[b] Costs include second-line drugs, programme management and supervision, hospital stays and clinic visits.

TABLE 5.2 NTP budgets, available funding, cost of utilization of general health-care services and total funding required for TB care and control, 2013 (current US$ millions)[a,b]

	NTP BUDGET REQUIRED	AVAILABLE FUNDING			REPORTED FUNDING GAP	COST OF GENERAL HEALTH-CARE SERVICES (ESTIMATED)	TOTAL FUNDING REQUIRED	% OF DOMESTIC FUNDING IN NTP BUDGET	% OF DOMESTIC FUNDING IN TOTAL AVAILABLE[c]
		GOVERNMENT (INCLUDING LOANS)	GLOBAL FUND	GRANTS (EXCLUDING GLOBAL FUND)					
Afghanistan	11	0.4	2.2	1.1	7.2	2.8	14	10	30
Bangladesh	50	1.2	15	0	34	3.2	54	7.1	15
Brazil	86	70	0	0.1	16	22	108	100	100
Cambodia	25	1.1	2.9	4.8	17	6.8	32	12	31
China	341	239	48	0	55	0	341	83	83
Democratic Republic of the Congo	14	0	8.6	0	5.2	0.2	14	0	1.1
Ethiopia	52	0	13	0	39	12	64	0	24
India	207	120	81	5.7	0	93	300	58	71
Indonesia[d]	117	2.7	29	0	85	39	156	8.5	59
Kenya	51	8.6	3.6	3.5	36	9.5	61	55	64
Mozambique	35	1.9	3.7	2.5	27	6.7	42	24	41
Myanmar	31	0.7	8.3	0.3	22	6.6	38	7.5	27
Nigeria	39	8.7	12	8.3	10	17	57	30	56
Pakistan	52	0	17	0	35	12	63	0	41
Philippines	78	28	0	0	50	98	176	100	100
Russian Federation								–	–
South Africa								–	–
Thailand	44	40	1.0	0	2.7	3.5	48	98	98
Uganda								–	–
United Republic of Tanzania	57	7.6	4.6	2.8	42	1.9	59	51	53
Viet Nam	63	5.6	13	0	45	49	113	31	81
Zimbabwe	38	2.8	7.5	3.5	24	17	54	20	42
22 high-burden countries[e]	**1 390**	**538**	**270**	**33**	**549**	**401**	**1 791**	**64**	**73**
AFR	821	383	129	38	272	680	1 501	70	85
AMR	177	123	15	1.5	37	170	347	88	95
EMR	126	32	44	1.9	48	65	192	41	66
EUR	1 590	1 547	30	0	14	522	2 227	98	99
SEA	479	181	145	6.5	146	162	642	54	68
WPR	541	293	69	6.1	173	225	765	80	87
Low income	467	37	125	24	283	85	551	20	32
Lower middle income	831	264	250	27	291	517	1 348	49	74
Upper middle income	2 435	2 257	57	3.2	117	1 221	3 774	97	98
Low- and middle-income countries	**3 733**	**2 558**	**431**	**54**	**691**	**1 823**	**5 673**	**84**	**89**

Blank cells indicate data not reported.

– indicates values that cannot be calculated.

[a] Values in this table may differ from those presented in the figures of this chapter, as they have not been adjusted to constant 2012 US$.

[b] Region, income group and global totals include estimates for those countries that did not report data for 2013.

[c] Total available is the sum of funding available in the NTP budget plus the cost of general health-care services. In low-income countries, the percentage of general health-care services cost that is domestically funded is assumed to equal the midpoint between the percentage of NTP funding from domestic sources and 100%. In all other countries it is assumed to equal 100%. Sensitivity to this assumption is analyzed in Figure 5.5.

[d] Indonesia was not able to report funding expected from provincial and district budgets in 2013; these numbers reflect only the central government's expected contribution.

[e] These totals do not include estimates for countries that did not report data for 2013 (Russian Federation, South Africa and Uganda).

BOX 5.1

Funding for diagnosis and treatment of MDR-TB, 2009–2013

The geographical distribution of MDR-TB cases differs considerably from that of all TB cases. Of the estimated 310 000 MDR-TB cases among notified pulmonary TB cases in 2011, almost 60% were accounted for by three countries: (in rank order) India, China and the Russian Federation (**Chapter 4**). Of the 27 high MDR-TB burden countries that account for about 85% of estimated cases globally, 15 are in the European Region, where the prevalence of MDR-TB among new and previously treated cases is highest (ranging from 9%–32% in new cases and 29%–76% among previously treated cases). The costs of diagnosing and treating MDR-TB are also much higher than the costs of diagnosing and treating drug-susceptible TB. The regimens recommended in WHO guidelines, which last 20 months for most patients, can cost several thousands of US dollars. Other costs associated with patient care are also high.[1]

The funding available for MDR-TB treatment in the 104 countries that reported financial data, and which have 75% of the world's estimated cases of MDR-TB, increased from US$ 0.5 billion in 2009 to US$ 0.6 billion in 2011 (**Table B5.1.1**).[1] This figure is expected to increase to more than US$ 0.7 billion in 2012 and 2013. NTP spending on second-line drugs and programme management accounts for about three quarters of the total. Second-line drugs alone now amount to more than US$ 0.3 billion per year. The remaining funding (about US$ 0.2 billion) is channelled through general health-care services (GHS) for inpatient and outpatient treatment of patients with MDR-TB.

TABLE B5.1.1
Funding available and reported gaps for MDR-TB in 104 low- and middle-income countries, US$ millions

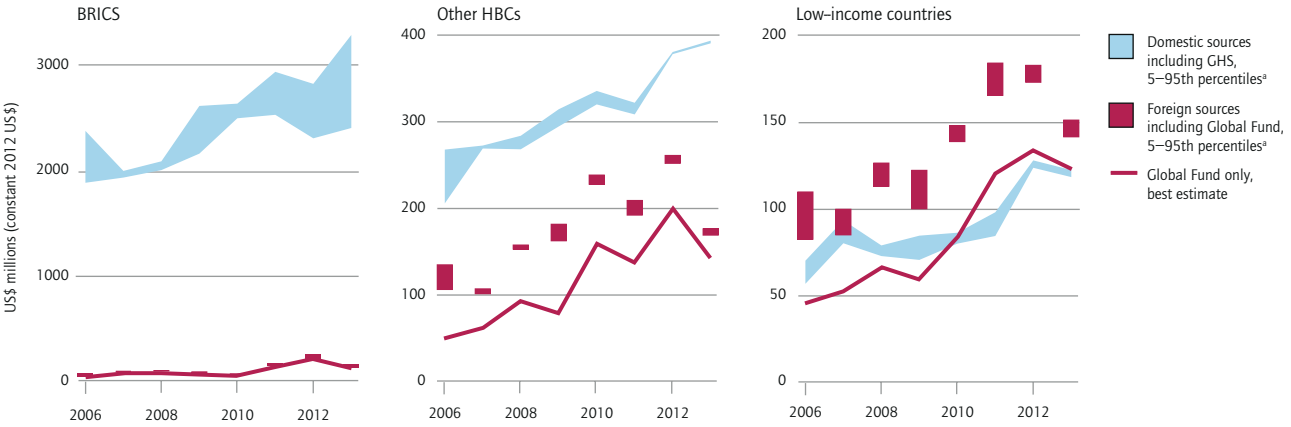
		2009	2010	2011	2012	2013
Low- and middle-income countries	Available funding[a]	450	566	615	719	705
	Avaliable (NTP only)[b]	353	445	443	541	523
	Avaliable (GHS only)	97	121	172	178	183
	% domestic[c]	*89*	*90*	*85*	*71*	*78*
	Reported gap	117	58	81	115	84
High MDR-TB burden countries	Available funding[a]	384	490	526	610	600
	Avaliable (NTP only)[b]	315	409	408	492	472
	Avaliable (GHS only)	68	81	118	119	128
	% domestic[c]	*90*	*91*	*85*	*70*	*77*
	Reported gap	109	42	58	94	61
Upper middle-income countries	Available funding[a]	387	501	513	533	521
	Avaliable (NTP only)[b]	307	400	373	389	374
	Avaliable (GHS only)	80	101	140	144	148
	% domestic[c]	*95*	*97*	*93*	*86*	*92*
	Reported gap	99	6	11	67	8
Lower middle-income countries	Available funding[a]	48	54	82	158	162
	Avaliable (NTP only)[b]	33	35	53	128	131
	Avaliable (GHS only)	15	19	28	30	31
	% domestic[c]	*57*	*42*	*46*	*32*	*40*
	Reported gap	11	38	49	26	42
Low-income countries	Available funding[a]	14	11	20	28	21
	Avaliable (NTP only)[b]	13	9	16	24	18
	Avaliable (GHS only)	1	2	3	4	3
	% domestic[c]	*38*	*29*	*34*	*26*	*31*
	Reported gap	6	15	22	23	33

GHS, general health-care services for hospital stays and clinic visits; MDR-TB, multidrug-resistant TB; NTP, national TB control programme or equivalent
[a] Includes funding for second-line drugs, MDR-TB programme management and supervision and estimated cost of GHS for patients with MDR-TB.
[b] Includes funding for second-line drugs, MDR-TB programme management and supervision only.
[c] Assumes GHS is domestically funded.

About 85% of the funding available is concentrated in the high MDR-TB burden countries, in particular upper middle-income countries. In absolute terms, China and India have the largest external grants for MDR-TB, at US$ 41 million and US$ 43 million respectively from the Global Fund in 2013. Meanwhile, low-income and lower middle-income countries report a funding gap of US$ 75 million in 2013, leaving almost one third of their budgets for MDR-TB unfunded.

[1] Fitzpatrick C, Floyd K. A systematic review of the cost and cost effectiveness of treatment for multidrug-resistant tuberculosis. *Pharmacoeconomics*, 2012, 30:63–80.

FIGURE 5.5 **Trends in domestic and donor funding for TB care and control, 2006–2013, by country group[a]**



[a] In probabilistic sensitivity analysis, the percentage of GHS costs that is domestically funded in low-income countries is assumed to follow a uniform distribution, ranging from the percentage of NTP funding from domestic sources up to 100%.

grants from the Global Fund (Table 5.2). Funding reported by NTPs from other donor sources amounts to only US$ 54 million in 2013, although bilateral and multilateral funds are not always channelled through NTPs. For example, donors may provide funding directly to nongovernmental organizations and to technical agencies. Recent data on technical assistance compiled by TB-TEAM (TB Technical Assistance Mechanism) are provided in Box 5.2.

International donor funding for TB care and control has increased from US$ 0.2 billion in 2006 to almost US$ 0.5 billion in 2013, but still falls short of funding for malaria (US$ 2.0 billion in 2010)[1] and HIV (US$ 6.9 billion in 2010).[2]

Global statistics on sources of funding conceal important variations in the extent to which countries rely on domestic and donor financing (Figure 5.5, Figure 5.6, Table 5.2). Differences among BRICS, the other 17 HBCs and the group of low-income countries are especially striking (Figure 5.5). In BRICS, domestic funding has consistently accounted for most of the funding for TB care and control (for example, >95% in 2012 and 2013), although India is an outlier at 71% in 2013. In the other 17 HBCs (listed in Table 5.2), the share of total funding from donor sources was in the range 28–41% between 2006 and 2013. The group of low-income countries (24 African countries as well as Afghanistan, Bangladesh, Cambodia, Haiti, Myanmar, Nepal and Somalia) are most reliant on donor funding: for example, in 2012, 59% of total funding was from donor sources. In 2013, ≥70% of available funding will be from donor sources in five HBCs: Afghanistan, Bangladesh, the Democratic Republic of the Congo, Ethiopia and Myanmar (Table 5.2).

Throughout the period 2006–2011, donor funding exceeded domestic funding in low-income countries, and in 2010 and 2011 financing from the Global Fund alone exceeded domestic contributions. The data reported in 2012 suggest that this pattern will persist in 2012 and 2013. The Global Fund has a crucial role in sustaining and ensuring further progress in TB care and control.

Of particular concern is the expectation that donor funding will be lower in 2013 compared with 2012 in the 17 HBCs outside BRICS and low-income countries (current data suggest decreases of up to 33% and 18%, respectively). Donor funding is essential to safeguard recent gains in TB control in the 17 HBCs outside BRICS and low-income countries.

5.4 Funding for TB care and control compared with total government expenditures on health care

In general, spending on TB control as a proportion of public sector health expenditures[3] is relatively low (Figure 5.7). In most countries, TB control accounts for less than 3% of public health expenditures. Countries with higher levels of spending on TB relative to total government expenditures on health are mostly in Africa, eastern Europe (for example, Ukraine) or central Asia. Part of the explanation for countries in eastern Europe and central Asia is comparatively high levels of MDR-TB (see Chapter 4), which is more expensive to treat. 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[4] and 96%

[1] *World malaria report 2011*. Geneva, World Health Organization, 2011.

[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* (also available at www.unaids.org).

[3] 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 2012.

[4] For case definitions, see Chapter 3.

BOX 5.2

Technical assistance for TB care and control

The Global Plan to Stop TB 2011–2015 highlights the important role of technical assistance to NTPs. The funding required over five years was estimated at US$ 2.1 billion, or approximately US$ 400 million per year.

The TB Technical Assistance Mechanism (TB-TEAM) of the Stop TB Partnership was established in 2007 to monitor and coordinate the provision of technical assistance to NTPs. The secretariat function is carried out by WHO's Stop TB Department. Requests from countries for technical assistance are matched to appropriate technical partners via the TB-TEAM web site. Technical partners are expected to provide information about the purpose of the mission, the dates of travel, funding sources and a mission report via the website. All technical partners are invited to review and comment on quarterly and annual analyses of data.

TABLE B5.2.1
Number of missions conducted by technical partners and reported to TB-TEAM, 2011

PROVIDER OF TECHNICAL ASSISTANCE	NUMBER OF MISSIONS IN 2011	% OF TOTAL
WHO regional offices	126	20
The Union	86	13
KNCV Tuberculosis Foundation	67	10
Centers for Disease Control and Prevention (CDC), USA	60	9
WHO headquarters	55	9
Global Drug Facility	39	6
WHO country offices	35	5
Grant Management Solutions (GMS) project	33	5
NTP/national TB-TEAM	25	4
TB-REACH	19	3
Other	100	16
Total	**645**	**100**

In 2011, 645 missions were completed and reported to TB-TEAM (Table B5.2.1). About one third of recorded missions were organized by WHO, mainly by regional offices, and one third by the Union, the KNCV Tuberculosis Foundation and the United States Centers for Disease Control and Prevention (CDC).

In 2011, the main technical areas for which assistance was provided were MDR-TB and XDR-TB; monitoring and evaluation linked to impact measurement; the grant processes of the Global Fund; review missions; and laboratory strengthening (Table B5.2.2). The data also show that the number of missions fell between 2009 and 2011. This downward trend occurred among most major technical partners, including WHO, the KNCV Tuberculosis Foundation and the Union (data not shown), and was especially noticeable for three topics: MDR and XDR-TB, management of drugs and commodities, and development of Global Fund proposals.

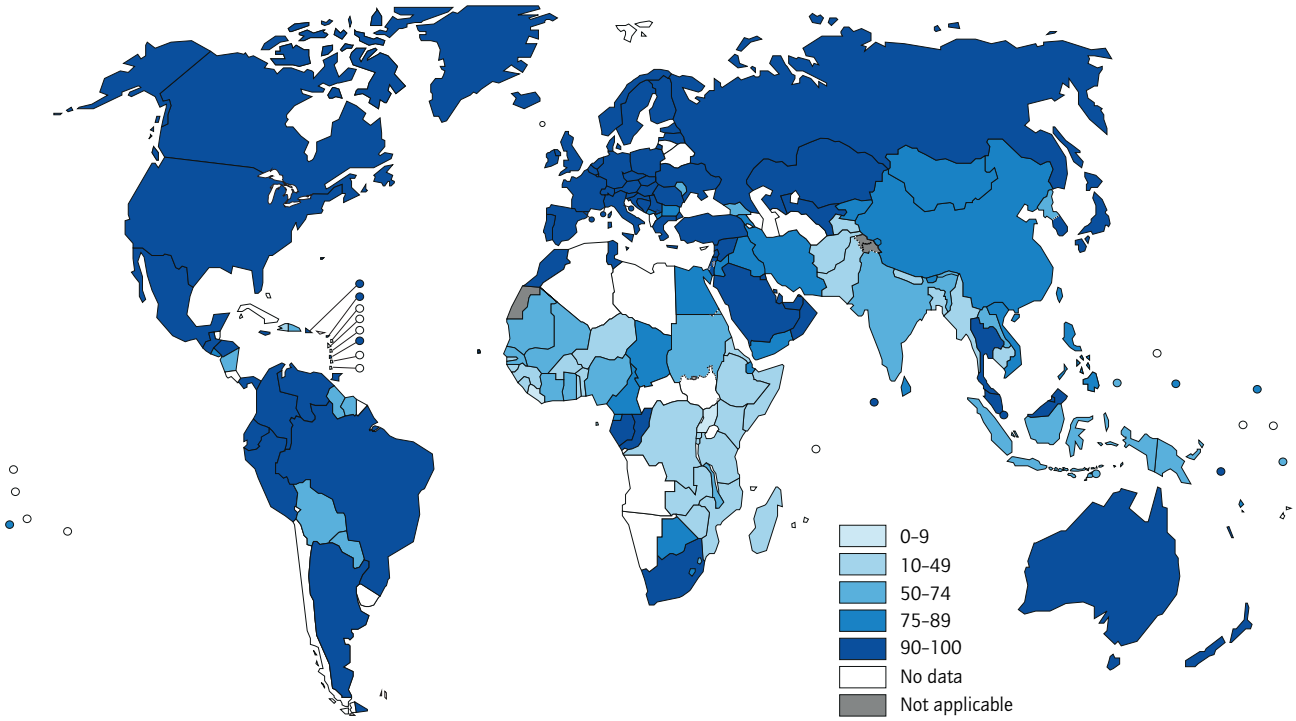
Information on sources of funding is often not recorded; in the first half of 2012, the source of funding was not recorded for 40% of missions. Of the 389 missions for which information on funding was provided, 78% was from agencies of the US government, notably the United States Agency for International Development (USAID) and OGAC (the Office of the Global AIDS Coordinator). The remaining 22% was from Eli Lilly and the Canadian International Development Agency (CIDA).

