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Annexes

Abbreviations

ART	antiretroviral therapy
ARV	antiretroviral (drug)
BCG	Bacille-Calmette-Guérin
BRICS	Brazil, Russian Federation, India, China, South Africa
CDR	case detection ratio
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CPT	co-trimoxazole preventive therapy
CTD	Central TB Division (India)
CROI	Conference on Retroviruses and Opportunistic Infections
CRS	creditor reporting system
DST	drug susceptibility testing
EMA	European Medicines Agency
EQA	external quality assessment
FDA	US Food and Drug Administration
FIND	Foundation for Innovative New Diagnostics
GDP	gross domestic product
GHE	government health expenditures
HBC	high-burden country
HIV	human immune-deficiency virus
HVTN	HIV Vaccine Trials Network
IDRI	Infectious Disease Research Institute
IGRA	interferon gamma release assays
IMPAACT	International Maternal Pediatric Adolescent AIDS Clinical Trials Group
IPT	isoniazid preventive therapy
LED	light-emitting diode microscopy
LF-LAM	urine lateral flow lipoarabinomannan
LPA	line probe assay
LTBI	latent TB infection
MDGs	Millennium Development Goals
MDR-TB	multidrug-resistant TB
NAAT	nucleic acid amplification test
NHA	National Health Account
NHI	national health insurance
NIAID	US National Institute of Allergy and Infectious Diseases
NRL	national reference laboratory
NTP	national TB programme
OBR	optimized background regimen
OECD	Organization for Economic Cooperation and Development
OOP	out-of-pocket
PK	pharmacokinetic
PMDT	programmatic management of drug-resistant TB
PPM	public-private mix
RNTCP	Revised National Tuberculosis Control Programme (India)
RR-TB	rifampicin-resistant TB
SDGs	Sustainable Development Goals
SMS	short messaging services
SRL	Supranational Reference Laboratory
SRL-CE	SRL National Centres of Excellence
TAG	Treatment Action Group
TB	tuberculosis
TBTC	TB Trial Consortium
TBVI	Tuberculosis Vaccine Initiative
TPP	target product profile
TST	tuberculin skin test
UHC	universal health coverage
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	US Agency for International Development
VR	vital registration
WHA	World Health Assembly
WHO	World Health Organization
XDR-TB	extensively drug-resistant TB
ZN	Ziehl-Neelsen

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Preface

Dr Mario Raviglione

At a meeting of stakeholders and donors to the Global Tuberculosis Programme held in Oslo in September 1995, a key discussion point related to the need to monitor progress towards global targets set in 1991 by the World Health Assembly. The targets – the popular 70% case detection rate and 85% cure rate for new cases of smear-positive pulmonary TB – were to be reached by 2000.

At the time of the meeting, no standardized global monitoring system existed. While clear definitions of TB cases and treatment outcomes were key components of WHO's then-new global TB strategy – DOTS – the only data available to assess trends in the disease came from the epidemiological bulletins of better-off countries and occasional ad-hoc reports from low-income countries following reviews and monitoring missions.

Since TB is primarily a disease of poor countries, this was not good enough for the influential people meeting in Oslo. Their request came loud and clear: WHO should start immediately to develop a system that would request all Member States to report essential information on TB notifications and treatment outcomes, so that progress – or lack of progress – could be monitored and discussed at their next meeting.

Though global targets had been set in 1991, it nevertheless took four years before such a system was recognized as a necessity: this was not yet the era of precision, accountability, and evidence-based evaluation. Since only a couple of other programmes had developed such systems by then, the field of TB was among the pioneers in this endeavour.

As a result of the discussions in Oslo, Dr Arata Kochi, then the Director of the Global TB Programme, asked me to move quickly to create a global monitoring and evaluation system that would satisfy the request.

Exactly 20 years ago, in October 1995, I started setting up a team composed of a handful of people charged with globalizing the local recording and reporting system recommended within the DOTS strategy. That strategy was based on the model programmes that Dr Karel Styblo had developed in several countries where the KNCV Tuberculosis Foundation and the Union were implementing modern TB control efforts.

During several months of intensive work, we created a database and a standard data collection form (in paper and electronic formats) that was distributed to all Member States. By the summer of 1996, most countries had provided information to WHO Headquarters using standardized definitions so that data from one country could be compared easily with data from another. For the first time, we could assess global progress toward the 2000 targets. The results were presented at the September 1996 meeting of donors and other stakeholders. They showed that fewer than 20% of all cases estimated worldwide were being detected and that the global cure rate was less than 80%.

In the following years, our global monitoring and evaluation system for TB evolved further, with the inclusion of additional information and more sophisticated analyses. For example, our team – led first by Dr Christopher Dye and later by Dr Katherine Floyd

– began to monitor the financing of TB control to assess whether Member States were investing as required. Later, we integrated data from the drug resistance surveillance system to enable us to assess comprehensively all the key indicators needed to monitor progress and to identify and correct problems. Our team, under the guidance of Dr Philippe Glaziou, developed more precise estimates of the burden of TB, improving the methodology to measure incidence, prevalence and mortality. In particular, since 2006, concerted efforts have been guided by the WHO Global Task Force on TB Impact Measurement, resulting in substantially increased data from national TB prevalence surveys and much greater use of mortality data from vital registration systems.

As a result of these efforts, 20 years later, we are able to judge fairly precisely the status of the epidemic and the response of Member States. We can assess where people with TB are missing from notification systems; where cure rates remain low and failure rates are high; where multidrug- resistant TB is a serious issue; and where domestic funding must be complemented by international financing. None of this was possible in 1995.

We are now entering the era of the Sustainable Development Goals, in which paradigm shifts are expected in all sectors, including health. TB is an infectious disease that, despite all progress, claims a number of deaths paralleled only by those from HIV/AIDS. To end the epidemic (defined as an incidence of fewer than 100 cases per million people) by 2035 will require a rapid upgrade of care and managerial standards.