TABLE B5.2.2
Number of missions by topic reported to TB-TEAM, 2009–2011

TOPIC	2009	2010	2011	% OF TOTAL IN 2011
MDR-TB and XDR-TB	120	129	91	14
Monitoring and evaluation, supervision and impact measurement	46	63	73	11
Global Fund grant processes, bottlenecks	34	40	72	11
TB programme planning and review; regional meetings	77	107	64	10
Laboratory strengthening	54	79	57	9
Drugs and commodities management	89	70	53	8
Infection control	26	34	36	6
Operational and basic science research	9	17	34	5
TB/HIV	13	17	31	5
Human resources development	27	39	23	4
Global Fund proposal development	52	30	19	3
Advocacy, communication and social mobilization	26	18	12	2
Childhood TB	3	4	9	1
Drug resistance surveillance	2	8	9	1
Other	217	114	62	10
Total	**795**	**769**	**645**	**100**

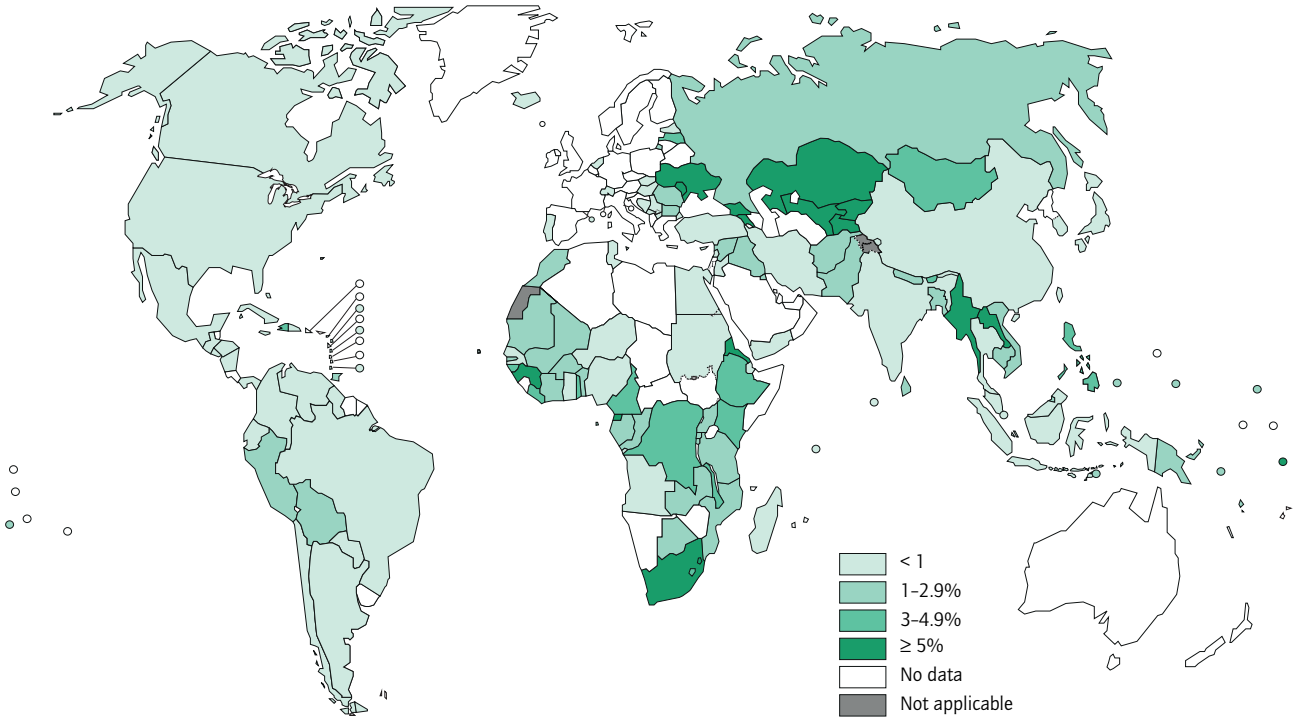
The regional distribution of missions broadly correlates to TB burden (data not shown). An exception is the European Region, which accounts for 19% of missions but for 5% of TB cases reported globally. Most of the missions in this region are related to MDR-TB and laboratory strengthening. The South-East Asia Region has a comparatively low share of missions (12%) while reporting almost 40% of TB cases globally. One explanation may be that technical assistance provided from within-country sources in India is not captured in the database.

FIGURE 5.6 **Domestic funding as a percentage of total funding available for TB care and control,[a] average 2009–2011**



[a] General health-care services are assumed to be domestically funded in all but the low-income countries, where the share of domestic funding is instead taken to be the median value obtained through the probabilistic sensitivity analysis described in Figure 5.5.

FIGURE 5.7 **Expenditures for TB care and control as a percentage of public sector health expenditures, average 2007–2009**



of smear-positive cases are hospitalized, with average lengths of stay of 60 and 100 days respectively; 35% of MDR-TB cases are hospitalized for 160 days. Nonetheless, there are signs that countries are reducing their reliance on hospitalization. For example, Uzbekistan reported a reduction in the number of dedicated TB beds from more than 15 000 in 2008 to less than 11 000 in 2012; the average duration of hospitalization for MDR-TB patients decreased from 270 to 90 days during the same period.

5.5 Unit costs and cost effectiveness of TB care

The estimated cost per patient successfully treated for TB with first-line drugs is shown for each of the 22 HBCs in Figure 5.8. The cost generally lies in the range US$ 100–500 per patient successfully treated. The exceptions are Bangladesh, India and Myanmar (under US$ 100); Brazil (above US$ 500); and the Russian Federation and South Africa (both above US$ 1000). From 2006 to 2011, the cost per patient treated increased in almost all of the HBCs, as did GDP [gross domestic product] per capita.

It is noticeable that in all of the HBCs, the cost per patient treated is less than GDP per capita (that is, all values lie below the solid **red** line in Figure 5.8). Besides GDP, 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 5.8).

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. It should also be highlighted that the characteristics of the patient population in the Russian Federation (such as high rates of alcohol dependency 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.

The cost per patient successfully treated with first-line drugs at country level is summarized in Figure 5.9. In most countries in the African, South-East Asia and Western Pacific regions, the cost per patient successfully treated is under US$ 1000 (exceptions include Botswana and South Africa in the African Region, and Malaysia and Mongolia in the Western Pacific Region). Costs are higher in the Region of the Americas and the European Region (notably in Kazakhstan).

Evidence on the cost effectiveness of interventions for TB care and control is summarized in Box 5.3.

Data reported by countries also allow analysis of the funding available for first- and second-line anti-TB drugs, and the unit cost (per patient) for first- and second-line regimens (Figure 5.10). The total funding amounts to about US$ 0.2 billion per year for first-line drugs, with a cost per patient of less than US$ 40 in low- and lower middle-income countries, and around US$ 50 in upper middle-income countries. The Global Drug Facility's Stop TB Patient Kit costs only US$ 22.30 for new cases; freight, quality control, inspection, agent fees and insurance may explain why some low-income countries continue to report unit costs in excess of these prices.

Public spending on second-line drugs is at least US$ 0.2 billion. Unfortunately, Figure 5.10 does not include amounts being spent in the Russian Federation and South Africa, which are known to be large but for which reliable data are not available for the years 2009–2013; if these were included, spending on second-line drugs would greatly exceed spending on first-line drugs. The unit cost for second-line anti-TB drugs is much higher than that for first-line drugs. National programmes spent US$ 1200–3800 per patient treated with second-line drugs in 2011. They appear to be budgeting for increases in 2013: from about US$ 2600 per patient in low-income countries to US$ 4700 per patient in upper middle-income countries.

5.6 Funding gaps reported by countries, 2006–2013

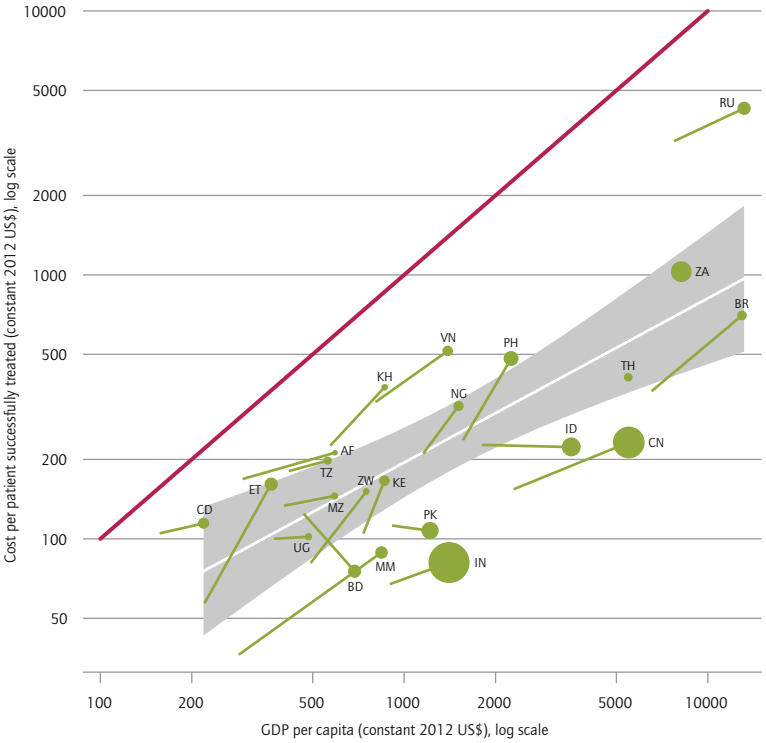
Despite increases in funding and 10 completed rounds of proposals[1] to the Global Fund, NTPs continue to report funding gaps (Figure 5.11). Since 2007, these gaps have been in the range US$ 0.4–0.7 billion per year. In 2013, funding gaps are anticipated for several elements of TB care and control, including first-line drugs. It is also evident that while countries have developed budgets for activities to strengthen and enhance the basics of TB care and control (such as public–public and public–private mix initiatives to increase reporting of cases and improve treatment outcomes, and advocacy, communication and social mobilization), gaps relative to available funding for these activities (shown in Figure 5.2) are comparatively large.

Funding gaps have persisted and widened during the past decade.[2] Funding gaps reported for 2013 are more than 20% of the budgets developed by NTPs in 38 countries, including 16 HBCs (Table 5.2).

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

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

FIGURE 5.8 Cost per TB patient successfully treated with first-line drugs,[a] 22 high TB burden countries,[b] 2006 and 2011[c]



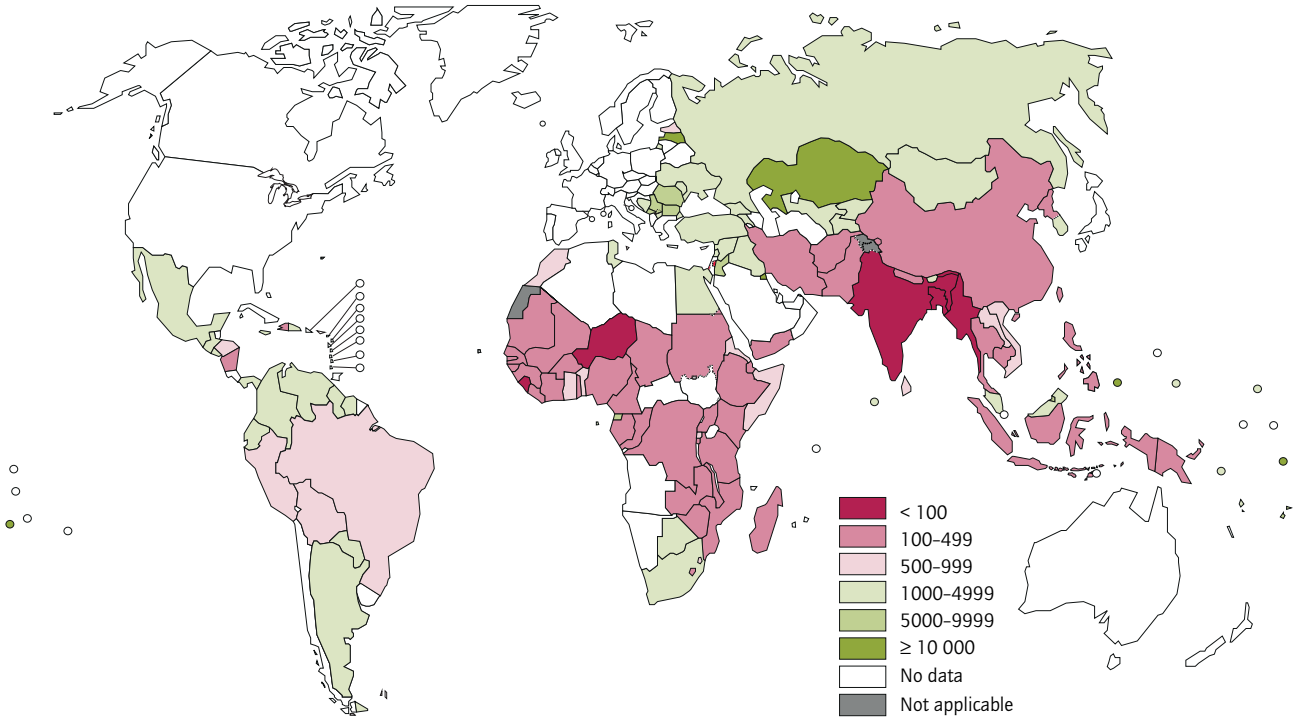
- The size of the green circle is proportional to the number of patients treated in 2011.
- The green tail attached to each circle depicts the change in cost per patient successfully treated and GDP per capita between 2006 and 2011.
- The grey area depicts the 95% confidence interval for the prediction (= white line) of the unweighted log–log regression of cost per patient successfully treated on GDP per capita in 2011.
- The red line marks where cost per patient successfully treated equals GDP per capita.

[a] Costs include first-line drugs, NTP staff, programme management and supervision, laboratory equipment and supplies, collaborative TB/HIV activities, PPM, PAL, ACSM, CBC, operational research, surveys, hospital stays and clinic visits.

[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 case-weighted three-year averages, 2004–2006 and 2009–2011, to minimize distortions associated with non-annual expenses on items such as buildings, equipment and buffer stocks of drugs. No time trend is provided for South Africa and Thailand, due to lack of data.

FIGURE 5.9 Cost per TB patient successfully treated with first-line drugs[a] (US$), average 2009–2011



[a] Costs include first-line drugs, NTP staff, programme management and supervision, laboratory equipment and supplies, collaborative TB/HIV activities, PPM, PAL, ACSM, CBC, operational research, surveys, hospital stays and clinic visits.

BOX 5.3

Cost effectiveness of interventions for TB care and control

National TB control programmes have provided good value for the US$ 23 billion they received in the years 2006–2011. A total of 34 million TB cases were detected and treated over the same period. Treatment success rates have risen (Table 3.5, Table 3.6) while unit costs have remained low relative to income levels (Figure 5.8). The cost effectiveness of core interventions for TB care and control is strongly supported by reviews and meta-analyses of economic evaluations, as summarized in Table B5.3.1.

The disability adjusted life year (DALY) is a commonly-used metric for measuring and comparing health outcomes across interventions. Applied to TB treatment, a DALY averted is approximately equal to a year of life saved. For patients with smear-positive pulmonary TB that is sensitive to first-line drugs, a short course of chemotherapy for 6 months costs as little as US$ 5–50 per year of life saved. Treating smear-negative forms of drug-sensitive TB costs somewhat more, at US$ 60–200 per year of life saved (reflecting a lower case fatality rate in the absence of treatment and less transmission). TB that is resistant to both isoniazid and rifampicin (MDR-TB) requires longer and more expensive treatment with second-line drugs and costs US$ 200–800 per year of life saved.

TABLE B5.3.1
Summary of the available evidence on the cost effectiveness of interventions for TB care and control[1,2,3,4]

POPULATION	INTERVENTION	COST PER DALY AVERTED (US$)[a]
Patients with smear-positive TB	First-line treatment under DOTS	5–50
Patients with smear-negative or extrapulmonary TB	First-line treatment under DOTS	60–200
Patients with MDR-TB	18–24 months of second-line treatment under WHO guidelines	200–800
People living with HIV, infected with TB	Isoniazid preventive therapy	15–300
People living with HIV, with TB disease	First-line drugs under DOTS plus ART	100–365
People in whom TB is suspected	Diagnosis of TB using *Xpert MTB/RIF* as an add-on to smear	40–200

[a] For those unfamiliar with the DALY, this column may be interpreted as the cost per year of life saved.

WHO defines an intervention as "highly cost effective" if the cost per DALY averted is less than the GDP per capita of the country in which it is being implemented. According to this benchmark, interventions for TB care and control are highly cost effective even in the lowest-income countries. The high cost effectiveness of TB care and control was recognized by the Disease Control Priorities Project in 2006: TB treatment was listed as one of the "best buys" in public health.[5] More recently, the Copenhagen Consensus included the expansion of TB treatment among its top five investments, out of some 40 proposals designed by experts to address urgent global challenges including armed conflict, climate change, education, hunger and control of infectious diseases.[6]

1 Dye C, Floyd K. Tuberculosis. In: *Disease control priorities in developing countries*, 2nd ed. New York, Oxford University Press, 2006:289–312.

2 Baltussen, R, Floyd K, Dye C. Achieving the millennium development goals for health: cost effectiveness analysis of strategies for tuberculosis control in developing countries. *BMJ*, 2005, 331:1364–1368.

3 Fitzpatrick C, Floyd K. A Systematic Review of the Cost and Cost Effectiveness of Treatment for Multidrug-Resistant Tuberculosis. *Pharmacoeconomics*, 2012, 30:63–80.

4 Vassall A et al. Rapid diagnosis of tuberculosis with the Xpert MTB/RIF assay in high burden countries: a cost-effectiveness analysis. *PLoS Medicine*, 2011, 8(11):e1001120 (doi:10.1371/journal.pmed.1001120).

5 www.dcp2.org/main/Home.html

6 Nobel laureates: more should be spent on hunger, health: top economists identify the smartest investments for policy-makers and philanthropists [press release dated 14 May 2012]. Denmark, Copenhagen Consensus, 2012 (available at www.copenhagenconsensus.com/Projects/CC12/Outcome.aspx; accessed July 2012).

5.7 Projections of potential funding from domestic sources and funding requirements specified in the Global Plan

The *Global Plan to Stop TB 2011–2015* was published 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 in 149 low- and middle-income countries,[2] and the associated funding requirements (Table 5.3). The total requirement over five years amounts to US$ 47 billion. Excluding research and development for new TB drugs, diagnostics and vaccines (Chapter 8), which are not the responsibility of NTPs, the total is US$ 37 billion.

Funding needs for TB care and control in the Global Plan (i.e. amounts excluding those for research) were estimated to grow from around US$ 6 billion in 2011 to US$ 8 billion in 2015. Diagnosis and treatment with first-line drugs for drug-susceptible TB following the DOTS approach account for 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

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.