During the next 20 years, we will need to change our mentality and adopt all effective innovations, including those exploiting digital technology, especially in the realm of information management. Novel ways of diagnosing and reporting already exist and their adoption will help us evolve further towards interventions that are more user-friendly, cheaper and more sustainable. If fully adopted, these technologies will not only transform the way we handle care and surveillance, but will increase the effectiveness of managerial and training efforts for the benefit of those who suffer from TB.

On the occasion of the publication of this 20th WHO global TB report, which coincides with the assessment of the 2015 global TB targets set as part of the Millennium Development Goals, I am humbled by the progress in terms of impact and operations that we have witnessed in many countries over two decades. The Global Report is a testimony to the tireless efforts of many people worldwide, from National TB Programme staff to community members, from clinicians and nurses to those working for non-governmental organizations who have devoted themselves to the noble fight against a classic example of a disease of poverty.

Mario Raviglione
Director of the Global TB Programme

Executive summary

Background

The year 2015 is a watershed moment in the battle against tuberculosis (TB). It marks the deadline for global TB targets set in the context of the Millennium Development Goals (MDGs), and is a year of transitions: from the MDGs to a new era of Sustainable Development Goals (SDGs), and from the Stop TB Strategy to the End TB Strategy. It is also two decades since WHO established a global TB monitoring system; since that time, 20 annual rounds of data collection have been completed.

Using data from 205 countries and territories, which account for more than 99% of the world's population, this global TB report documents advances in prevention, diagnosis and treatment of the disease. It also identifies areas where efforts can be strengthened.

Main findings and messages

The advances are major: TB mortality has fallen 47% since 1990, with nearly all of that improvement taking place since 2000, when the MDGs were set.

In all, effective diagnosis and treatment of TB saved an estimated 43 million lives between 2000 and 2014.

The MDG target to halt and reverse TB incidence has been achieved on a worldwide basis, in each of the six WHO regions and in 16 of the 22 high-burden countries that collectively account for 80% of TB cases. Globally, TB incidence has fallen by an average of 1.5% per year since 2000 and is now 18% lower than the level of 2000.

This year's report describes higher global totals for new TB cases than in previous years, but these reflect increased and improved national data rather than any increase in the spread of the disease.

Despite these advances and despite the fact that nearly all cases can be cured, TB remains one of the world's biggest threats.

In 2014, TB killed 1.5 million people (1.1 million HIV-negative and 0.4 million HIV-positive). The toll comprised 890 000 men, 480 000 women and 140 000 children.

TB now ranks alongside HIV as a leading cause of death worldwide. HIV's death toll in 2014 was estimated at 1.2 million, which included the 0.4 million TB deaths among HIV-positive people.[1]

Worldwide, 9.6 million people are estimated to have fallen ill with TB in 2014: 5.4 million men, 3.2 million women and 1.0 million children. Globally, 12% of the 9.6 million new TB cases in 2014 were HIV-positive.

To reduce this burden, detection and treatment gaps must be addressed, funding gaps closed and new tools developed.

In 2014, 6 million new cases of TB were reported to WHO, fewer than two-thirds (63%) of the 9.6 million people estimated to have fallen sick with the disease. This means that worldwide, 37% of new cases went undiagnosed or were not reported. The quality of care for people in the latter category is unknown.

Of the 480 000 cases of multidrug-resistant TB (MDR-TB) estimated to have occurred in 2014, only about a quarter of these – 123 000 – were detected and reported.

Although the number of HIV-positive TB patients on antiretroviral therapy (ART) improved in 2014 to 392 000 people (equivalent to 77% of notified TB patients known to be co-infected with HIV), this number was only one third of the estimated 1.2 million people living with HIV who developed TB in 2014. All HIV-positive TB cases are eligible for ART.

Funding gaps amounted to US$ 1.4 billion for implementation of existing interventions in 2015. The most recent estimate of the annual funding gap for research and development is similar, at about US$ 1.3 billion.

From 2016, the goal is to end the global TB epidemic by implementing the End TB Strategy. Adopted by the World Health Assembly in May 2014 and with targets linked to the newly adopted SDGs, the strategy serves as a blueprint for countries to reduce the number of TB deaths by 90% by 2030 (compared with 2015 levels), cut new cases by 80% and ensure that no family is burdened with catastrophic costs due to TB.

[1] The cause of TB deaths among HIV-positive people is classified as HIV in the *International classification of diseases* system.

Additional highlights from the report

Disease burden and 2015 targets assessment

- The quantity and quality of data available to estimate TB disease burden continue to improve. These include direct measurements of mortality in 129 countries and final results from 18 national TB prevalence surveys completed since 2009, six of them in the past year (Ghana, Indonesia, Malawi, Sudan, Zambia and Zimbabwe).
- Revised estimates for Indonesia (1 million new cases per year, double the previous estimate) explain the upward revision to WHO's global estimates of incident cases compared with those published in 2014. Importantly, however, revisions also affect estimates for previous years and the trend in TB incidence globally as well as in Indonesia is still downward since around 2000.
- Of the 9.6 million new TB cases in 2014, 58% were in the South-East Asia and Western Pacific regions.
- The African Region had 28% of the world's cases in 2014, but the most severe burden relative to population: 281 cases for every 100 000 people, more than double the global average of 133.
- India, Indonesia and China had the largest number of cases: 23%, 10% and 10% of the global total, respectively.
- Globally, TB prevalence in 2015 was 42% lower than in 1990. The target of halving the rate compared with 1990 was achieved in three WHO regions – the Region of the Americas, the South-East Asia Region and the Western Pacific Region – and in nine high-burden countries (Brazil, Cambodia, China, Ethiopia, India, Myanmar, the Philippines, Uganda and Viet Nam).
- The target of halving the TB mortality rate by 2015 compared with 1990 was met in four WHO regions – the Region of the Americas, the Eastern Mediterranean Region, the South-East Asia Region and the Western Pacific Region – and in 11 high-burden countries (Brazil, Cambodia, China, Ethiopia, India, Myanmar, Pakistan, the Philippines, Uganda, Viet Nam and Zimbabwe).
- All three of the 2015 targets (for incidence, prevalence and mortality) were met in nine high-burden countries – Brazil, Cambodia, China, Ethiopia, India, Myanmar, the Philippines, Uganda and Viet Nam.

TB case notifications and treatment outcomes

- In the 20 years since WHO established a global reporting system in 1995, it has received reports of 78 million TB cases, 66 million of which were treated successfully.
- In 2014, that system measured a marked increase in global TB notifications for the first time since 2007. The annual total of new TB cases, which had been about 5.7 million until 2013, rose to slightly more than 6 million in 2014 (an increase of 6%). This was mostly due to a 29% increase in notifications in India, which followed the introduction of a policy of mandatory notification in May 2012, creation of a national web-based reporting system in June 2012 and intensified efforts to engage the private health sector. India accounted for 27% of global TB notifications in 2014.
- Globally, the treatment success rate for people newly diagnosed with TB was 86% in 2013, a level that has been sustained since 2005. Treatment success rates require improvement in the Region of the Americas and the European Region (75% in both regions in 2013).

Drug-resistant TB

- Globally, an estimated 3.3% of new TB cases and 20% of previously treated cases have MDR-TB, a level that has changed little in recent years.
- In 2014, an estimated 190 000 people died of MDR-TB.
- More TB patients were tested for drug resistance in 2014 than ever before. Worldwide, 58% of previously treated patients and 12% of new cases were tested, up from 17% and 8.5% respectively in 2013. This improvement is partly due to the adoption of rapid molecular tests.
- If all of the TB cases notified in 2014 had been tested for drug resistance, an estimated 300 000 would have been found to have MDR-TB, with more than half of them (54%) occurring in India, China and the Russian Federation.
- The number of cases detected (123 000) worldwide represented just 41% of this global estimate, and only 26% of the 480 000 incident cases of MDR-TB estimated to have occurred in 2014. Detection gaps were worst in the Western Pacific Region, where the number of cases detected was only 19% of the number of notified cases estimated to have MDR-TB (the figure for China was 11%).
- A total of 111 000 people started MDR-TB treatment in 2014, an increase of 14% compared with 2013.
- The ratio of patients enrolled in treatment to patients newly notified as having MDR-TB or rifampicin-resistant TB was 90% globally. The ratio was above 90% in 15 of the 27 high MDR-TB burden countries as well as in the European Region and the Region of the Americas.
- Globally, only 50% of MDR-TB patients were successfully treated. However, the 2015 treatment success target of ≥75% for MDR-TB patients was reached by 43 of the 127 countries and territories that reported outcomes for the 2012 cohort, including three high MDR-TB burden countries (Estonia, Ethiopia and Myanmar).
- Extensively drug-resistant TB (XDR-TB) had been reported by 105 countries by 2015. An estimated 9.7% of people with MDR-TB have XDR-TB.

Diagnostics and laboratory strengthening

- The use of the rapid test Xpert MTB/RIF® has expanded substantially since 2010, when WHO first recommended its use. In all, 4.8 million test cartridges were procured in 2014 by 116 low- and middle-income countries at concessional prices, up from 550 000 in 2011.
- By 2015, 69% of countries recommended using Xpert MTB/RIF as the initial diagnostic test for people at risk of

drug-resistant TB, and 60% recommended it as the initial diagnostic test for people living with HIV.

Addressing the co-epidemics of TB and HIV

- In 2014, an estimated 1.2 million (12%) of the 9.6 million people who developed TB worldwide were HIV-positive. The African Region accounted for 74% of these cases.
- The number of people dying from HIV-associated TB peaked at 570 000 in 2004 and had fallen to 390 000 in 2014 (a 32% decrease).
- Globally, 51% of notified TB patients had a documented HIV test result in 2014, a small increase from 49% in 2013. The figure was highest in the African Region, at 79%.
- The number of people living with HIV who were treated with isoniazid preventive therapy reached 933 000 in 2014, an increase of about 60% compared with 2013. A large proportion of these people (59%) were in South Africa.

Financing

- The funding required for a full response to the global TB epidemic in low- and middle-income countries is estimated at US$ 8 billion per year in 2015, excluding research and development. Projections made in 2013 suggested that, by 2015, about US$ 6 billion could be mobilized from domestic sources, leaving a balance of US$ 2 billion needed from international donors.
- Based on self-reporting by countries, funding for TB prevention, diagnosis and treatment reached US$ 6.6 billion in 2015, up from US$ 6.2 billion in 2014 and more than double the level of 2006 (US$ 3.2 billion).
- Overall, 87% (US$ 5.8 billion) of the US$ 6.6 billion available in 2015 is from domestic sources.
- International donor funding reported by countries to WHO has increased since 2006, reaching US$ 0.8 billion in 2015.
- The total amount of international donor funding recorded in the creditor reporting system of the Organization for Economic Cooperation and Development (OECD) is higher: the latest data show total contributions of US$ 1 billion in 2013. Of this amount, 77% was from the Global Fund. The largest country donor was the government of the United States of America, which contributed about one third of the TB funding channelled via the Global Fund as well as bilateral funds of US$ 362 million for TB and TB/HIV in 2013.[1]
- Domestic funding accounts for more than 90% of the total funding in 2015 in three country groups: Brazil, the Russian Federation, India, China and South Africa (BRICS); upper-middle-income countries; and regions outside Africa and Asia.
- International donor funding dominates in the group of 17 high-burden countries outside BRICS (72% of the total funding available in 2015) and in low-income countries (81% of the total funding available in 2015).
- The cost per patient treated for drug-susceptible TB in 2014 ranged from US$ 100–500 in most countries with a high burden of TB. The cost per patient treated for MDR-TB was typically US$ 5000–10 000.