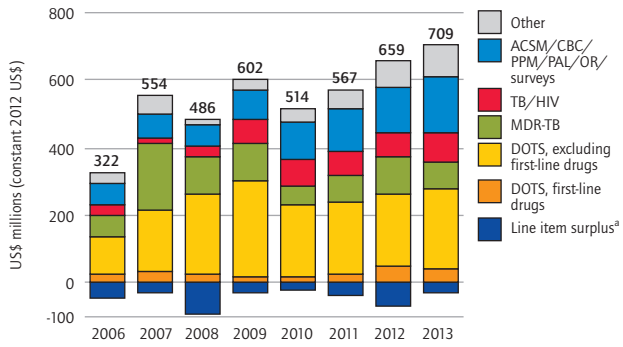
FIGURE 5.10 Total cost and unit cost of first- and second-line anti-TB drugs in 99 countries,[a] 2009–2013,[b] by income group

[a] These 99 countries account for 85% of global drug-susceptible TB cases and 29% of MDR-TB cases receiving treatment. See also note (c).

[b] Values for 2012 and 2013 are based on country plans and budgets, not actual expenditures. Unit costs are case-weighted two-year averages to adjust for purchases of buffer stock.

[c] The Russian Federation (R) and South Africa (S) were excluded as they did not report expenditures for 2011 or funding expected for 2012–2013. Together, they account for about 9% of global drug-susceptible TB cases and 45% of MDR-TB cases receiving treatment.

FIGURE 5.11 Funding gaps for TB care and control as reported by countries, by line item, 2006–2013

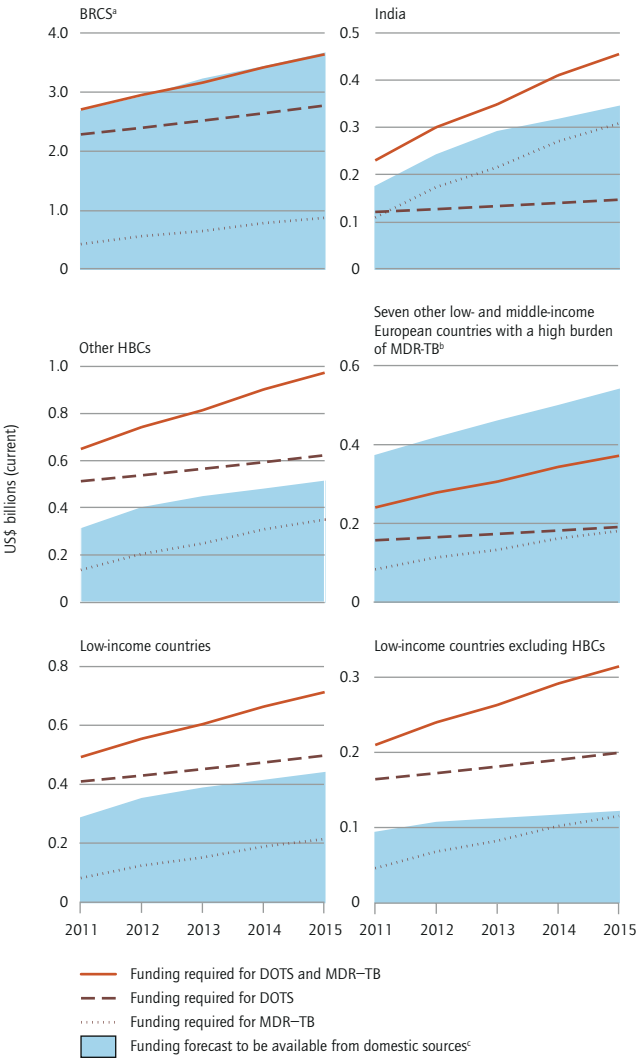


[a] Funding available for a given line item may exceed that required for the same line item under a country's plan and budget.

TABLE 5.3 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%]	not estimated
Research and development	9.8 [21%]	
Fundamental research	2.1 [5%]	
New diagnostics	1.7 [4%]	
New drugs	3.7 [8%]	
New vaccines	1.9 [4%]	
Operational research	0.4 [1%]	
All components	**46.7 [100%]**	**45.9–47.5**

FIGURE 5.12 Funding required for DOTS and MDR-TB in the Global Plan 2011-2015 compared with projections of potential funding from domestic sources, for six country groups



[a] Brazil, Russian Federation, China and South Africa (BRICS excluding India)

[b] The seven countries included in this group are Armenia, Georgia, Kyrgyzstan, Republic of Moldova, Tajikistan, Ukraine and Uzbekistan. Of the funding available in 2012, approximately half is accounted for by Ukraine. The countries in this group continue to hospitalize TB patients for lengthy periods of time, while in the Global Plan it was assumed that reliance on inpatient hospital care in the European Region would be progressively reduced between 2006 and 2015 to an average of 60 days per patient with drug-susceptible TB by 2015. This explains why the funding amounts estimated to be needed in the Global Plan are lower than the funding available in this group of countries.

[c] Assumes that: 1) international donor funding received by BRICS in 2011 is substituted by domestic sources; and 2) domestic funding for TB care and control in all low and middle-income countries will keep pace with IMF forecasts of growth in GDP per capita.

treatment of MDR-TB, for which the funding requirement was estimated at US$ 1 billion in 2011, rising to US$ 1.9 billion in 2015. The funding required for collaborative TB/HIV activities (see **Chapter 7**) increases to about US$ 1 billion by 2015, mostly (about 90% of the total) for antiretroviral therapy for HIV-positive TB patients that would be funded via HIV programmes (not NTPs).

The funding requirements set out in the Global Plan are considerably more than the funding amounts reported by countries. For example, the funding required in 2015 according to the Global Plan is about US$ 2 billion more than the funding reported to be available in 2013.[1] In this context – and with international funding constrained by economic stagnation or recession in traditional donor countries – assessing the funding that can be mobilized from domestic sources is of increasing importance.

Figure 5.12 shows estimates of the funding required for treatment of TB and MDR-TB in the Global Plan, and for selected groupings of countries defined by their TB burden and income level. Amounts for collaborative TB/HIV activities are deliberately excluded because ART, the main intervention in terms of cost, is not funded through NTPs. It is therefore not appropriate to compare funding needs for collaborative TB/HIV activities with funding reported by NTPs. Also shown in **Figure 5.12** are projections of the funding that could be mobilized from domestic sources in each country group, on the assumption that: (i) international donor funding received by BRICS in 2011 is substituted by domestic sources; and (ii) domestic allocations for TB care and control in all low- and middle-income countries will keep pace with IMF forecasts of growth in GDP per capita.

The data shown in **Figure 5.12** provide insights that could inform future discussions about investments in TB care and control, including prioritization of donor funding among countries and interventions and targets for resource mobilization. For example:

- There is domestic capacity to fund the investments needed for basic TB care and control (DOTS) in BRICS.
- An increase in domestic allocations for TB care and control in line with forecast growth in GDP per capita would be sufficient to mobilize the funding needed for diagnosis and treatment of MDR-TB in Brazil, the Russian Federation, China and South Africa (all of which are upper middle-income countries).
- In India, without growth in domestic allocations for TB above forecast growth in GDP per capita, about US$ 0.1 billion per year is needed from donor sources.

[1] This is excluding amounts for TB/HIV that are mostly for ART funded through HIV programmes, and allowing for funding in the 34 countries considered in the Global Plan that are not in the group of 115 countries for which data were available for 2011 or 2012 (**Table 5.1**). It is anticipated that most of the funding for TB/HIV interventions will need to come from international donors.

- The 14 countries not included in the list of 22 HBCs but that are part of the list of the 27 high MDR-TB burden countries are all European countries. Of these 14 countries, six are upper middle-income countries and one is a high-income country (Estonia). Among the seven low- and lower middle-income countries, available funding from domestic sources appears to be sufficient, although some rationalization in the use of hospital care may be required.
- The 17 HBCs outside BRICS require donor funding of about US$ 0.3–0.5 billion per year to reach Global Plan targets for implementing DOTS and scaling up diagnosis and treatment for MDR-TB. This amount could be lowered if reductions in the price of second-line anti-TB drugs needed for treatment of MDR-TB could be achieved.
- Low-income countries require donor funding of about US$ 0.2–0.3 billion per year to reach Global Plan targets for implementing DOTS and scaling up diagnosis and treatment for MDR-TB, of which US$ 0.1–0.2 billion per year is in countries outside HBCs.

In addition to the funding needs for DOTS and MDR-TB set out in the Global Plan, additional investments will be needed for the scale-up of new rapid molecular diagnostics. Further details about these diagnostics are provided in Chapter 6.

Overall, these observations suggest that international donor funding of up to US$ 1 billion per year is needed for diagnosis and treatment of TB and MDR-TB in low- and middle-income countries 2013–2015 to close funding gaps. It is anticipated that most of the funding required for TB/HIV interventions will also need to come from international donor sources.

CHAPTER 6

Diagnostics and laboratory strengthening

KEY FACTS AND MESSAGES

- Conventional technologies have been constraining diagnosis of TB and drug-resistant TB, but the recent availability of new rapid tests has the potential to revolutionize TB care.
- The roll-out of Xpert MTB/RIF, a new rapid molecular test that can diagnose TB and rifampicin-resistant TB within hours, has been impressive. Between its endorsement by WHO in December 2010 and the end of June 2012, 1.1 million test cartridges were procured in 67 (46%) of the 145 countries eligible to purchase them at concessional prices. Acceleration in uptake is still needed to realize the full potential of the technology.
- Scaling up use of the Xpert MTB/RIF assay is expected to be greatly accelerated by a 41% drop in the cartridge price from US$ 16.86 to US$ 9.98 announced in August 2012. It is essential that expansion in capacity to diagnose drug-resistant TB is closely aligned with expansion in capacity to provide treatment.
- Laboratory capacity to conduct sputum smear microscopy still requires strengthening: only 15 of the 22 high TB burden countries met the target of having 1 microscopy centre per 100 000 population in 2011.
- Substantial strengthening of laboratory capacity to detect DR-TB is needed. Among the 36 countries with a high burden of TB and MDR-TB, 19 did not have the recommended capacity of 1 laboratory to perform culture and DST per 5 million population in 2011.
- The WHO/GLI Supranational Reference Laboratory (SRL) Network has assumed a greater role in global efforts to strengthen TB laboratories. It now comprises 29 laboratories in all WHO regions, with 4 additional candidate SRLs under development.
- WHO has developed more comprehensive policies on the proper use of TB diagnostics, which now include guidance on approved tests as well as 'negative' guidance to dissuade practitioners from using poorly performing and/or overly costly tests. Countries should take decisive action to ban poorly-performing and overly costly tests and introduce WHO-recommended technologies.

A high-quality laboratory system that uses modern diagnostics is a prerequisite for early, rapid and accurate detection of TB. Of the estimated 8.7 million incident TB cases in 2011, only 66% were diagnosed and notified to national TB control programmes, due in part to inadequate laboratory capacity in many low- and middle-income countries. Furthermore, of the notified cases of pulmonary TB, around one-third were not bacteriologically confirmed using a WHO-recommended laboratory method, and a proportion of the patients in whom TB was clinically diagnosed without laboratory confirmation may not have had TB. These numbers do not capture the significant delay that many patients experience in receiving a diagnosis of TB because of poorly functioning laboratory systems, resulting in delays to the start of their treatment, additional suffering and expenses, and adverse treatment outcomes.

As described in Chapter 4, diagnosis of drug resistance remains a particular challenge for laboratory systems in many low- and middle-income countries. Only 19% of the 310 000 cases of multidrug-resistant TB (MDR-TB) estimated to exist among patients with pulmonary TB received a laboratory-confirmed diagnosis of their disease and were notified in 2011. Rapid and timely detection of TB cases and strengthened capacity to diagnose cases of drug-resistant TB are thus global priorities for TB care and control.

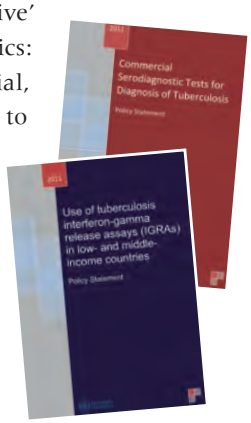
This chapter has three parts. The first describes developments in WHO's policies on TB diagnostics during 2011–2012; the second provides the status of laboratory capacity globally, regionally and nationally, focusing on 36 countries in the combined list of 22 high TB burden countries and 27 high MDR-TB burden countries; the third describes the strengthening of laboratories with a focus on the EXPAND-TB project, the Supranational Reference Laboratory Network and laboratory accreditation.

6.1 Developments in WHO policies on TB diagnostics

WHO has established a systematic process for the timely formulation of policy on new TB diagnostics in response to the active research and development pipeline in recent years and resultant new tools (see Chapter 8). This dynamic process involves synthesizing the available evidence through systematic reviews and meta-analyses, assessing the evidence and its expected impact

on public health by an external Expert Group using the recommended GRADE approach,[1] and preparing policy guidance[2] for dissemination to Member States and other stakeholders.[3] Policy documents are reviewed every 3–5 years, taking into account new evidence.

In 2011, WHO issued two 'negative' policy statements on TB diagnostics: one against the use of commercial, antibody-based serodiagnostic tests to diagnose active TB disease; the other a caution against commercial interferon-gamma release assays (IGRAs) as a public health intervention to detect latent TB infection in low- and middle-income settings.



An Expert Group that reviewed the evidence on use of commercial, antibody-based serodiagnostic tests found that they provide inconsistent and imprecise results with highly variable values for sensitivity and specificity. No evidence was found that existing commercial serological assays improve outcomes that are important to patients. As a result of this policy, in June 2012 the Government of India banned the import, manufacture, distribution and sale of commercial serodiagnostic tests for TB, which have been profligately used in the private sector to diagnose TB. This bold action is expected to greatly reduce the frequency of false diagnoses of TB and facilitate the introduction of WHO-approved diagnostics into the market.

After reviewing the available evidence on commercial IGRAs, an Expert Group concluded that:

- there are insufficient data and low-quality evidence on the performance of IGRAs in low- and middle-income countries, typically those with a high burden of TB and/or HIV;
- IGRAs and the tuberculin skin test (TST) cannot accurately predict the risk of infected individuals developing active TB disease;
- neither IGRAs nor the TST should be used to diagnose active TB disease; and
- IGRAs are more costly and technically complex to perform than the TST.

Given their comparable performance but increased cost, replacing the TST with IGRAs as a public health intervention in resource-constrained settings is not recommended. These guidelines are not intended to apply to high-income countries or to supersede their national guidelines.

In 2012, Expert Groups were convened to review the available evidence on two commercially available diagnostic tests: a manual assay using the loop-mediated isothermal amplification (LAMP) platform to detect TB DNA in sputum specimens (TB-LAMP®, Eiken Chemical Co. Ltd., Japan), and a line probe assay for detecting resistance to second-line anti-TB drugs (GenoType® MTBDRsl, Hain Lifescience, Germany).

The Expert Group reviewing the TB-LAMP assay concluded that there was insufficient evidence to proceed with the development of policy guidance.

For Genotype MTBDR*sl*, the Expert Group found that while the test's specificity for detecting resistance to fluoroquinolones and second-line injectables was high, its sensitivity was suboptimal. Therefore, while the test has the potential to be used as a rule-in test for XDR-TB where capacity to use line probe assays is available, it cannot be used as a replacement test for conventional phenotypic drug susceptibility testing (DST). The Expert Group also noted that there is incomplete cross-resistance between the second-line injectables, and that the assay does not allow for specific resistance to individual second-line injectables to be determined. Detailed conclusions of the Expert Group meetings will be described in reports to be published on the website.[4]

6.2 Status of laboratory capacity globally, regionally and nationally

Despite the development in recent years of more sensitive technologies, diagnosis of TB in most low- and middle-income countries continues to rely on sputum smear microscopy. Maintaining a high level of quality to perform smear microscopy is therefore critical. Of the 144 low- and middle-income countries and territories reporting on numbers of smear microscopy laboratories, only 42% indicated the existence of an external quality assessment programme that encompassed all smear laboratories in the country.

While globally the target of 1 microscopy centre per 100 000 population has been reached, considerable disparities remain at regional and country levels (**Table 6.1**). The Western Pacific and Eastern Mediterranean regions had only 0.5 and 0.8 centres per 100 000 population in 2011, respectively, and 7 of the 22 high TB burden countries also failed to meet the target.

In 2009, WHO recommended the use of the more sensitive fluorescent light-emitting diode (LED) microscopy instead of traditional Ziehl–Neelsen (ZN) microscopy. Roll-out, however, has been slow. As of 2011, only 2% of microscopy laboratories globally were using LED microscopes, with little variability between regions and no high TB burden country reporting more than 10% absorption.

The current target for both culture and DST capacity is 1 laboratory per 5 million population; this target was

[1] **www.gradeworkinggroup.org**
[2] *WHO handbook for guideline development*. Geneva, World Health Organization, 2012.
[3] WHO policies on TB diagnostics are available at: **www.who.int/tb/laboratory/policy_statements**
[4] **www.who.int/tb/laboratory/policy_statements**

TABLE 6.1 **Laboratory capacity, 2011**[a]

YES ■ NO □	HIGH TB BURDEN	HIGH MDR-TB BURDEN	SMEAR MICROSCOPY			CULTURE		DRUG SUSCEPTIBILITY TESTING		LINE PROBE ASSAY		XPERT MTB/RIF
			NUMBER OF LABORATORIES	LABORATORIES PER 100 000 POPULATION	PERCENTAGE OF LABORATORIES USING LED MICROSCOPES	NUMBER OF LABORATORIES	LABORATORIES PER 5 MILLION POPULATION	NUMBER OF LABORATORIES	LABORATORIES PER 5 MILLION POPULATION	NUMBER OF LABORATORIES	LABORATORIES PER 5 MILLION POPULATION	NUMBER OF SITES
Afghanistan	■	□	600	1.9	2	3	0.5		–		–	
Armenia	□	■	30	1.0	0	1	1.6	1	1.6	1	1.6	0
Azerbaijan	□	■		–	–		–		–		–	
Bangladesh	■	■	1 057	0.7	1	3	<0.1	2	<0.1	0	0	0
Belarus	□	■	196	2.1	2	41	21	20	10	1	0.5	0
Brazil	■	□	4 028	2.0	< 1	306	7.8	45	1.1	0	0	0
Bulgaria	□	■	34	0.5	–	33	22	13	8.7	3	2.0	0
Cambodia	■	□	211	1.5	9	3	1.0	1	0.3	0	0	1
China	■	■	3 328	0.2	2	594	2.2	195	0.7	20	<0.1	16
DR Congo	■	■	1 508	2.2	0	1	<0.1	1	<0.1	0	0	0
Estonia	□	■	5	0.4	40	2	7.5	2	7.5	2	7.5	2
Ethiopia	■	■	1 947	2.3	–	2	0.1	1	<0.1	2	0.1	
Georgia	□	■	29	0.7	–	2	2.3	1	1.2	1	1.2	1
India	■	■	13 026	1.0	2	37	0.1	37	0.1	17	<0.1	18
Indonesia	■	■	5 566	2.3	0	46	0.9	5	0.1	2	<0.1	5
Kazakhstan	□	■	466	2.9	0	100	31	22	6.8	10	3.1	0
Kenya	■	□	1 581	3.8	9	6	0.7	1	0.1	1	0.1	3
Kyrgyzstan	□	■	122	2.3	0	4	3.7	3	2.8		–	
Latvia	□	■	16	0.7	0	4	8.9	1	2.2	1	2.2	1
Lithuania	□	■		–	–		–		–		–	
Mozambique	■	□	430	1.8	< 1	2	0.4	2	0.4	0	0	1
Myanmar	■	■	415	0.9	< 1	2	0.2	2	0.2	2	0.2	2
Nigeria	■	■	1 229	0.8	2	5	0.2	4	0.1	3	<0.1	8
Pakistan	■	■	1 187	0.7	< 1	12	0.3	10	0.3	2	<0.1	16
Philippines	■	■	1 986	2.1	0	10	0.5	2	0.1	1	<0.1	14
Republic of Moldova	□	■		–	–		–		–		–	
Russian Federation	■	■	3 746	2.6	–	117	4.1		–		–	
South Africa	■	■	244	0.5	–	15	1.5	15	1.5	10	1.0	55
Tajikistan	□	■	92	1.3	0	3	2.1	1	0.7	2	1.4	2
Thailand	■	□	1 100	1.6	< 1	65	4.7	15	1.1	2	0.1	11
Uganda	■	□	1 081	3.1	1	7	1.0	8	1.2	8	1.2	18
Ukraine	□	■		–	–		–		–	0	0	0
UR Tanzania	■	□	945	2.0	3	5	0.5	1	0.1	1	0.1	6
Uzbekistan	□	■	320	1.2	< 1	7	1.3	2	0.4	3	0.5	0
Viet Nam	■	■	800	0.9	< 1	25	1.4	2	0.1	2	0.1	2
Zimbabwe	■	□	151	1.2	3	2	0.8	2	0.8	0	0	11
High-burden countries			**–**	**1.1**	**1**	**–**	**1.5**	**–**	**0.4**	**–**	**<0.1**	**–**
High MDR-TB burden countries			**–**	**0.9**	**< 1**	**–**	**1.3**	**–**	**0.4**	**–**	**0.1**	**–**
AFR			–	1.5	3	–	0.7	–	0.4	–	0.2	–
AMR			–	2.4	< 1	–	17	–	0.9	–	0.1	–
EMR			–	0.8	< 1	–	1.8	–	0.4	–	<0.1	–
EUR			–	1.1	< 1	–	9.4	–	4.4	–	1.0	–
SEAR			–	1.2	3	–	0.4	–	0.2	–	<0.1	–
WPR			–	0.5	1	–	3.6	–	0.7	–	0.2	–
Global			**–**	**1.1**	**2**	**–**	**3.9**	**–**	**0.8**	**–**	**0.2**	**–**

Blank cells indicate data not reported.
– indicates values that cannot be calculated.
[a] The regional and global figures are aggregates of data reported by low- and middle-income countries and territories. Data for the variables shown in the table are not requested from high-income countries in the WHO data collection form.

revised as a result of the introduction of new technologies in which culture and DST are invariably performed together. In 2011, 19 of the 36 countries in the combined list of 22 high TB burden countries and 27 high MDR-TB burden countries did not reach the target (Table 6.1). Of these 36 countries, 9 reported more than 1 laboratory per 5 million population using line probe assays – a high-throughput tool used at central and regional levels to rapidly detect resistance to rifampicin and, in some cases, isoniazid. These numbers are changing quickly, as laboratory strengthening efforts including EXPAND-TB (see Section 6.3) come to fruition.

Quality-assured DST is critical to ensure accurate detection of drug resistance for subsequent treatment decisions and to avoid false diagnoses. External quality assessment schemes for DST appear to be comprehensively installed more commonly than those for microscopy. While 42% of countries claim to have a comprehensive scheme for microscopy (as stated above), 71% of the 115 low- and middle-income countries and territories indicating capacity for DST reported an external quality assessment scheme encompassing all DST laboratories.

The target for culture and DST capacity of 1 laboratory per 5 million population is likely to be revised downwards in future following the introduction of the WHO-recommended automated nucleic amplification assay Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA). Xpert MTB/RIF technology (see Box 6.1) can detect rifampicin resistance-conferring mutations, has sensitivity for TB detection equivalent to that of solid culture, and compared with culture methods it can be used at lower levels of the laboratory network. Importantly, however, culture will remain essential for testing of susceptibility to drugs other than rifampicin, and is currently the only tool available for monitoring the response to treatment of the growing number of patients being treated for MDR-TB. Ongoing evaluation of evidence on the use of Xpert MTB/RIF and its impact on the workload of other laboratory diagnostics, including microscopy, culture and DST, will allow for refinement of the current targets.

While a number of countries report suboptimal capacity to detect TB and drug resistance, patients in many parts of the world still access laboratory testing by seeking care in the private sector. The quality of diagnostic services in this sector is highly variable, and some private practitioners continue to use diagnostic tests that are not recommended by WHO. In addition, in some settings laboratories in the public sector that are not under the auspices of the national TB control programme also diagnose TB without necessarily following recommended guidelines and quality assurance procedures. Collaboration between national TB control programmes and all laboratories offering TB diagnosis is therefore critical to ensure that national guidelines are followed, that appropriate diagnostic tests are used, and that patients diagnosed with TB are notified to the national TB control programme and receive proper care. In 2011, 15 of 36 high burden countries reported some level of collaboration with laboratories in the private sector; 17 reported collaboration with laboratories in the public sector.

6.3 Strengthening TB laboratories globally, regionally and nationally

One of the main prerequisites for strengthening TB laboratory capacity in countries is dynamic policy reform, adapting WHO guidelines on TB diagnostics into national TB control programme guidelines. Table 6.2 presents the uptake of selected WHO policy guidance at global, regional and country levels, focusing on the 36 countries in the combined list of 22 high TB burden countries and 27 high MDR-TB burden countries.

All reporting high MDR-TB burden countries and 85% of reporting countries globally had incorporated into their national guidelines the WHO policy guidance on conventional phenotypic DST by 2011. Countries in the African Region have the lowest uptake (69%).

Incorporation of policy guidance on liquid culture is highly variable, ranging from as low as 45% in the Eastern Mediterranean Region to 84% in the European Region. Globally, uptake of policy on line probe assays is relatively low (44%) for all countries; only 17% of countries in the Region of the Americas reported incorporation of the guidance in their national guidelines.

Although recommended by WHO only in December 2010, WHO's policy guidance on Xpert MTB/RIF has been incorporated into national guidelines by one third (33%) of reporting countries; two thirds (64%) of the high TB burden countries and half (50%) of the high MDR-TB burden countries have already incorporated the assay in their revised diagnostic policies.

The EXPAND-TB project is a global initiative of multiple partners that aims to strengthen laboratory capacity for detecting drug-resistant TB and establish rapid diagnostics in 27 countries. Launched in 2008, the project is a collaboration among WHO, the Global Laboratory Initiative (GLI), FIND and the Global Drug Facility, funded by UNITAID and other partners. As shown in Figure 6.1, the participating countries are at various stages of project implementation: 17 were in the final phase of routine testing and monitoring as of July 2012, compared with 6 in July 2011. Given the time required to establish the necessary infrastructure for central level laboratories capable of using liquid culture and line probe assays, the EXPAND-TB project is now coming to fruition in the routine detection and reporting of drug-resistant TB cases. Several of the countries participating in the project have reported considerable increases in the numbers of drug-resistant cases during recent years (Figure 6.2).

The WHO/GLI TB Supranational Reference Laboratory (SRL) Network is another driving force in strengthening

BOX 6.1

Rolling out Xpert MTB/RIF globally

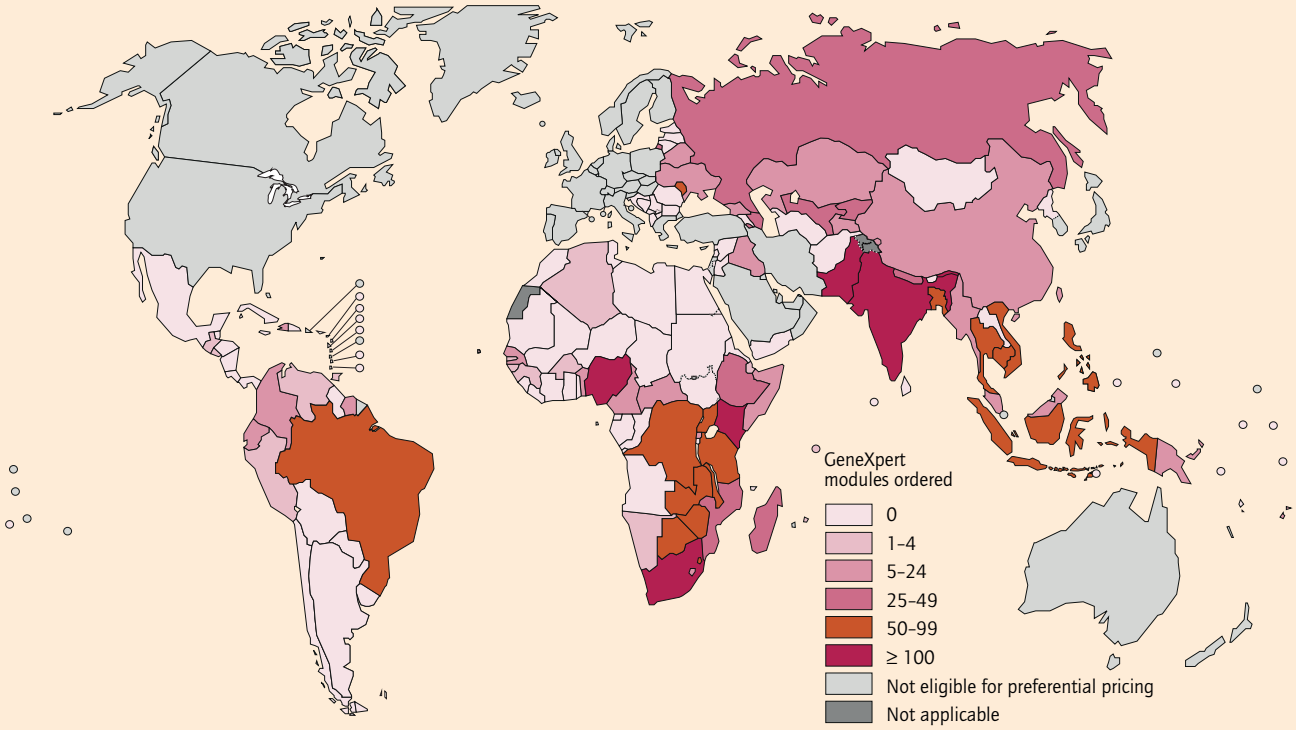
In December 2010, WHO recommended use of the Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA) assay for the rapid and simultaneous detection of TB and rifampicin resistance using the GeneXpert platform. The test entails fewer biosafety and human resource requirements than conventional culture or DST. Furthermore, its sensitivity for detecting TB is significantly higher than that of microscopy, particularly in patients with HIV infection.

By the end of June 2012, Xpert MTB/RIF had been rolled out in 67 of the 145 countries eligible to purchase instruments and cartridges at concessional prices. 1.1 million test cartridges and 3602 GeneXpert instrument modules had been procured, with technical and financial assistance from many partners and donors. South Africa has led the adoption of the technology and intends to use it countrywide as a replacement for microscopy for the diagnosis of TB; as of June 2012, the country accounted for 37% of the modules and 53% of the cartridges procured globally. The most up-to-date data on procurement and country-specific site locations and plans, together with WHO guidance documents on use of the test, are available on a dedicated WHO website.[1]

To gain evidence on Xpert MTB/RIF for the refinement of its global policy guidance, WHO has been systematically collecting data from early implementers of Xpert MTB/RIF on the tests conducted and algorithms used, the effects of introducing the technology on laboratory workload, and operational and logistic challenges encountered.[2] As of July 2012, 31 sites in 12 countries had contributed data. Systematic collection of complementary laboratory and patient indicators is also underway by partners including TBCARE I, TB REACH, the South Africa National Health Laboratory Services and Médecins Sans Frontières. Operational research projects, including those inventoried by the TREAT-TB initiative,[3] are expected to yield further critical information on the impact and cost effectiveness of Xpert MTB/RIF in various diagnostic algorithms.

Scaling up use of the Xpert MTB/RIF assay globally is expected to be greatly accelerated by a drop in the price per test from US$ 16.86 to US$ 9.98, following execution of a novel financing agreement between the manufacturer (Cepheid) and the Bill & Melinda Gates Foundation, the United States Agency for International Development (USAID), the United States President's Emergency Plan for AIDS Relief (PEPFAR) and UNITAID in August 2012. The catalytic effect of the price reduction on such global scale-up will be complemented by a US$ 25.9 million grant from UNITAID to WHO's Stop TB Department and the Stop TB Partnership. The new three-year TBXpert project will provide the Xpert MTB/RIF technology to 21 recipient countries by linking a broad network of implementing partners with existing initiatives for TB laboratory strengthening, using innovative approaches to expand access to vulnerable populations in the public and private sectors.

FIGURE B6.1.1
Progress in the roll-out of Xpert MTB/RIF, by July 2012



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

[2] More detail on this initiative can be found at: www.who.int/tb/features_archive/xpert_use_web/

[3] http://xrmt.treattb.org/

TABLE 6.2 Incorporation of WHO policy guidance for diagnosis of TB, 2011[a]

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 PEOPLE LIVING WITH HIV	XPERT MTB/ RIF ASSAY
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			**95%**	**73%**	**64%**	**86%**	**64%**
High MDR-TB burden countries			**100%**	**75%**	**74%**	**87%**	**50%**
AFR			69%	69%	43%	76%	32%
AMR			96%	61%	17%	78%	13%
EMR			86%	45%	40%	52%	45%
EUR			100%	84%	63%	75%	32%
SEAR			90%	50%	40%	80%	40%
WPR			78%	72%	56%	82%	44%
Global			**85%**	**67%**	**44%**	**74%**	**33%**

Blank cells indicate data not reported.

[a] The regional and global figures are aggregates of data reported by low- and middle-income countries and territories. Data for the variables shown in the table are not requested from high-income countries in the WHO data collection form.

FIGURE 6.1 **The EXPAND-TB project – progress by July 2012**

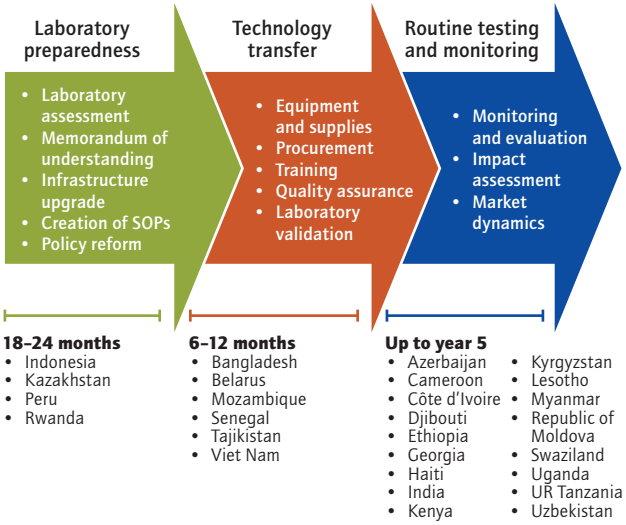
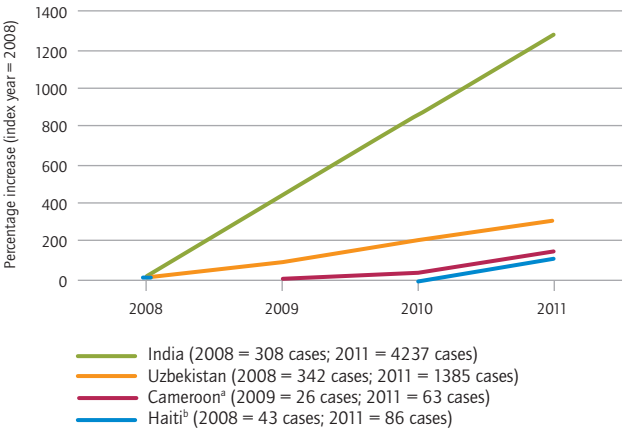


FIGURE 6.2 **Increase in cases of MDR-TB reported by selected countries participating in the EXPAND-TB project, 2008–2011**



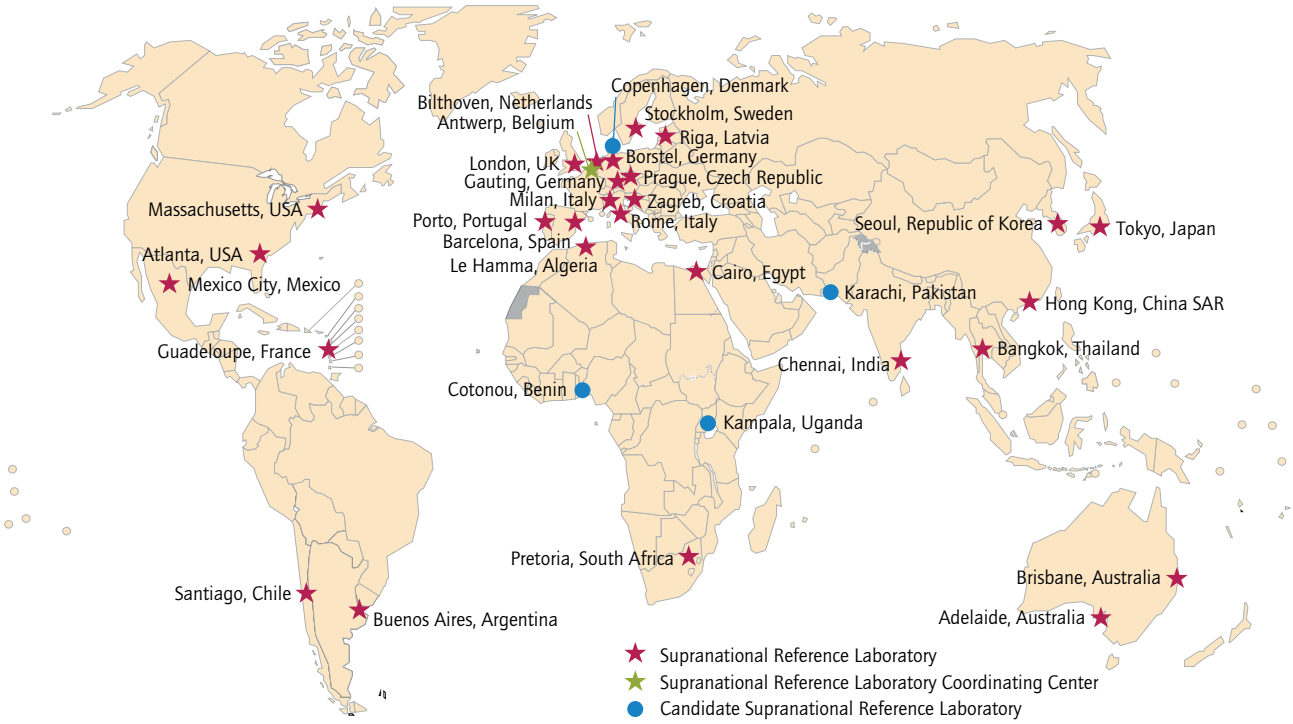
[a] Index year for Cameroon is 2009, as data were not reported for 2008.
[b] Data were not reported for Haiti for 2009.

laboratories globally. Created in 1994 to provide quality-assured DST within the framework of the Global Project on Anti-TB Drug Resistance Surveillance, the network today plays a more comprehensive role in strengthening laboratory capacity in partner countries. Its terms of reference were revised in 2009 and, with increased funding via the US President's Emergency Plan for AIDS Relief (PEPFAR) and other sources, SRLs have been able to formalize their relationships with partner countries and increase the scope of their activities. The network has grown in size and comprises 29 laboratories in all regions (Figure 6.3). Additionally, 4 candidate SRLs are under mentorship, including the national TB reference laboratories of Benin, Denmark and Uganda, and the Aga Khan University of Pakistan. Pending completion of successful mentorship and the establishment of country partners, these new laboratories will help widen the geographical reach of the network, in particular in the African and Eastern Mediterranean regions.