Research and development

- In the diagnostics pipeline, tests based on molecular technologies are the most advanced.
- A diagnostic platform called the GeneXpert Omni® is in development. It is intended for point-of-care testing for TB and rifampicin-resistant TB using Xpert MTB/RIF cartridges. The device is expected to be smaller, lighter and less expensive than currently available platforms for point-of-care nucleic acid detection and will come with a built-in, 4-hour battery. WHO expects to evaluate the platform in 2016.
- A next-generation cartridge called Xpert Ultra® is also in development. It is intended to replace the Xpert MTB/RIF cartridge and could potentially replace conventional culture as the primary diagnostic tool for TB.
- Eight new or repurposed anti-TB drugs are in advanced phases of clinical development. For the first time in six years, an anti-TB drug candidate (TBA-354) is in Phase I testing.
- Several new TB treatment regimens for drug-susceptible and/or drug-resistant TB are being tested in Phase II or Phase III trials; at least two more trials are scheduled to start towards the end of 2015 or in early 2016.
- WHO has issued interim guidance on the use of bedaquiline (in 2013) and delamanid (in 2014).
- By the end of 2014, 43 countries reported having used bedaquiline to treat patients as part of efforts to expand access to treatment for MDR-TB.
- Recent observational studies of the effectiveness of short treatment regimens for MDR-TB in Niger and Cameroon found that a 12-month regimen was effective and well-tolerated in patients not previously exposed to second-line drugs. At least 16 countries in Africa and Asia have introduced shorter regimens as part of trials or observational studies under operational research conditions, and WHO will reassess current guidance on their use in 2016.
- Fifteen vaccine candidates are in clinical trials. Their emphasis has shifted from children to adolescents and adults.
- New diagnostics, drugs and vaccines will be needed to achieve the targets set in the End TB Strategy.

[1] Not all of these bilateral funds are captured in the OECD database. For example, this does not record flows of funds between OECD countries, and funding for TB/HIV may be coded as funding for HIV.

Box 1.1 Basic facts about 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. Overall, a relatively small proportion (5–15%) of the estimated 2–3 billion people infected with *M. tuberculosis* will develop TB disease during their lifetime. However, the probability of developing TB is much higher among people infected with HIV.

The most common method for diagnosing TB worldwide remains sputum smear microscopy (developed more than 100 years ago), in which bacteria are observed in sputum samples examined under a microscope. However, developments in TB diagnostics in the last few years mean that the use of rapid molecular tests to diagnose TB and drug-resistant TB is increasing, and some countries are phasing out use of smear microscopy for diagnostic (as opposed to treatment monitoring) purposes. In countries with more developed laboratory capacity, cases of TB are also diagnosed via culture methods (the current reference standard).

Without treatment, the death rate is high. Studies from the pre-chemotherapy era found that about 70% of people with sputum smear-positive pulmonary TB died within 10 years, and that this figure was 20% among culture-positive (but smear-negative) cases of pulmonary TB.[a]

Effective drug treatments were first developed in the 1940s. The most effective first-line anti-TB drug, rifampicin, became available in the 1960s. The currently recommended treatment for new cases of drug-susceptible TB is a six-month regimen of four first-line drugs: isoniazid, rifampicin, ethambutol and pyrazinamide. Treatment success rates of 85% or more for new cases are regularly reported to WHO by its Member States. 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 more toxic drugs. For most patients with MDR-TB, the current regimens recommended by WHO last 20 months, and treatment success rates are much lower.

New TB drugs are now emerging from the pipeline, and combination regimens that include new compounds are being tested in clinical trials. There are several TB vaccines in Phase I or Phase II trials. For the time being, however, a vaccine that is effective in preventing TB in adults remains elusive.

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[a] 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.

CHAPTER 1

Introduction

Tuberculosis (TB) is a major global health problem. It causes ill-health among millions of people each year and ranks alongside the human immunodeficiency virus (HIV) as a leading cause of death worldwide.[1] In 2014, there were an estimated 9.6 million new TB cases: 5.4 million among men, 3.2 million among women and 1.0 million among children. There were also 1.5 million TB deaths (1.1 million among HIV-negative people and 0.4 million among HIV-positive people), of which approximately 890 000 were men, 480 000 were women and 140 000 were children. The number of TB deaths is unacceptably high: with a timely diagnosis and correct treatment, almost all people with TB can be cured. Basic facts about TB are summarized in **Box 1.1**.

The World Health Organization (WHO) has published a global TB report every year since 1997. The main aim of these reports is to provide a comprehensive and up-to-date assessment of the TB epidemic and progress in prevention, diagnosis and treatment of the disease at global, regional and country levels, in the context of recommended global TB strategies and targets endorsed by WHO's Member States. For the past decade, the focus has been on progress towards 2015 global targets for reductions in TB disease burden set in the context of the Millennium Development Goals (MDGs). The targets are that TB incidence should be falling (MDG Target 6.c) and that TB prevalence and mortality rates should be halved compared with their 1990 levels. The Stop TB Strategy,[2] developed for the period 2006–2015, has been WHO's recommended approach to achieving these targets (**Box 1.2**).

With 2015 marking the MDG and global TB target deadline, the special emphasis and most important topic of this 2015 global TB report is an assessment of whether the 2015 targets have been achieved. This assessment is made for the world, for the six WHO regions and for the 22 high-burden countries that collectively account for 80% of TB cases. The topics covered in the remaining six chapters of the report are: TB case notifications and treatment outcomes; drug-resistant TB; diagnostics and laboratory strengthening; addressing the co-epidemics of TB and HIV; financing; and research and development. Since the end of 2015 also marks the end of the MDG and Stop TB Strategy eras and the start of a post-2015 development framework (2016–2030) of Sustainable Development Goals (SDGs)[3] and an associated post-2015 global TB strategy,[4] each chapter of the report features content related to the transition to the new End TB Strategy (**Box 1.3**).