Implementing quality management systems in TB laboratories, especially in resource-constrained settings, has been a particular focus of laboratory strengthening efforts during 2011–2012. In 2011, the GLI Stepwise Process toward TB Laboratory Accreditation tool was launched,[1] led by the Union, the United States Centers for Disease Control and Prevention, the Royal Tropical Institute in the Netherlands and WHO. The GLI tool provides both guidance and an incentive for improving laboratory quality towards meeting requirements for international standards of accreditation. The Global Plan includes a target that more than half of all national TB reference laboratories should have implemented a quality management system by 2015. In 2012, field testing of the tool was started in Uganda and Benin; further uptake is expected in 2012–2013.

[1] www.gliquality.org

FIGURE 6.3 **The Supranational Reference Laboratory Network**



CHAPTER 7

Addressing the co-epidemics of TB and HIV

KEY FACTS AND MESSAGES

- In 2011, 1.1 million (13%) of the 8.7 million people who developed TB worldwide were HIV-positive; 79% of these HIV-positive TB cases were in the African Region.
- WHO's recommended package of collaborative TB/HIV activities to reduce the burden of TB/HIV includes HIV testing for TB patients; CPT and early initiation of ART for HIV-positive TB patients; and screening for TB among people living with HIV and provision of IPT to those eligible for it.
- Substantial progress in the implementation of collaborative TB/HIV activities has occurred since WHO recommendations were first issued in 2004, and further progress was evident in 2011.
- The percentage of notified TB patients with a documented HIV test result in the African Region rose from 60% in 2010 to 69% in 2011; 46% of those tested in 2011 were HIV-positive, ranging from 8% in Ethiopia to 77% in Swaziland. Worldwide, 40% of TB patients notified in 2011 had a documented HIV test result, up from 33% in 2010 and more than ten times the level of 2004.
- In 2011, 79% of TB patients known to be HIV-positive, were provided with CPT, and 48% were started on ART, similar to levels achieved in 2010. More work remains to be done to ensure that all HIV-positive TB patients are rapidly started on ART, in line with WHO recommendations. Their progress on treatment should also be closely monitored.
- In 2011, 3.2 million people enrolled in HIV care were reported to have been screened for TB, up 39% from 2.3 million in 2010. Of those without active TB disease, 0.45 million were provided with IPT, more than double the number started on IPT in 2010 (mostly the result of progress in South Africa).
- The scale-up of collaborative TB/HIV activities saved a total of 1.3 million lives between 2005 and the end of 2011.

People living with HIV who are also infected with TB are much more likely to develop TB disease than 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, which persisted throughout the 1990s and up to around 2004, especially in southern and east Africa (**Chapter 2**, **Chapter 3**).

In 2011, 1.1 million (13%) of the 8.7 million people who developed TB worldwide were HIV-positive (**Chapter 2**, **Table 2.1**); 79% of these HIV-positive TB cases were in the African Region. Globally, there were an estimated 0.4 million HIV-associated TB deaths in 2011, with approximately equal numbers among men and women (see **Chapter 2**). WHO, UNAIDS and the Stop TB Partnership have set a target of halving TB mortality rates among people who are HIV-positive by 2015 compared with 2004 (the year in which TB mortality among HIV-positive people is estimated to have peaked).[2]

WHO recommendations on the interventions needed to prevent, diagnose and treat TB in people living with HIV have been available since 2004,[3,4] and are collectively known as collaborative TB/HIV activities. They include testing TB patients for HIV, providing antiretroviral therapy (ART) and co-trimoxazole preventive therapy (CPT) to TB patients living with HIV, providing HIV prevention services for TB patients, intensifying TB case-finding among people living with HIV, offering isoniazid preventive therapy (IPT) to people living with HIV who do not have active TB, and controlling the spread of TB infection in health-care and congregate settings (the latter three activities are referred to as the "*Three Is for HIV/TB*").

Antiretroviral therapy significantly reduces the risk of morbidity and mortality from TB. A meta-analysis published in 2012 found that ART reduces the individual risk

[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 155 countries for which data were available in 2011 was 14 (inter-quartile range 12–20).

[2] *Getting to zero: 2011–2015 strategy*. Geneva, Joint United Nations Programme on HIV/AIDS, 2010.

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

[4] *WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders*. Geneva, 2012 (WHO/HTM/TB/2012.1).

of TB disease by 65%, irrespective of CD4 cell-count.[1] IPT and ART given together can have an additive effect and substantially reduce the risk of developing active TB disease among people living with HIV. This evidence is the reason why updated WHO policy guidance on collaborative TB/HIV activities (issued in 2012) includes *earlier initiation of ART* along with the *Three Is for HIV/TB* as key interventions to prevent TB among people living with HIV.[2] ART is recommended for all TB patients living with HIV, irrespective of their CD4 cell-count.

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 can also be done by NTPs, especially to facilitate better access to care. When NTPs do not provide ART directly, they are responsible for referring TB patients living with HIV to ART services.

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 2004 up to 2011.[3]

7.1 HIV testing for TB patients

In 2011, the number of notified TB patients who had a documented HIV test result reached 2.5 million (**Figure 7.1**), equivalent to 40% of notified TB cases (**Table 7.1**, **Figure 7.2**); this was an increase from 2.1 million and 33% respectively in 2010, and more than 10 times the level of 3.1% reported in 2004 (**Figure 7.2**).

The coverage of HIV testing for TB patients was particularly high in the African Region, where 69% of TB patients had a documented HIV test result in 2011, up from 60% in 2010. Impressively, in 28/46 African countries, ≥75% of TB patients had a documented HIV test result in 2011 (**Figure 7.3**), up from 22 countries in 2010. In Kenya, Rwanda, Mozambique, Swaziland, Togo, the United Republic of Tanzania, Zambia and Zimbabwe, >85% of TB patients had a documented HIV result (**Table 7.1**). Globally, there were 80 countries in which ≥75% of TB patients had a documented HIV test result.

FIGURE 7.1 Number of TB patients with known HIV status, 2004–2011

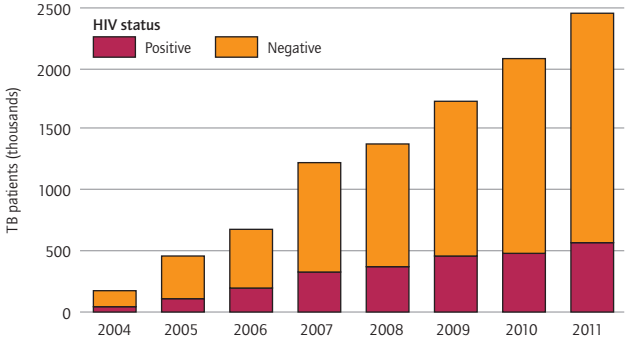
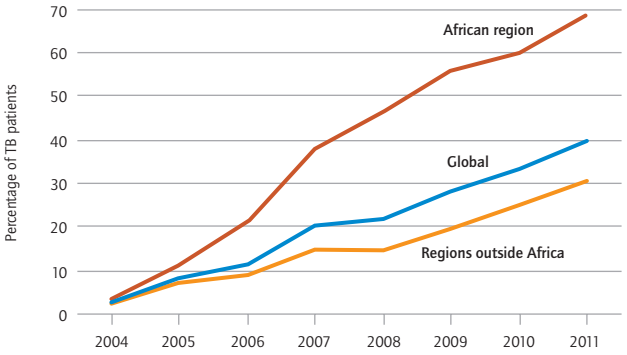


FIGURE 7.2 Percentage of TB patients with known HIV status, 2004–2011



Outside the African Region, in 2011 the percentage of TB patients who had a documented HIV test result exceeded 50% in the European Region and the Region of the Americas (mostly influenced by the numbers of TB patients with a documented HIV test result in the Russian Federation and Brazil, respectively). In other regions, the percentage ranged from 11% in the Eastern Mediterranean Region to 32% in the South-East Asia Region. In the 41 high TB/HIV burden countries identified as priorities for TB/HIV at the global level in 2002 (listed in **Table 7.1**), overall 45% of TB patients notified in 2011 had a documented HIV test result; levels of HIV testing were especially low in Indonesia and Myanmar (**Table 7.1**).

The highest rates of HIV coinfection were reported for TB patients in the African Region (**Table 7.1**), where 46% of those with an HIV test result were HIV-positive (compared with 44% in 2010). The percentage of TB patients found to be HIV-positive in the 28 African countries in the list of 41 priority countries ranged from 8% in Ethiopia to 77% in Swaziland. Besides Swaziland, ≥50% of the TB patients with an HIV test result were HIV-positive in Botswana, Lesotho, Malawi, Mozambique, Namibia, South Africa, Uganda, Zambia and Zimbabwe.

[1] Suthar AB et al. Antiretroviral Therapy for Prevention of Tuberculosis in Adults with HIV: A Systematic Review and Meta-Analysis. *PLoS Medicine*, 2012, 9(7): e1001270. (doi:10.1371/journal.pmed.1001270).

[2] *WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders*. Geneva, 2012 (WHO/HTM/TB/2012.1).

[3] This chapter does not discuss infection control or services aimed at preventing HIV among TB patients. Data for infection control 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 collected by WHO's HIV department and UNAIDS as part of their joint monitoring of progress towards universal access and the global response to AIDS.

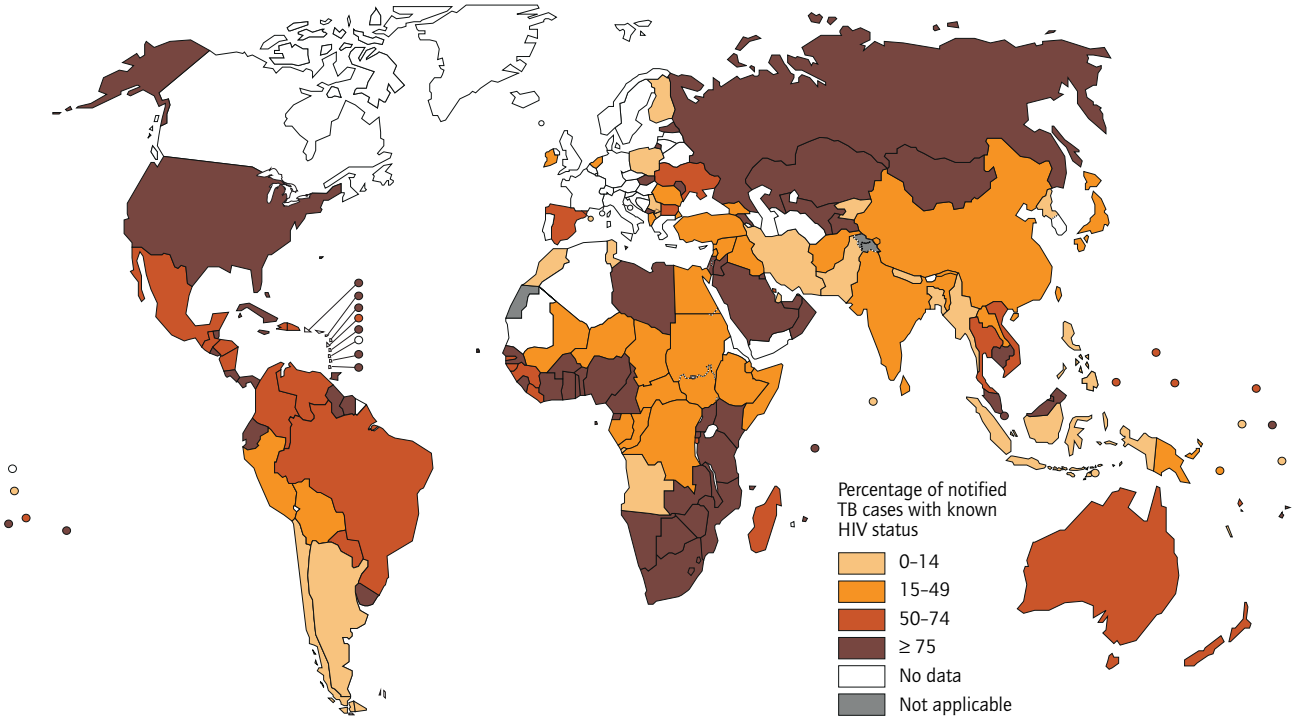
TABLE 7.1 **HIV testing, treatment for HIV-positive TB patients and prevention of TB among people living with HIV, 41 high TB/HIV burden countries and WHO regions, 2011.** Numbers in thousands except where indicated.

	ESTIMATED 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	8.5	6.2	11	5.1	10	19	80	80		
Botswana	5.9	5.3	6.6	5.4	80	64	82	45	0.2	
Brazil	16	13	19	49	58	20		92		
Burkina Faso	1.6	1.4	1.9	4.6	82	17	94		3.6	
Burundi	2.6	2.2	2.9	4.8	71	22	95	48		0
Cambodia	3.1	2.6	3.6	33	82	5.1	88	79	4.7	1.3
Cameroon	19	15	22	20	81	38				1.4
Central African Republic	7.1	5.7	8.7	1.9	33	39	12	9.3	0.6	
Chad	5.2	4.1	6.4	4.1	38	23				
China	13	8.6	17	209	23	2.3		36		
Congo	4.9	3.9	6.1	2.2	20	31	24	26	2.8	
Côte d'Ivoire	10	8.7	12	18	80	26	80	36		
Djibouti	0.6	0.5	0.7	1.3	34	14				
DR Congo	34	27	41	31	27	16	54	23		
Ethiopia	38	28	49	65	41	8.4	62	39	174	31
Ghana	4.6	4.0	5.2	13	79	23	71	28		
Haiti	4.3	3.6	5.2	10	73	19	12	17		
India	94	72	120	689	45	6.5	91	59	386	
Indonesia	15	11	20	3.5	1.1	36	92	42		
Kenya	47	45	49	97	93	39	97	64		
Lesotho	11	9.2	12	10	82	76	90	40		
Malawi	18	16	19	17	83	60	89	60	297	
Mali	1.5	1.3	1.7	2.0	35	21	72	69	29	
Mozambique	83	58	110	42	88	63	91	29		17
Myanmar	18	15	22	4.5	3.1	20	100	80	12	0.4
Namibia	8.4	6.6	10	10	84	50	98	54	13	14
Nigeria	50	23	86	76	81	26	68	43	224	1.0
Russian Federation	9.3	7.3	11	79[a]						
Rwanda	2.9	2.6	3.3	6.6	97	28	97	80		
Sierra Leone	3.8	3.1	4.6	10	78	8.9	25	28	4.0	
South Africa	330	270	390	323	83	65	76	44	1 256	373
Sudan	2.8	2.1	3.6	3.1	15	9.5	0	100		
Swaziland	12	10	15	8.4	92	77	95	51	58	
Thailand	13	10	15	50	74	15	75	59	41	
Togo	1.0	0.8	1.2	3.0	100	22				
Uganda	35	28	42	39	80	53	93	32	553	
Ukraine	8.1	6.7	9.6	29	72	20		44		
UR Tanzania	30	28	32	54	88	38	95	38	148	
Viet Nam	14	11	18	59	59	8.0	72	48		
Zambia	38	35	42	42	86	64	87	53		
Zimbabwe	46	36	58	35	86	60	29	67		
High TB/HIV burden countries	**1 100**	**990**	**1 100**	**2 170**	**45**	**25**	**80**	**48**	**3 208**	**439**
AFR	870	800	950	1 002	69	46	79	46	2 770	438
AMR	37	34	40	124	53	17	43	64	2.7	1.7
EMR	8.7	7.6	9.9	45	11	4.0	59	48	1.0	0.1
EUR	23	20	25	187	52	6.5	64	47	9.2	4.6
SEAR	140	120	170	750	32	7.2	89	59	440	0.4
WPR	36	31	42	352	25	3.9	71	47	11	1.8
Global	**1 100**	**1 000**	**1 200**	**2 460**	**40**	**23**	**79**	**48**	**3 234**	**446**

Blank cells indicate data not reported.

[a] This number is for new TB patients only. It was not possible to calculate the percentage of all TB patients with known HIV status.

FIGURE 7.3 **Percentage of TB patients with known HIV status by country, 2011[a]**



[a] Data for the Russian Federation are for new TB patients only.