As usual, the 2015 global TB report is based on data collected in annual rounds of global TB data collection from countries and territories, including 194 Member States. This is done using a web-based system (https://extranet.who.int/tme), which was opened for reporting in mid-March. In 2015, 205 countries and territories that account for more than 99% of the world's population and estimated TB cases reported data; this included 183 of WHO's 194 Member States. Data about the provision of isoniazid preventive therapy (IPT) to people living with HIV and antiretroviral therapy (ART) for HIV-positive TB patients, which were collected by the HIV department in WHO and the Joint United Nations Programme on HIV/AIDS (UNAIDS), were also used. Following review and follow-up with countries, the results presented in the main part of this report are based on data available on 6 August 2015.

The report has four annexes. Annex 1 describes the contents of the global TB database, how data were collected and how to access the data. Annex 2 contains country profiles for the 22 high-burden countries (profiles for other countries are available online[5]) and Annex 3 contains regional profiles. Annex 4 provides detailed data tables for key indicators for the most recent year for which data or estimates are available, for all countries.

As the 20th in the series, this 2015 global TB report marks an important landmark in global TB monitoring by WHO.

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[1] In 2014, there were an estimated 1.2 million deaths due to HIV; this includes 0.4 million deaths from TB among HIV-positive people. See unaids.org.

[2] Raviglione M, Uplekar M. WHO's new Stop TB strategy. *The Lancet*, 2006; 367: 952–5.

[3] http://sustainabledevelopment.un.org/focussdgs.html

[4] Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM, et al. WHO's new End TB Strategy. *The Lancet*. 2015;385:1799–801.

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

Box 1.2 The *Stop TB Strategy* at a glance (2006–2015)

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 (defined as <1 case per 1 million population per year)

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 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.

Box 1.3 The *End TB Strategy* at a glance (2016–2035)

VISION	**A WORLD FREE OF TB** — zero deaths, disease and suffering due to TB			
GOAL	**END THE GLOBAL TB EPIDEMIC**			
INDICATORS	**MILESTONES**		**TARGETS**	
	2020	2025	SDG 2030[a]	End TB 2035
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015 (%)	20% (<85/100 000)	50% (<55/100 000)	80% (<20/100 000)	90% (<10/100 000)
TB-affected families facing catastrophic costs due to TB (%)	0	0	0	0

PRINCIPLES

1. Government stewardship and accountability, with monitoring and evaluation
2. Strong coalition with civil society organizations and communities
3. Protection and promotion of human rights, ethics and equity
4. Adaptation of the strategy and targets at country level, with global collaboration

PILLARS AND COMPONENTS

1. INTEGRATED, PATIENT-CENTRED CARE AND PREVENTION

A. Early diagnosis of TB including universal drug-susceptibility testing, and systematic screening of contacts and high-risk groups
B. Treatment of all people with TB including drug-resistant TB, and patient support
C. Collaborative TB/HIV activities, and management of co-morbidities
D. Preventive treatment of persons at high risk, and vaccination against TB

2. BOLD POLICIES AND SUPPORTIVE SYSTEMS

A. Political commitment with adequate resources for TB care and prevention
B. Engagement of communities, civil society organizations, and public and private care providers
C. Universal health coverage policy, and regulatory frameworks for case notification, vital registration, quality and rational use of medicines, and infection control
D. Social protection, poverty alleviation and actions on other determinants of TB

3. INTENSIFIED RESEARCH AND INNOVATION

A. Discovery, development and rapid uptake of new tools, interventions and strategies
B. Research to optimize implementation and impact, and promote innovations

[a] Targets linked to the Sustainable Development Goals (SDGs).

CHAPTER 2

Disease burden and 2015 targets assessment

Key facts and messages

The data available to estimate TB disease burden (incidence, prevalence, mortality) continue to improve. In 2014, data from vital registration (VR) systems and/or mortality surveys were used to estimate TB mortality in 129 countries (up from three countries in 2008). There has been substantial progress in the implementation of national population-based surveys of the prevalence of TB disease since 2008, with 18 surveys (of which 12 were first-ever national surveys) completed between 2009 and August 2015. Of these, results from six surveys were finalized in the past year (Ghana, Indonesia, Malawi, Sudan, Zambia, Zimbabwe), and additional survey results became available for the United Republic of Tanzania. Three additional surveys were begun in late 2014 or 2015. Notification data for 2014 were reported by 205 countries and territories.

This chapter presents the latest WHO estimates of TB disease burden between 1990 and 2015. Special emphasis is given to assessment of whether 2015 targets set in the context of the Millennium Development Goals (MDGs) were achieved. The targets were that incidence should be falling by 2015 (MDG target 6c) and that prevalence and mortality rates should be halved compared with 1990 levels.

Globally in 2014, there were an estimated 9.6 million incident cases of TB: 5.4 million among men, 3.2 million among women and 1.0 million among children. The global total is a considerable upward revision compared with estimates published in 2014, following results from the national prevalence survey in Indonesia. It is now estimated that there are about 1 million new TB cases per year in Indonesia, twice the previously estimated level.

Globally in 2014, there were an estimated 1.2 million new HIV-positive TB cases (12% of all TB cases). Almost three-quarters of these cases were in the African Region.

Globally in 2014, there were an estimated 1.5 million deaths from TB: 1.1 million deaths among people who were HIV-negative and 390 000 deaths among people who were HIV-positive.* TB ranks alongside HIV (1.2 million deaths in 2014, including the 390 000 TB deaths among HIV-positive people) as a leading cause of death worldwide.

The South-East Asia and Western Pacific Regions collectively accounted for 58% of the world's TB cases in 2014. The African Region had 28% of the world's cases, but the most severe burden relative to population (281 incident cases per 100 000 population on average, more than double the global average of 133). India, Indonesia and China had the largest numbers of cases (23%, 10% and 10% of the global total, respectively).

The MDG target of halting and reversing TB incidence by 2015 was achieved globally, in all six WHO regions and in 16 of the 22 high TB burden countries (HBCs). The TB incidence rate has fallen at an average rate of 1.5% per year since 2000.

Globally, the TB mortality rate in 2015 was 47% lower than in 1990: the target of a 50% reduction was almost met. The target was achieved in four WHO Regions (the exceptions were the African and European regions), and in 11 HBCs.

Globally, the TB prevalence rate in 2015 was 42% lower than in 1990. The target of a 50% reduction was met in three WHO regions and in nine HBCs.

All three 2015 targets were met in the Region of the Americas, the South-East Asia Region and the Western Pacific Region, and in nine HBCs: Brazil, Cambodia, China, Ethiopia, India, Myanmar, the Philippines, Uganda and Viet Nam.

Between 2000 and 2014, TB treatment alone saved 35 million lives among HIV-negative people; TB treatment and anti-retroviral therapy saved an additional 8 million lives among HIV-positive people.

* *The underlying cause of TB deaths among HIV-positive people is classified as HIV in the international classification of diseases system.*

The burden of TB disease 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 the latest WHO estimates of TB incidence, prevalence and mortality between 1990 and 2015. Special emphasis is given to assessment of whether 2015 targets set in the context of the Millennium Development Goals (MDGs) were achieved at global level, in the six WHO regions and in the 22 high TB burden countries (HBCs) that collectively account for about 80% of the world's TB cases. The targets were that incidence should be falling by 2015 (MDG target 6c) and that prevalence and mortality rates should be halved compared with their levels in 1990 (**Box 2.1**).

WHO updates estimates of the burden of disease caused by TB annually, using the latest available data and analytical

methods.[1,2] Since 2006, concerted efforts have been made to improve the available data and methods used, under the umbrella of the WHO Global Task Force on TB Impact Measurement (**Box 2.1**). Notification data are consistently reported by about 200 countries and territories each year (205 in 2014). For this report, direct measurements of TB mortality from national or sample vital registration (VR) systems were available for 127 countries (up from three countries in 2008) and data from mortality surveys were available for two countries. Between 2009 and August 2015, 18 population-based surveys of the prevalence of TB disease (of which 12 were first-ever national surveys) were completed. Of these, results from six surveys were finalized in the past year (Ghana, Indonesia, Malawi, Sudan, Zambia, Zimbabwe), and additional survey results became available for the United Republic of Tanzania. These results are reflected in prevalence estimates published in this report, and have also allowed improvements to estimates of TB incidence and mortality. Those for Indonesia in particular have had a major impact on global estimates of TB incidence and prevalence. A summary of the main updates to available data and methods is provided in **Box 2.2**.

The chapter has five major sections. The first three cover estimates of TB incidence, prevalence and mortality in turn, including assessment of whether the 2015 target was met. The section on TB mortality includes estimates of the lives saved through TB treatment (including the additional benefit from antiretroviral therapy for HIV-positive TB patients) between 2000 and 2014. The fourth section presents estimates disaggregated by age and sex. The fifth and final section explains how WHO will update the current lists of HBCs for the post-2015 era.

2.1 TB incidence

TB incidence has never been measured at national level because this would require long-term studies among large cohorts of people (hundreds of thousands), involving high costs and challenging logistics. Notifications of TB cases provide a good proxy indication of TB incidence in countries that have both high-performance surveillance systems (for example, there is little under-reporting of diagnosed cases) and where the quality of and access to health care means that few cases are not diagnosed. In the large number of countries where these criteria are not yet met, better estimates of TB incidence can be obtained from an inventory study (an inventory study is a survey to quantify the level of under-reporting of detected TB cases; if certain conditions are met, capture-recapture methods can also be used to estimate TB incidence).[3] To date, such studies have been undertaken in only a few countries: examples include Egypt, Iraq, Pakistan and Yemen. A recent example, from the Republic of Korea, is profiled in **Box 2.3**.

The ultimate goal is to directly measure TB incidence from TB notifications in all countries. This requires a combination of strengthened surveillance, better quantification of under-reporting (i.e. the number of cases that are missed by surveillance systems) and universal access to health care. A *TB surveillance checklist* developed by the WHO Global Task Force on TB Impact Measurement defines the standards that need to be met for notification data to provide a direct measure of TB incidence (**Box 2.1**). By August 2015, a total of 38 countries including 16 HBCs had completed the checklist (**Figure 2.1**).

Methods currently used by WHO to estimate TB incidence can be grouped into four major categories (**Figure 2.2**). These are:

1. **Case notification data combined with expert opinion about case detection gaps.** Expert opinion, elicited in regional workshops or country missions, is used to estimate levels of under-reporting and under-diagnosis. Trends are estimated using either mortality data, surveys of the annual risk of infection or exponential interpolation using estimates of case detection gaps for three years. In this report, this method is used for 120 countries that accounted for 51% of the estimated global number of incident cases in 2014.
2. **Results from national TB prevalence surveys.** Incidence is estimated using prevalence survey results combined with either a dynamic model or estimates of the duration of disease. This method is used for 19 countries that accounted for 46% of the estimated global number of incident cases in 2014.
3. **Notifications in high-income countries adjusted by a standard factor to account for under-reporting and under-diagnosis.** This method is used for 73 countries (all high-income countries except the Netherlands and the United Kingdom), which accounted for 3% of the estimated global number of incident cases in 2014.
4. **Results from inventory/capture-recapture studies.** This method is used for 5 countries: Egypt, Iraq, the Netherlands, the United Kingdom and Yemen. They accounted for 0.5% of the estimated global number of incident cases in 2014.