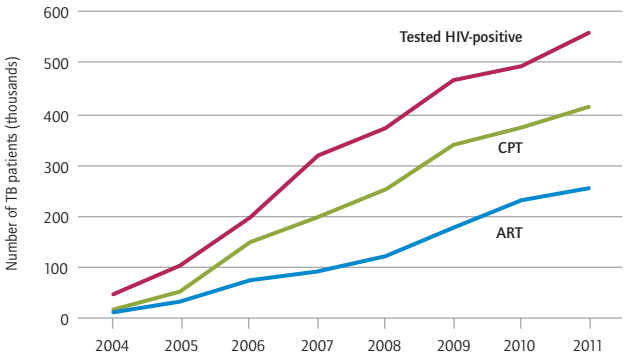
In the Region of the Americas, the percentage of TB patients with a documented HIV test result who were HIV-positive was 17%. In the Eastern Mediterranean, European, South-East Asia and Western Pacific regions, less than 10% of TB patients with a documented HIV test result were HIV-positive. The global average across all regions was 23%, and 25% among the 41 high TB/HIV burden countries.

7.2 Co-trimoxazole preventive therapy and antiretroviral therapy for TB patients living with HIV

Globally, the number of TB patients living with HIV who were enrolled on CPT increased to 0.41 million in 2011, up from a negligible number in 2004 and 0.37 million in 2010 (Figure 7.4). The coverage of CPT among TB patients with a documented HIV-positive test result was 79% in 2011 (Table 7.1, Figure 7.5). Further progress is needed to reach the target of 100% that is included in the *Global Plan to Stop TB, 2011–2015*[1] (see Chapter 1). The African and South-East Asia regions achieved particularly high levels of enrolment on CPT: 79% and 89% of TB patients known to be living with HIV, respectively (Table 7.1). Countries that achieved rates of enrolment on CPT of >90% in 2011 included Burkina Faso, Burundi, India, Indonesia, Kenya, Lesotho Mozambique, Myanmar, Namibia, Rwanda, Swaziland, Uganda and the United Republic of Tanzania.

The number of HIV-positive TB patients on ART has

FIGURE 7.4 **Number of HIV-positive TB patients enrolled on co-trimoxazole preventive therapy (CPT) and antiretroviral therapy (ART), 2004–2011**

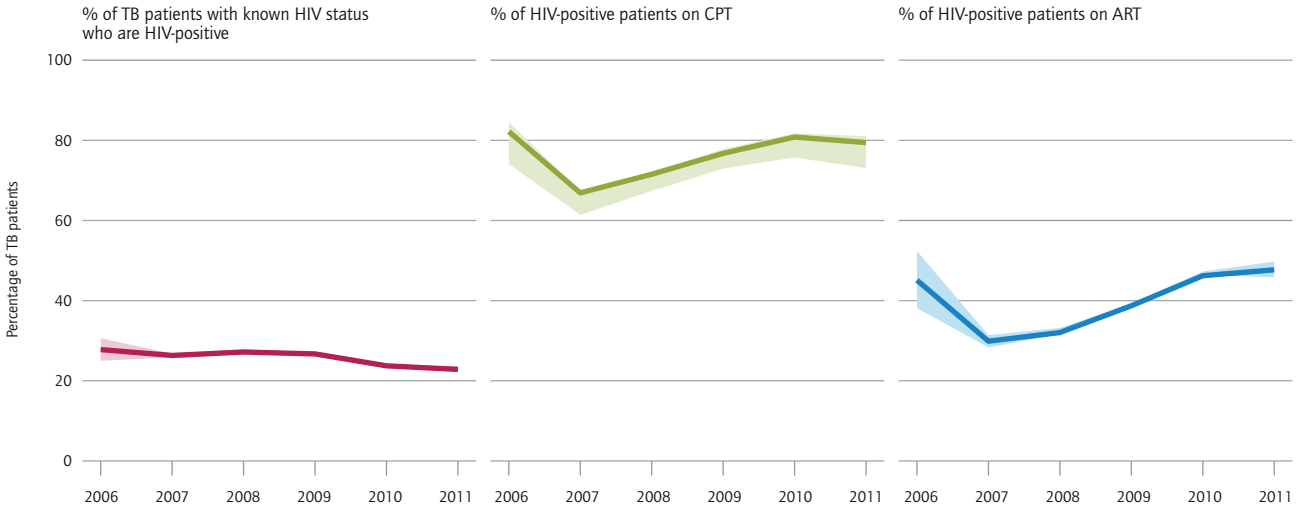


grown from a very low level in 2004 (Figure 7.4) to reach 258 000 in 2011. Among TB patients notified in 2011[2] and who had a documented HIV-positive test result, 48% were on ART globally in 2011 (Table 7.1, Figure 7.5), a small improvement from 46% in 2010. In the African Region, 46% of the TB patients notified in 2011 who had a documented HIV-positive test result were on ART in

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

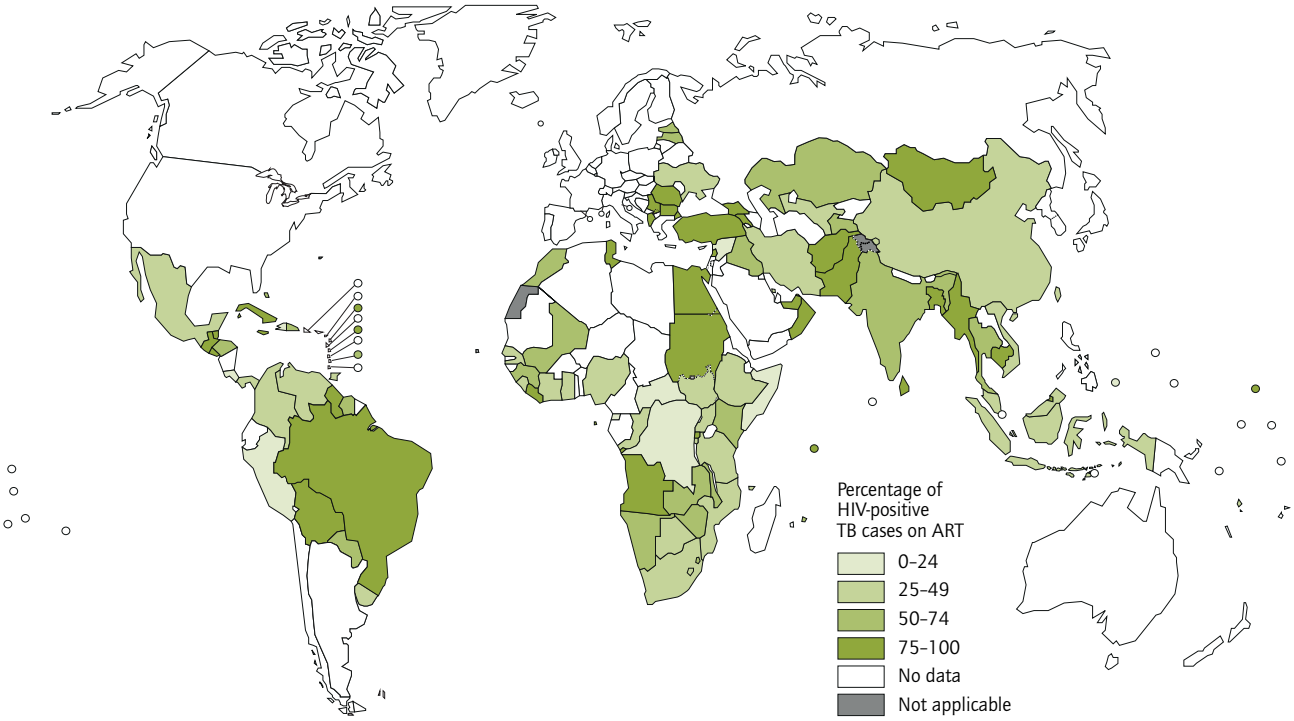
[2] In the annual WHO TB data collection form, countries are asked to report the number of TB patients notified in the most recent calendar year who were living with HIV and who "started or continued on ART".

FIGURE 7.5 **Percentage of TB patients with known HIV status who were HIV positive, and percentage of HIV-positive TB patients enrolled on co-trimoxazole preventive therapy (CPT) and antiretroviral therapy (ART), 2006–2011[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 7.6 **Percentage of HIV-positive TB patients enrolled on antiretroviral therapy (ART), 2011**



2011 (up from 44% in 2010). Among the 41 high TB/HIV burden countries, 15 reported enrolling more than 50% of notified TB patients known to be living with HIV on ART in 2011 (Table 7.1, Figure 7.6).

Given WHO's recommendation that all HIV-positive TB patients are eligible for ART irrespective of their CD4 cell-count and the Global Plan's target of providing ART to all TB patients known to be living with HIV by 2015 (Chapter 1), the coverage of ART for HIV-positive TB patients needs to be improved. This could be facilitated by using TB services and infrastructure to allow decentralization of care delivery according to national guidelines and the local context (Box 7.1).

7.3 Intensifying 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

BOX 7.1

Accelerating progress in providing ART to TB patients living with HIV

People with HIV-associated TB have a high risk of mortality. For example, in autopsy studies of people who were HIV-positive, TB was identified in 30–79%.[1,2] Expanding access to ART will have a significant impact on mortality among HIV-positive TB patients, in addition to reducing the risk of developing TB among people living with HIV who do not have active TB.

Since 2010, WHO has recommended ART for TB patients regardless of CD4 cell-count. Furthermore, the optimum time to start ART in patients with HIV-associated TB has now been established in three large randomized controlled trials.[3,4,5] These studies collectively showed that ART should be given concurrently with TB treatment regardless of CD4 cell-count. The risk of AIDS and death in those with profound immunosuppression (CD4 cell-count <50 cells/mm3) was minimized by starting ART in weeks 2–4 of TB treatment. WHO now recommends initiating TB treatment first, then starting ART as soon as possible within the first 8 weeks of TB treatment. Those with profound immunosuppression should be started on ART within the first 2 weeks of TB treatment.

Despite the current policy recommendations, only 48% of TB patients known to be living with HIV were started on ART in 2011 (**Figure 7.5**, **Table 7.1**). There are several explanations for this, including the availability and allocation of resources and the attitude and capacity of health-care providers. Delayed and inconsistent uptake and adaptation of global policies by national authorities and the relative centralization of ART services compared with the greater decentralization of TB services to more peripheral levels of the health-care system merit special attention.

In a recent analysis of TB and HIV policies and guidelines covering 72 countries,[6] ART was recommended for all TB patients living with HIV, irrespective of their CD4 cell-count, in 24 countries. However, in 24 countries ART was recommended for TB patients living with HIV only if their CD4 cell-count was ≤350 cells/mm^3. In one country, ART was recommended for TB patients living with HIV if their CD4 cell-count was ≤200 cells/mm^3. In the remaining 23 countries, guidelines did not specify any criteria for when to initiate ART in TB patients living with HIV.

TABLE B7.1.1
Distribution of facilities providing TB and ART services in five high TB/HIV burden countries contributing 60% of the global burden of HIV-associated TB, 2011

COUNTRY	TB TREATMENT FACILITIES	ART FACILITIES
India	32 583	1080
Mozambique[a]	1333	229
Nigeria	4387	491
South Africa	4203	3222
Zimbabwe	1548	590

[a] Data for 2010.

The results from a study of the availability of TB and ART services in five high TB/HIV burden countries are shown in **Table B7.1.1**. In each country, there were far more facilities providing TB services. The ratio of TB to ART facilities ranged from 1.3 in South Africa to 30 in India.

These analyses show that to increase the coverage of ART for TB patients living with HIV, national authorities need to adopt national policies and programme guidelines that promote and ensure access to ART. The widely decentralized TB services and staffing offer an opportunity to further decentralize ART services to peripheral-level health-care facilities.

1 Martinson NA et al. Causes of death in hospitalized adults with a premortem diagnosis of tuberculosis: an autopsy study. *AIDS*, 2007, 21:2043–2050.

2 Lawn SD, Harries AD, Meintjes G et al. Reducing deaths from tuberculosis in antiretroviral treatment programmes in sub-Saharan Africa. *AIDS*, 2012 (epub ahead of print).

3 Blanc FX et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *New England Journal of Medicine*, 2011, 365:1471–1481.

4 Havlir DV et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *New England Journal of Medicine*, 2011, 365:1482–1491.

5 Abdool Karim SS et al. Integration of antiretroviral therapy with tuberculosis treatment. *New England Journal of Medicine*, 2011, 365:1492–1501.

6 Gupta SS et al. Three I's for HIV/TB and early ART to prevent HIV and TB: policy review of HIV and TB guidelines for high HIV/TB-burden African countries (in press).

the global TB data collection form. In 2011, in an effort to streamline efforts to collect data and improve their quality, information about these two interventions was collected by WHO's HIV/AIDS Department from national HIV programmes as part of reporting on universal access. UNAIDS – the Joint United Nations Programme on HIV/AIDS – also collects data on the multisectoral response to the HIV epidemic, including health system indicators. In 2012, information on TB screening and IPT was collected through the UNAIDS monitoring system. This alternation between systems for data collection may help to explain why fewer countries reported data on TB screening and IPT provision in 2011 compared with 2010. Recording and reporting of TB screening among people living with HIV and provision of IPT to those without active TB is a particular challenge in many countries; further efforts are needed to facilitate and improve the tracking of progress nationally and globally.

Among the 53 countries that reported data, 3.2 million people enrolled in HIV care were screened for TB in 2011,

FIGURE 7.7 **Intensified TB case-finding among people living with HIV, 2005–2011**

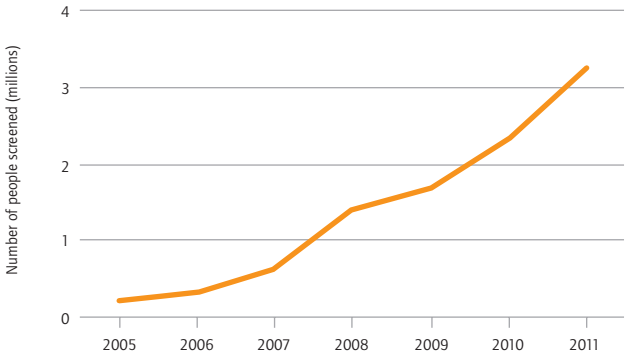


FIGURE 7.8 **Provision of isoniazid preventive therapy (IPT) to people living with HIV without active TB, 2005–2011**

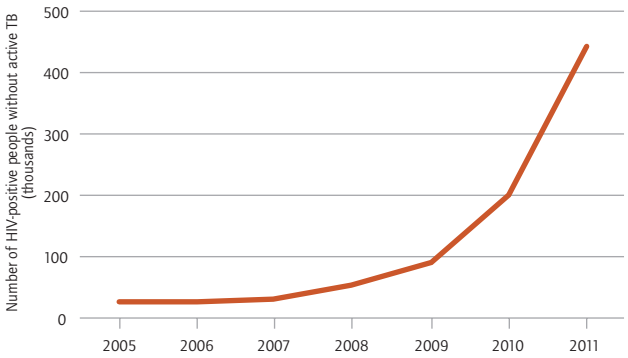
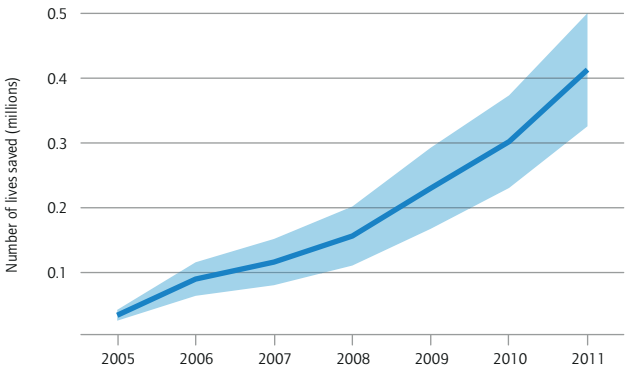


FIGURE 7.9 **Estimated number of lives saved globally by the implementation of TB/HIV interventions, 2005–2011.** The blue band represents the uncertainty interval.



compared with 2.3 million in 71 countries in 2010 (Figure 7.7). Unfortunately, at the time this report went to press, the total number of people enrolled in HIV care in 2011 was not available (the figure was 4.0 million in 2010). Nonetheless, it is clear that further progress is needed to approach the target in the Global Plan, which is to screen all those enrolled in HIV care for TB by 2015.

Among 29 countries that reported data, IPT was provided to almost 450 000 people living with HIV in 2011, more than double the 201 000 people provided with IPT in 2010 (Figure 7.8). Most of the increase occurred in South Africa, where 373 000 people were reported to have been provided with IPT in 2011, followed by Ethiopia (31 000), Mozambique (17 000) and Namibia (14 000). Unfortunately, at the time this report went to press, the total number of people newly enrolled in HIV care in 2011 and potentially eligible for IPT was not available (the figure was 1.5 million in 2010). However, as with TB screening among people in HIV care, it is clear that further efforts are needed to reach the Global Plan's 2015 target of providing IPT to all those eligible for it – estimated at approximately 50% of those newly enrolled in HIV care.

7.4 Lives saved by the implementation of collaborative TB/HIV activities, 2005–2011

In the years between the publication of WHO's first policy on collaborative TB/HIV activities in 2004 and updated guidance launched in 2012,[1,2] considerable progress in implementing the recommended package of interventions occurred, as documented in Section 7.1, Section 7.2 and Section 7.3. At the time that updated guidance was published in March 2012, the lives saved as a result of the implementation of collaborative TB/HIV activities between 2005 and 2010 were estimated. Here, the analysis is extended to 2011 and methods are explained.

Four interventions were considered:

- ART provided during TB treatment for people living with HIV;
- CPT provided during TB treatment for people living with HIV;
- IPT for HIV-positive people enrolled in HIV care;
- Early TB diagnosis through systematic screening for TB among people living with HIV.

These interventions were compared with a counterfactual scenario defined as no ART, no CPT, no IPT and no TB screening.

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

[2] *WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders*. Geneva, 2012 (WHO/HTM/TB/2012.1).

TABLE 7.2 **Assumptions used to estimate lives saved by ART, CPT, screening for TB among people living with HIV and IPT**

INTERVENTION	MEAN EFFICACY IN PREVENTING TB DEATHS	DISTRIBUTION	ASSUMPTIONS
ART for TB patients	0.7	Uniform, 0.6–0.8	
CPT for TB patients[a]	0.21	Normal, standard error 0.09	CPT has no additional benefit if ART is also provided.
IPT for people living with HIV without active TB disease	0.3	Uniform, 0.25–0.35	Efficacy of IPT in preventing TB 0.6; case fatality rate of 50% among HIV-positive TB cases.
Systematic screening of people living with HIV to detect cases of TB, followed by early initiation of TB treatment	0.01	Uniform, 0.0043–0.0157	The probability of detecting TB in systematic screening, per person screened, is 0.05. Detected cases of TB are already on CPT and the proportion started on ART is equal to the global ART:CPT ratio. TB screening has no additive effect for people already on ART. Additional impact of early TB treatment for people not on ART but on CPT is 0.2.