Further details about these methods are provided in the **online technical appendix**[1] and in background documents prepared for the global review of methods used to produce TB burden

[1] The online technical appendix is available at www.who.int/tb/data.

[2] It should be highlighted that these updates affect the entire time-series back to 1990. For this reason, estimates presented in this chapter for 1990–2013 supersede those of previous reports and direct comparisons (for example, 2013 estimates in this report and 2013 estimates in the last report) are not appropriate.

[3] Inventory studies can be used to measure the number of cases that are diagnosed but not reported. A guide on inventory studies is available at: www.who.int/tb/publications/inventory_studies.

Box 2.1 2015 global TB targets assessment

Background

Global targets for reductions in TB disease burden by 2015 were set within the context of the United Nations' Millennium Development Goals (MDGs). The targets were that TB incidence should be falling, and that TB mortality and prevalence rates should be halved by 2015 compared with their level in 1990. The targets were adopted at regional and country levels. The Stop TB Strategy (2006–2015) developed by WHO had the overall goal of achieving these targets (**Chapter 1**).

Since 2005, WHO has published estimates of TB incidence, prevalence and mortality and an assessment of progress towards 2015 targets in its annual global TB report. With 2015 marking the MDG and global TB target deadline, the special emphasis and most important topic of this 2015 global TB report is an assessment of whether the 2015 targets were achieved. This assessment is made for the world, for the six WHO regions and for the 22 high-burden countries (HBCs) that collectively account for 80% of TB cases. It is built on the work of the WHO Global Task Force on TB Impact Measurement.

The WHO Global Task Force on TB Impact Measurement

The WHO Global Task Force on TB Impact Measurement was established in 2006, with the aim of ensuring that assessment of whether 2015 targets were met should be as rigorous, robust and consensus-based as possible.

To fulfil this mandate, the Task Force agreed upon three strategic areas of work:

1. **Strengthened surveillance** in all countries, towards the ultimate goal of direct measurement of TB incidence and TB mortality using notification and vital registration data, respectively;
2. **National TB prevalence surveys** in 22 global focus countries;
3. **Periodic review and updating of methods** used to translate surveillance and survey data into TB disease burden estimates.

A wide range of technical, financial and development agencies, countries and individual experts have been engaged in the work of the Task Force, and full details can be found on the Task Force website.[a]

The Task Force's work on strengthened surveillance has covered four main topics. These are:

- Development of a TB surveillance checklist of standards and benchmarks (with ten core and three supplementary standards).[b] This can be used to systematically assess the extent to which a surveillance system meets the standards required for notification and vital registration data to provide a direct measurement of TB incidence and mortality, respectively. By August 2015, 38 countries including 16 HBCs had used the checklist (**Figure 2.1**).
- Electronic recording and reporting. Case-based electronic databases are the reference standard for recording and reporting TB surveillance data. A guide was produced in 2011,[c] and efforts to introduce such systems have been supported.
- Development of a guide on inventory studies to measure under-reporting of detected TB cases,[d] and support to such studies in priority countries. One of the main reasons for uncertainty in estimates of TB incidence is that in many countries, especially those with a large private sector, cases may be detected but not reported. An inventory study can be used to quantify the number of cases that are detected but not reported to national surveillance systems, and serve as a basis for addressing gaps in reporting.
- Expanded use of data from vital registration (VR) systems and mortality surveys to produce estimates of the number of TB deaths, and contributions to wider efforts to promote VR systems. In this report, estimates of TB mortality are based on such data sources for 129 countries (**Figure 2.15**).

There has been substantial success in the implementation of national TB prevalence surveys. Between 2009 and 2015, 18 countries including 15/22 global focus countries completed a survey and more are scheduled to do so by 2016 (**Figure 2.11**, **Figure 2.12**). Results from these surveys have provided a large body of new evidence about the burden of TB disease (**Box 2.2**) and also have important policy, programmatic and funding implications (**Box 2.4**).

A Task Force subgroup undertook a major review and update of methods between June 2008 and October 2009. Recommendations were endorsed at a full meeting of the Task Force in March 2010. A second thorough and comprehensive review of these methods as well as possible alternatives was undertaken in 2015, with the purpose of reaching consensus on methods to be used for reporting in the 2015 global TB report on whether 2015 targets were met. The key recommendation from the group of experts was that existing methods should be used – the consensus was to "finish the cycle with established methods".[e]

Looking forward: TB burden estimates post-2015

The End TB Strategy includes ambitious targets for reductions in TB incidence and TB mortality (**Chapter 1**). During the expert review of current methods used to estimate these indicators, there was strong agreement that the main goal is to strengthen TB surveillance so that TB cases and TB deaths can be directly measured using notification and vital registration systems.[e] Therefore, the Task Force strategic area of work related to strengthened surveillance needs to be continued. In the interim, for countries without high-performance surveillance systems, options for improving current methods that were identified included the use of new statistical models, use of dynamic models (especially for estimation of TB incidence in countries with recent prevalence survey data), and implementation of more inventory studies to measure under-reporting. It was also agreed that a strategic selection of priority countries in which repeat prevalence surveys should be done to measure trends is important.