[a] www.aidsmap.com/Cotrimoxazole-prophylaxis-cuts-risk-of-death-for-HIV-positive-patients-with-TB-in-Zambia/page/1430833/

The effectiveness of the four interventions was estimated using the parameters defined in **Table 7.2**.

Between 2005 and 2011, the number of lives saved rose from less than 50 000 in 2005 to over 0.4 million in 2011 (**Figure 7.9**); the total cumulative number of lives saved was 1.3 million (range 1.2–1.5 million).

Four limitations of the analysis should be noted. First, any errors and inconsistencies in data reported by countries could not be accounted for. Second, the impact of TB screening among people living with HIV is hard to estimate; the frequency of TB screening determines how early TB diagnosis will be made compared with no screening, and no global data on the frequency of screening were available. Third, only four of the 12 collaborative activities were considered. Fourth, the impact of collaborative TB/HIV activities on the transmission of TB and HIV was not accounted for. For the latter two reasons, the estimates presented here are likely to be conservative.

CHAPTER 8

Research and development

KEY FACTS AND MESSAGES

- Conventional technologies have been constraining progress in TB care and control, but efforts to develop new TB diagnostics, drugs, and vaccines have intensified during the past decade and considerable progress has been made.
- WHO has endorsed several new diagnostic tests or methods since 2007, including Xpert MTB/RIF that has the potential to transform TB care. Other new tests, including point-of-care tests, are in development.
- For the first time in 40 years, a coordinated portfolio of promising new anti-TB drugs is in development, with 11 new or repurposed anti-TB drugs in clinical trials.
- Results from two Phase III trials of 4-month regimens for the treatment of drug-susceptible TB are expected in 2013. In addition, 2 new compounds are being evaluated for use as an adjunct to current optimized regimens for MDR-TB; one compound recently moved to a Phase III trial and the other is expected to do so before the end of 2012.
- A new three-drug combination regimen that could be used to treat both drug-sensitive TB and MDR-TB and shorten treatment duration has been tested in a Phase II study of early bactericidal activity, with encouraging results.
- There are 11 vaccine candidates for TB prevention in Phase I or Phase II trials and one immunotherapeutic vaccine in a Phase III trial. It is hoped that one or two of the candidates 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, but stagnated between 2009 and 2010. At US$ 630 million in 2010, funding falls far short of the annual target of US$ 2 billion specified in the Global Plan to Stop TB 2011–2015.

There has been major progress in TB care and control since the mid-1990s (**Chapters 2–7**). However, achievement of the Stop TB Partnership's target of eliminating TB by 2050 (**Chapter 1**) requires the development of new diagnostics, drugs and vaccines as well as better and wider use of existing technologies. For example, modeling studies show that TB elimination by 2050 demands a combination of improved diagnosis of drug-susceptible and drug-resistant TB, better and shorter treatments for all forms of TB, treatment of people with latent TB infection on a massive scale (especially in high-risk populations) and mass vaccination with a vaccine that is more effective than BCG.[1]

During the past decade, efforts to develop new diagnostics, drugs and vaccines for TB have intensified. For example, public–private partnerships have been created to stimulate the development of novel tools for TB control. These include 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 for new vaccines against TB, Aeras (in 2003) and the TB Vaccine Initiative (in 2008). The Stop TB Partnership includes three working groups for new diagnostics, new drugs and new vaccines, which represent important forums for exchanging information and promoting research.

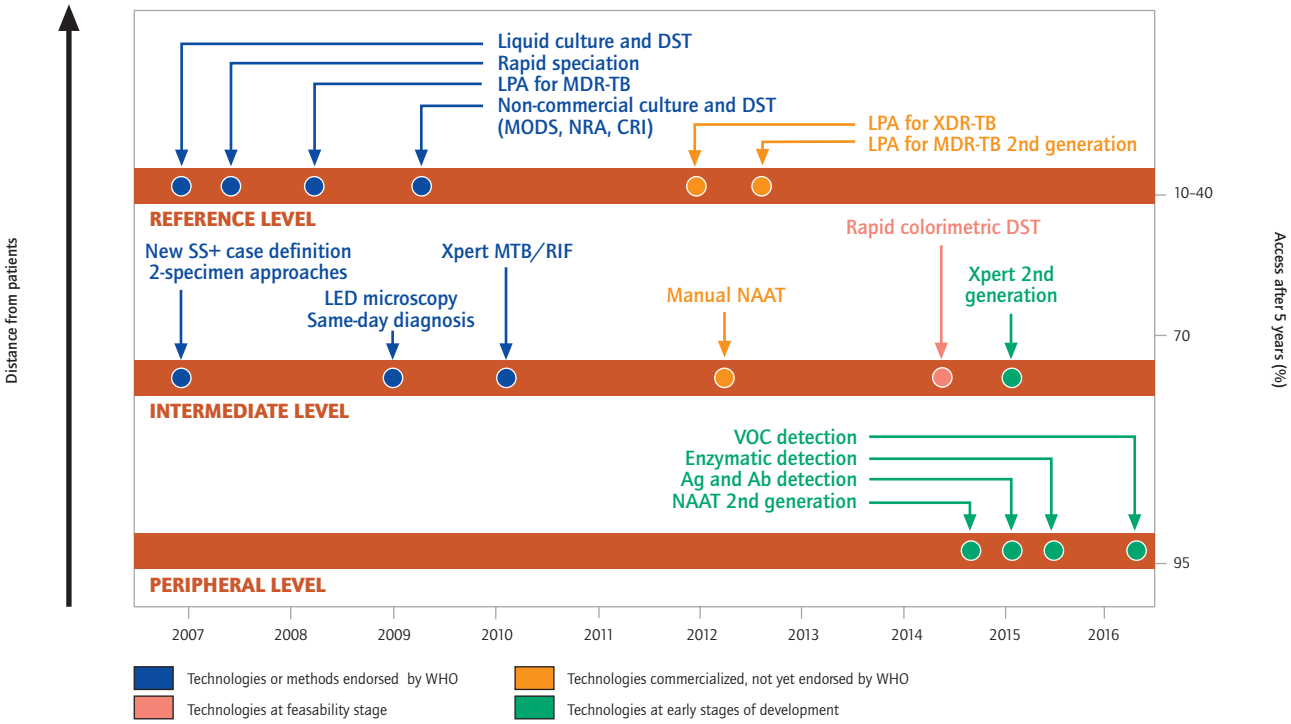
Funding for TB research and development increased from US$ 363 million in 2005 to US$ 630 million in 2010[2] but stagnated between 2009 and 2010. The 2010 level of funding falls about US$ 1.4 billion per year short of the needs described in the *Global Plan to Stop TB 2011–2015*.[3] Major sources of existing funding include the United States National Institutes of Health/National Institute of Allergy and Infectious Diseases (NIH/NIAID), the Bill & Melinda Gates Foundation, the European Commission (including the European Developing Countries Clinical Trials Partnership, EDCTP), USAID and DFID, as well as

[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.

[2] Jiménez-Levi E. *2011 Report on tuberculosis research funding trends, 2005–2010*, 2nd ed. New York, NY, Treatment Action Group, 2012.

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

FIGURE 8.1 **The development pipeline for new TB diagnostics, July 2012**



Abbreviations: **DST** Drug susceptibility test; **NAAT** Nucleic acid amplification test; **LTBI** Latent TB infection; **Ag** Antigen; **Ab** Antibody; **MODS** Microscopic observation drug-susceptibility; **NRA** Nitrate reductase assay; **CRI** Colorimetric redox indicator assay; **LED** Light-emitting diode; **LPA** Line probe assay; **VOC** Volatile organic compound.

several other national, bilateral and multilateral agencies, private companies and philanthropic organizations. To highlight the need for and catalyse further efforts in TB research, a roadmap outlining critical priority areas for future scientific investment across the research spectrum was published in 2011.[1]

In 2011, a chapter on the latest status of progress in TB research and development was introduced in the series of WHO global reports on TB for the first time. In this 2012 report, the status of progress as of July 2012 is summarized, drawing primarily on information provided by the secretariats of the relevant working groups of the Stop TB Partnership.

8.1 New diagnostics for TB

Sputum-smear microscopy – the most commonly used diagnostic test for TB – is more than 100 years old. This test is relatively insensitive and it cannot be used to identify paucibacillary or extrapulmonary TB. Diagnosis using culture methods – the current reference standard – requires laboratory infrastructure that is not widely available in countries with a high burden of TB (Chapter 6), and results are only available after a few weeks. Conventional methods used to diagnose multidrug-resistant TB (MDR-TB) also rely on culturing of specimens followed by drug susceptibility testing (DST); results take weeks to obtain and not all laboratories with the capacity to perform DST of first-line drugs have the capability to perform DST of second-line drugs.

The status of the pipeline for new TB diagnostics in July 2012 is shown in Figure 8.1. After decades of stagnation, accelerated development of new TB diagnostics in the past decade presents real hope that rapid diagnosis of TB and MDR-TB can become a reality, thus removing longstanding barriers to TB care and control.

In the past 5 years, WHO has endorsed several new tests and diagnostic approaches. These include:

- liquid culture with rapid speciation as the reference standards for bacteriological confirmation;
- molecular line probe assays for rapid detection of MDR-TB;
- non-commercial culture and DST methods;
- light-emitting diode fluorescence microscopes for improved smear microscopy; and
- Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) for the rapid diagnosis of TB and rifampicin-resistant TB.

Following WHO's endorsement of Xpert MTB/RIF in December 2010, research on its use has proliferated. By July 2012, more than 65 peer-reviewed publications had been published, covering the full spectrum of research and confirming initial findings on the test's performance.

[1] *An international roadmap for tuberculosis research*. Geneva, World Health Organization, 2011 (also available at: www.stoptb.org/assets/documents/resources/publications/technical/tbresearchroadmap.pdf; accessed July 2012).

BOX 8.1

Xpert MTB/RIF operational research projects mapped by TREAT-TB

TREAT-TB, a research programme implemented by the Union (an international NGO that conducts work on TB and other lung diseases) with funding from USAID, is monitoring and mapping operational research on Xpert MTB/RIF as part of its work. The topics for which research is being conducted and the number of studies per topic are summarized below.

Use in target populations
People suspected of having TB: 14 studies
People suspected of having MDR-TB: 9 studies
HIV-associated TB: 7 studies
Children: 4 studies

Use at different levels of the health-care system
Point-of-care level: 14 studies
District level: 11 studies
Central level: 7 studies

Impact assessment
Health-care system costs: 13 studies
Patient costs: 12 studies
Health-care system requirements: 12 studies
Equity issues: 3 studies

Further details are available from the TREAT-TB web site at www.treattb.org

BOX 8.2

Xpert MTB/RIF innovations, 2011–2012

There have been five innovations since WHO endorsed the Xpert MTB/RIF assay in December 2010:

- **refinements to the Xpert MTB/RIF assay cartridge**, implemented in 2011, resulting in increased rifampicin specificity without loss of sensitivity;
- **modifications to the software, fluidics and minor changes to Probe B**, resulting in reduced error rates compared with those observed with the earlier cartridges;
- **development of a calibration kit for users**, allowing users to recalibrate the optical system, verify the functioning of the thermal system and conduct a series of system-level tests to ensure full system functionality within specifications, thereby reducing the need for remote calibration of GeneXpert modules;
- **better packaging of cartridges**, resulting in reduced packaging requirements, thus reducing waste and shipping costs; and
- **development of validation panels**, allowing end-users to validate the expected performance of the GeneXpert instrument following installation, to demonstrate their ability to use the assay correctly, and to interpret and report results. Artificial sputum samples spiked with heat-killed TB bacilli, developed by the Global Laboratory Initiative, are now being shipped with each new GeneXpert instrument.

Of particular programmatic relevance are several operational research studies addressing key research questions identified following a WHO Global Consultation on Xpert MTB/RIF held in Geneva in December 2010. These studies are being mapped by an interactive tool developed by the Union-led and USAID-funded TREAT-TB initiative,[1] which complements the monitoring of Xpert MTB/RIF roll-out by WHO.[2] By July 2012, 24 operational research projects in 16 countries had been registered, covering multiple aspects of Xpert MTB/RIF implementation (Box 8.1).

The possibility of using Xpert MTB/RIF to improve the diagnosis of extrapulmonary TB and the diagnosis of TB in children is also being explored. The overall sensitivity and specificity in studies completed to date ranges from 75% to 95%, depending on the type of specimen, with excellent specificity of 99%–100% for all types of specimens investigated. WHO plans to evaluate the evidence in the first half of 2013. It should be noted that specimen collection remains problematic for extrapulmonary TB and in young children who cannot expectorate sputum. Developing safe and effective strategies for specimen collection and optimizing specimen processing for individuals with paucibacillary disease thus remain important topics for research. In the meantime, ongoing innovations to the Xpert MTB/RIF assay have already resulted in significant improvements to the technology (Box 8.2).

In 2011, WHO issued strong policy recommendations against the use of poorly-performing yet expensive commercial, antibody-based serological diagnostic tests, and cautioned against the use of commercial interferon-gamma release assays to detect latent TB infection in high-burden TB and HIV settings (further details about this policy guidance are provided in Chapter 6).

In 2012, WHO evaluated two tests that were already commercially available: a manual molecular assay to detect TB DNA in sputum specimens (TB-LAMP®, Eiken Chemical Co. Ltd., Japan); and a line probe assay for detecting resistance to second-line anti-TB drugs (GenoType® MTBDR*sl*, Hain Lifescience, Germany). The evidence-based process followed by WHO resulted in the conclusion that available data for the TB-LAMP assay were insufficient to proceed with the development of policy guidance. The same process also led to the conclusion that the line probe assay for detecting resistance to second-line anti-TB drugs cannot be used as a replacement test for conventional phenotypic DST, given its modest sensitivity to detect resistance to fluoroquinolones and second-line injectable agents. While the high specificity of the test may allow the assay to be used as a triage test to guide initial treatment – albeit limited to smear-positive

[1] www.treattb.org
[2] http://who.int/tb/laboratory/mtbrifrollout/en/index.html

sputum specimens and TB isolates from culture – conventional phenotypic testing remains the reference standard for detecting extensively drug-resistant TB (XDR-TB) until more data become available. Further details about the evaluation of these tests is provided in **Chapter 6**.

Consistent challenges in developing new TB diagnostics have been the sophisticated and costly laboratory infrastructure and specialized human resources required for the range of tests needed to diagnose TB in its various forms, and test utility being restricted to increasingly sophisticated levels of laboratory services. Only one DST technology – based on a rapid colorimetric method suitable for use at the intermediate laboratory level – is currently at the stage of being tested for feasibility. Second-generation Xpert assays and possible alternative molecular technologies are in the early or conceptual stages of development and are not expected to reach the market before the end of 2015.

TB remains unique among the major infectious diseases in lacking accurate and rapid point-of-care (POC) tests. Insufficient progress in biomarker research, technical difficulties in transforming sophisticated laboratory technologies into robust yet accurate POC platforms, and a lack of interest from industry have resulted in slow and suboptimal progress. The era of "omics" has seen large-scale searches for biological markers of disease and the application of emerging technologies to identify novel markers of disease, particularly from blood and urine. These have traditionally been directed at finding reliable surrogates for culture to assess and/or predict treatment prognosis and have only recently become a focus for the development of TB diagnostics.

Non-sputum based tests remain an attractive avenue to explore for POC development. Commercially available antigen detection assays can identify *Mycobacterium tuberculosis* lipoarabinomannan (LAM) in urine; however, their accuracy in routine clinical use has been suboptimal.[1] Two recent studies evaluating a low-cost, POC version of a commercial TB-LAM test (Determine® TBLAM, Alere Inc., Waltham, MA, USA) showed moderate sensitivity and high specificity in a subgroup of TB patients living with HIV who had advanced immunosuppression (CD4 cell-counts <50), but the overall sensitivity in patients with culture-confirmed TB remained low.[2,3] Further research is needed to evaluate the placement of this test in appropriate algorithms and assess its clinical impact.

The target product profile for an ideal POC test for TB has been described[4] and the evolving landscape of TB diagnostics offers greater promise for developing a user-friendly, robust POC test. Nonetheless, it remains to be seen whether a single test would meet all the requirements of accuracy, speed, robustness, ease-of-use, safety and affordability. In the foreseeable future, therefore, tools in the pipeline will need to be rapidly assessed and deployed if found to be good, while implementation of existing tools must be accelerated in dynamic diagnostic algorithms and at the appropriate levels of laboratory services.

Policy uptake and roll-out of contemporary, rapid TB diagnostics is encouraging (**Chapter 6**), but urgent expansion in their availability and use is required to achieve the testing targets set out in the Global Plan. In addition to the funding required for implementation and scale-up of new technologies endorsed by WHO and appropriate laboratory services (**Chapter 5**), increased investment in research and development in new TB diagnostics remains imperative. In 2010, funding represented only 8% (US$ 48 million) of the overall investment (US$ 630 million) in TB research and development. Indeed, TB diagnostics suffers the largest relative funding gap: US$ 48 million represents only 14% of the Global Plan's target of US$ 340 million/year, compared with 31% for new anti-TB drugs and 20% for new TB vaccines.[5]

8.2 New drugs to treat and prevent 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 requires 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). Regimens for MDR-TB treatment currently recommended by WHO entail 20 months of treatment with second-line drugs for most patients, and are associated with multiple (and sometimes serious) side-effects and lower cure rates (see **Chapter 4**). There are also interactions between anti-TB treatment and antiretroviral therapy (ART) for people living with HIV. New drugs are required to shorten and simplify treatment, to improve

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[1] Minion J et al. Diagnosing tuberculosis with urine lipoarabinomannan: systematic review and meta-analysis. *European Respiratory Journal*, 38(6):1398–1405, 2011.

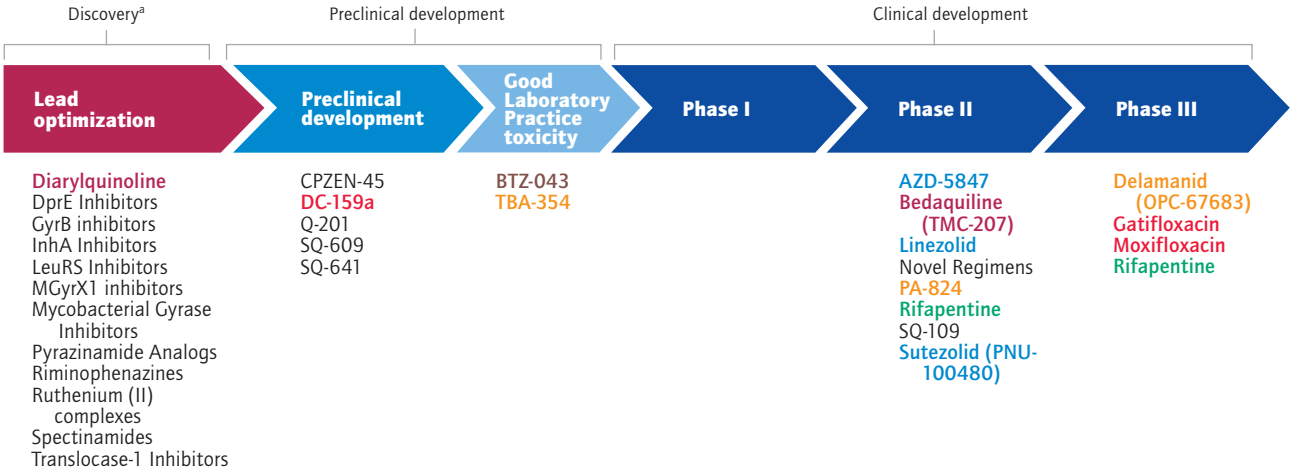
[2] Lawn SD et al. Screening for HIV-associated pulmonary tuberculosis prior to antiretroviral therapy: diagnostic accuracy of a low-cost, urine antigen, point-of-care screening assay for HIV-associated pulmonary tuberculosis before antiretroviral therapy: a descriptive study. *Lancet Infectious Diseases* [epub ahead of print, Oct. 17, 2011].

[3] Peter J et al. The clinical utility of urine lipoarabinomannan and the novel point-of-care lateral flow strip test (determine® TB) for the diagnosis of tuberculosis in hospitalised patients with HIV-related advanced immunosuppression. *American Journal of Respiratory and Critical Care Medicine*, 2011, 183:A5313.

[4] *Paris meeting on TB point-of-care test specifications*. Treatment Action Group, Médecins Sans Frontières, 2009 (available at: **http://www.msfaccess.org/TB_POC_Parismeeting/**; accessed July 2012).

[5] Jiménez-Levi E. *2011 Report on tuberculosis research funding trends, 2005–2010*, 2nd ed. New York, NY, Treatment Action Group, 2012.

FIGURE 8.2 **The development pipeline for new TB drugs, July 2012**



Chemical classes: fluoroquinolone, rifamycin, oxazolidinone, nitroimidazole, diarylquinoline, benzothiazinone

[a] Ongoing projects without a lead compound series can be viewed at www.newtbdrugs.org/pipeline-discovery

Source: Stop TB Partnership Working Group on New TB Drugs; see www.newtbdrugs.org

the efficacy and tolerability of treatment for MDR-TB and to improve the treatment of TB 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 2012 is shown in **Figure 8.2**. Of the new or repurposed TB drugs under clinical investigation, 4 are in Phase III (efficacy) trials and 7 are in Phase II (early bactericidal activity and sputum culture conversion) trials (rifapentine is in a Phase II and a Phase III trial). Two of the Phase III trials are evaluating 4-month combination regimens in which a fluoroquinolone (gatifloxacin or moxifloxacin) is substituted for either ethambutol or isoniazid; results are expected in 2013. A 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 for the treatment of drug-susceptible TB. Since mid-2011, the delamanid (OPC-67683) compound, which is being tested as an addition to optimized background therapy for the treatment of MDR-TB, has moved from a Phase II to a Phase III trial.

Of the seven individual compounds in Phase II trials, bedaquiline (TMC-207) is being tested as an addition to optimized background therapy for the treatment of MDR-TB. It is expected to move to a Phase III trial before the end of 2012. The other six compounds in Phase II trials are linezolid, which has been tested for the treatment of XDR-TB at a dose of 600 mg/day in the Republic of Korea; sutezolid (PNU-100480), an oxazolidinone analogue of linezolid; PA-824, a nitro-imidazole; SQ-109, originally synthesized as a derivative of ethambutol; rifapentine; and AZD-5847, another oxazolidinone.

Besides individual compounds, very promising results on the early bactericidal activity of a novel TB regimen (NC-001) that includes three drugs (PA-824, moxifloxacin and pyrazinamide) became available in July 2012 (**Box 8.3**).

These major advances in drug development mean that multiple trials will be needed in various high-burden countries. This presents several challenges. Trials are lengthy and costly, since patients need to be followed up for an extended period of time after completing treatment. New drugs have to be tested in various drug combinations with current and/or newly re-purposed drugs;[1] to facilitate this, novel biomarkers for treatment response and sterilizing activity, new approaches to the design of clinical trials[2] and increased capacity (including staff and infrastructure) to implement trials in accordance with international standards are required.

Several research groups and institutions worldwide are working to address and overcome these challenges. A good example is the NIH-funded AIDS Clinical Trials Group, whose goal is to transform TB treatment (including HIV-associated TB) by developing and optimizing regimens to treat and prevent TB more quickly and effectively. The group is working on the identification of biomarkers to better understand TB pathogenesis and treatment response and to shorten future clinical trials by using surrogate markers for clinical end-points.[3] This is closely linked to strengthening the capacity of clini-

[1] Lienhardt C et al. New drugs for the treatment of tuberculosis: needs, challenges, promise, and prospects for the future. *Journal of Infectious Diseases*, 2012; published online March 23 (doi: 10.1093/infdis/jis034).

[2] Phillips PJ et al. Innovative trial designs are practical solutions for improving the treatment of tuberculosis. *Journal of Infectious Diseases*, 2012 (doi:10.1093/infdis/JIS041).

[3] **https://actgnetwork.org/**

cal trial sites and building laboratory and pharmacology research capacity; efforts are coordinated with other clinical trial networks to optimize efforts to develop new combination regimens. The Critical Path to New TB Drug Regimens initiative, whose goal is to accelerate the development of novel regimens that will shorten TB treatment, is also an important example of a global effort to ensure that the necessary trials can be implemented.[1]

8.3 New vaccines to prevent TB

The BCG (Bacille-Calmette-Guérin) vaccine for the prevention of TB is almost 100 years old. The vaccine protects against severe forms of TB in children (TB meningitis and miliary TB), but its efficacy in preventing pulmonary TB in adults is highly variable. 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 developing new TB vaccines arose during the 1990s, following the development of techniques for genetic manipulation of mycobacteria and completion of the genome sequence of *M. tuberculosis*.

Two different approaches are being used to develop TB vaccines for prevention of TB.[2] The first approach is to develop vaccines that would do better than BCG and replace it – such as an improved version of BCG or a new attenuated live *M. tuberculosis* vaccine. The second approach is to develop a "prime-boost" strategy in which BCG continues to be given to neonates (as now), since it prevents TB in infants and children, and give the new vaccine as a "booster" dose at a later stage. Alternatively, the new vaccine would be delivered to infants alongside other vaccines at 3–9 months of age and as a separate booster in young adults. The vaccine candidates currently under development could be used to prevent either infection (pre-exposure), or to prevent primary progression to disease or reactivation of latent TB (post-exposure). Work is also being carried out to develop vaccines that could be used as immunotherapeutic agents, i.e. to improve responsiveness to chemotherapy.

The status of the pipeline for new vaccines in July 2012 is shown in **Figure 8.3**. Of the 12 vaccine candidates in clinical trials, 11 are for prevention of TB and one is an immunotherapeutic vaccine.

MVA85A is an attenuated vaccinia-vectored vaccine candidate designed as a booster vaccine for infants, adolescents and adults. Among existing vaccine candidates for TB prevention, it is the one that is most advanced in terms of clinical testing. The first Phase IIb trial of this vaccine was conducted in South Africa from 2009 to 2011, with 2797 infants enrolled. Results are expected in early 2013, and will provide the first efficacy data of a

[1] **http://www.c-path.org/CPTR.cfm**

[2] Kaufmann SHE, Hussey G, Lambert PH. New vaccines for tuberculosis. *Lancet*, 2010, 375:2110–2119.

BOX 8.3

Testing the new drug regimen PaMZ (NC-001): progress by mid-2012

Novel anti-TB drug regimens could transform therapy by shortening and simplifying the treatment of both drug-sensitive and drug-resistant TB with the same oral regimen. Novel regimens for treatment of MDR-TB have the potential to be much less expensive than currently recommended therapies (since they include fewer drugs and treatment duration is shorter), fostering expansion of treatment globally.

NC-001 – also known as New Combination 1 – is a trial of a novel TB regimen that includes the drug candidate PA-824 combined with moxifloxacin and the standard first-line anti-TB drug, pyrazinamide (PaMZ). The trial is being conducted in partnership with and sponsored by the TB Alliance. The regimen has been tested for early bactericidal activity against pulmonary TB over a 2-week period, with encouraging results.[1] The regimen had bactericidal activity at least comparable to a standard regimen of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E). This study also validated a new approach to the development of new anti-TB drug regimens, which has the potential to reduce the time required to complete clinical trials from decades to years. Research on NC001 has also included testing of some novel combinations of two drugs that may form the "core" of future regimens, thus informing other clinical trials being planned during the next 18 months and beyond.

The testing of the PaMZ regimen advanced to a 2-month trial (called NC-002) in March 2012. In this trial, carried out in Brazil, South Africa and the United Republic of Tanzania, PaMZ is being tested for patients with drug-sensitive TB and patients with drug-resistant TB who are sensitive to the drugs included in the new regimen. The NC-002 trial is a landmark trial: it is the first to simultaneously investigate treatment of both drug-sensitive and drug-resistant disease using the same regimen. Results are expected in the third quarter of 2013.

[1] Diacon AH et al. 14-day bactericidal activity of PA-824, bedaquiline, pyrazinamide, and moxifloxacin combinations: a randomised trial. *Lancet*, 2012;380(9846):986-93.

FIGURE 8.3 **The development pipeline for new vaccines, July 2012**

Source: Stop TB Partnership Working Group on New Vaccines

BOX 8.4

Tuberculosis vaccines: a strategic blueprint

Research into TB vaccines is at a pivotal moment as focus shifts from the discovery of novel approaches and moving new vaccine candidates from the laboratory to early clinical trials to building on the progress that has already been made. This includes learning from the efficacy of vaccine candidates in clinical development, establishing much-needed markers and correlates of immune protection that will help to identify the next generation of vaccine candidates, and laying the groundwork for the licensure and distribution of new TB vaccines.

In March 2012, the Stop TB Partnership's Working Group on New TB Vaccines published *Tuberculosis vaccines: a strategic blueprint*. This charts the future course of TB vaccine research and is intended as guidance for researchers, regulators, advocates, donors, policy and decision-makers, among other stakeholders. The blueprint outlines the major scientific challenges and priorities, critical activities and crucial questions that need to be addressed to develop life-saving TB vaccines in five key priority areas:

- Creativity in research and discovery. The major question to be answered is why certain individuals infected with *M. tuberculosis* are resistant to TB disease.
- Correlates of immunity and biomarkers for TB vaccines. Here, the focus is on identifying correlates of immunity for TB vaccines.
- Clinical trials: harmonization and cooperation. The main question to be addressed is whether TB vaccines can effectively reduce the transmission of *M. tuberculosis*.
- Rational selection of TB vaccine candidates. This priority area tackles the challenge of having all developers of vaccines agree to standardized criteria for the selection and development of novel TB vaccines.
- The critical need for advocacy, community acceptance and funding. Here, the emphasis is on innovative approaches to mobilizing funding for TB vaccines.

The blueprint is designed to initiate a renewed, intensified and well-integrated international effort to develop TB vaccines that will have a significant impact on global TB control.

The complete blueprint, including relevant opinion editorials, is available at http://www.stoptb.org/wg/new_vaccines/

new TB vaccine candidate. A Phase IIb trial of MVA85A is now being conducted in adults living with HIV in Senegal and South Africa; the trial started in 2011 and up to 1400 participants will be enrolled.

AERAS-402/Crucell Ad35 is an adeno-vectored vaccine candidate designed as a booster vaccine for infants, adolescents and adults. A Phase IIb multicentre clinical trial in healthy infants is under way in Kenya, Mozambique and South Africa; up to 4000 participants will be enrolled.

There are four vaccines in Phase II trials. M72 and Hybrid-1 are two distinct protein subunit vaccines, formulated in novel adjuvants to enhance their immunogenicity. Both vaccines, which are based on a combination of two immune-dominant antigens from *M. tuberculosis*, are being tested in Phase IIa trials in Europe and Africa. VPM 1002 is a live recombinant vaccine, derived from the Prague strain of the BCG vaccine into which the listerolysin gene from *Listeria* monocytogenes has been cloned and the urease gene deleted to improve immunogenicity. This vaccine is currently in a Phase IIa trial in South Africa. Finally, RUTI, a non-live vaccine based on fragmented *M. tuberculosis* bacteria, is in a Phase IIa trial in Spain.

Research on new TB vaccines is at a crucial juncture. While the past decade focused on the discovery of novel approaches and moving new vaccine candidates from the laboratory to early clinical trials, the next decade will focus on consolidating progress.[1] This will entail learning from the efficacy of vaccine candidates in clinical development and identifying much-needed markers and correlates of immune protection that will greatly assist in the selection of the next generation of vaccine candidates.[2] The future course of work on new TB vaccines has been charted in a new strategic document, *Tuberculosis vaccines: a strategic blueprint*, developed by the Stop TB Partnership's Working Group on New TB Vaccines and published in March 2012 (**Box 8.4**).

8.4 Fundamental science and operational research to stimulate innovation and optimize the use of available tools

Fundamental science is necessary to drive innovations in new tools for improved TB care and control. Fundamental research is required to better characterize *M. 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. Investments in basic science for TB worldwide, at US$ 129 million in 2010, represented 20% of global spending on TB research and development. The largest share of this funding (43%) was from NIH/NIAID.

Researchers supported to conduct biomedical and fundamental research on TB through NIAID and other major funding agencies are making great strides in redefining the spectrum of TB disease and the transition from latent to active TB, and developing a better understanding of the reasons why prolonged antibiotic treatment is needed. This progress is expected to deliver better knowledge about pathogenesis, identification of biomarkers and bio-signatures relevant to new TB diagnostics. It is also expected to point to new targets for anti-TB drugs as well as early indicators of protective immunity, vaccine efficacy and early response to treatment. Such developments will facilitate the selection and testing of new interventions. To catalyze further progress and pave the way for future research, an *International Roadmap for TB Research* has been developed.[3] This outlines critical priority areas for future scientific investment.

A guide on *Operational research priorities to improve TB care and control* was published in 2011.[4] It defines the critical questions that need to be addressed to improve current programmatic performance and to facilitate the introduction of novel strategies and interventions that use new tools.

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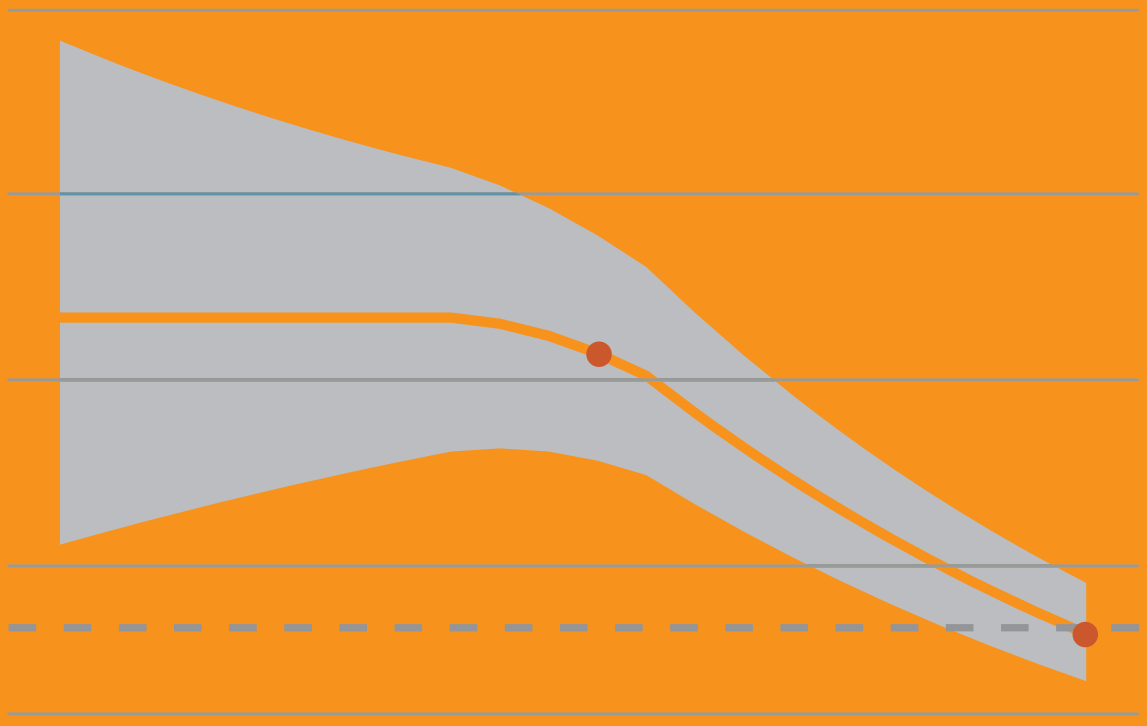
[1] Ottenhoff THM, Kaufmann SHE. Vaccines against tuberculosis: where are we and where do we need to go? *PLoS Pathogens*, 2012, 8(5):e1002607 (doi:10.1371/journal.ppat.1002607).

[2] Barker LF et al. Tuberculosis vaccine research: the impact of immunology. *Current Opinion in Immunology*, 2009, 21(3):331–338.

[3] Stop TB Partnership and World Health Organization. *An International Roadmap for Tuberculosis Research*. Geneva: World Health Organization, 2011 (also available at: **www.stoptb.org/assets/documents/resources/publications/technical/tbresearchroadmap.pdf**; accessed July, 2012).

[4] Stop TB Partnership, Global Fund to Fight AIDS, Tuberculosis and Malaria. *Priorities in operational research to improve tuberculosis care and control*. Geneva, World Health Organization, 2011 (also available at: **http://whqlibdoc.who.int/publications/2011/9789241548250_eng.pdf**; accessed July 2012).

The World Health Organization monitors the global tuberculosis epidemic in support of national TB control programmes.



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