[a] www.who.int/tb/advisory_bodies/impact_measurement_taskforce
[b] www.who.int/tb/publications/standardsandbenchmarks/en/
[c] *Electronic recording and reporting for TB care and control*. Geneva, World Health Organization, 2011 (WHO/HTM/TB/2011.22). Available at www.who.int/tb/publications/electronic_recording_reporting
[d] *Assessing tuberculosis underreporting through inventory studies*. Geneva, World Health Organization, 2013 (WHO/HTM/TB/2012.12). Available at: www.who.int/tb/publications/inventory_studies
[e] www.who.int/tb/advisory_bodies/impact_measurement_taskforce/meetings/global_consultation_meeting_report.pdf

Box 2.2 Updates to estimates of TB disease burden in this report and updates that are anticipated in the near future

UPDATES IN THIS REPORT

1. New data from national TB prevalence surveys

Between October 2014 and August 2015, final results from surveys in Ghana, Indonesia, Malawi, Sudan, the United Republic of Tanzania, Zambia and Zimbabwe became available. The size of Indonesia's population and TB burden means that upward revisions to estimates based on the prevalence survey affect global estimates of the absolute number of incident cases (although importantly, global trends in TB incidence are not affected and the impact on estimates of global TB deaths is small given a relatively low case fatality ratio in Indonesia). In the other countries, updated estimates are either higher (Ghana, Malawi, United Republic of Tanzania, Zambia) or lower (Sudan, Zimbabwe) than previous estimates. Post-survey estimates are almost always more precise than earlier estimates that were indirectly derived from incidence (**Figure B2.2.1**).

2. Newly reported data and updated estimates from other agencies

New VR data were reported to WHO between mid-2014 and mid-2015 and some countries made corrections to historical data. UNAIDS published updated HIV estimates in August 2014. The United Nations Population Division published new estimates in July 2015. In most instances, any resulting changes to TB burden estimates are well within the uncertainty intervals of previously published estimates, and trends are generally consistent.

For the first time, estimates of TB mortality (HIV-negative) in Indonesia could be produced using data from a sample vital registration system, after adjustment for incomplete coverage and ill-defined causes of death. For South Africa, estimates of TB mortality (HIV-negative) were obtained from the Institute of Health Metrics and Evaluation; these estimates use data from the national vital registration system, adjusted for widespread miscoding of deaths caused by HIV and TB,[a,b] and replace previous indirect estimates derived from TB incidence and the case fatality ratio.

3. Updated methods for estimating TB burden

In March 2015, the WHO Global Task Force on TB Impact Measurement convened an expert group to review methods for estimating TB disease burden (see **Box 2.1**). In general, the meeting recommended that current methods should be retained, especially for the purposes of reporting on whether 2015 targets were met. An exception was methods used to estimate the burden of TB disease among children, which have been published by WHO since 2013 and which are not relevant to reporting on 2015 targets. It was recommended that WHO should update methods used to estimate TB incidence among children by implementing an "ensemble" approach in which estimates derived from case notifications adjusted for under-detection and under-reporting[c] are combined with estimates derived from dynamic modelling.[d] An additional recommendation was that HIV-positive TB mortality in children should be estimated using a similar approach to that used for disaggregating TB/HIV mortality by sex. Estimates of childhood TB incidence and mortality presented in this report are based on these recommendations.

4. In-depth epidemiological reviews at country level

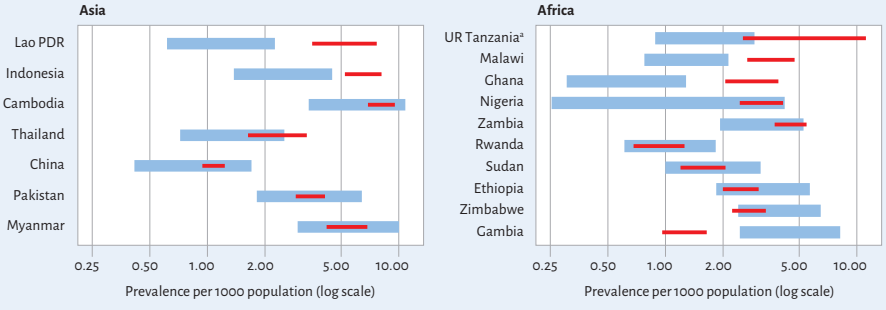
Estimates for Angola were revised based on discussions with experts from the NTP and partners. They should however be considered preliminary, pending the findings of an ongoing epidemiological review. Estimates for Kazakhstan were updated in February 2015 following an in-depth review conducted by WHO staff (headquarters and the Regional Office for Europe) in close collaboration with the Ministry of Health.

UPDATES ANTICIPATED IN THE NEAR FUTURE

Updates to estimates of disease burden are expected within the next year for three countries in which a national TB prevalence survey has been recently completed (Uganda, July 2015) or is scheduled for completion around the end of 2015 (Bangladesh, Mongolia). Estimates of TB incidence may be updated following the implementation of inventory studies to measure under-reporting of detected TB in China, Indonesia, the Philippines, Thailand and Viet Nam. An expert review of methods used to estimate the burden of MDR-TB is scheduled for 2016.

FIGURE B2.2.1

Estimates of TB prevalence (all ages, all forms of TB) for 17 countries, before (in blue) and after (in red) results from national prevalence surveys became available. Panels are ordered according to the before-after difference.[a]



[a] The wide uncertainty interval of the post-survey estimate for the United Republic of Tanzania is because laboratory challenges meant that it was only possible to directly estimate the prevalence of smear-positive (as opposed to bacteriologically confirmed) TB.

[a] Murray C, Ortblad K, Guinovart C et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990–2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet* 2014; 384: 1005–70. 25059949.

[b] Groenewald P, Nannan N, Bourne D et al. Identifying deaths from AIDS in South Africa. *AIDS* 2005; 19: 193–201. 15668545.

[c] Jenkins H, Tolman A, Yuen C et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. *Lancet* 2014; 383: 1572–9. 24671080.

[d] Dodd P, Gardiner E, Coghlan R et al. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. *Lancet Glob Health* 2014; 2: e453–9. 25103518

FIGURE 2.1

Countries that had completed a systematic assessment of TB surveillance using the WHO TB surveillance checklist of standards and benchmarks by August 2015

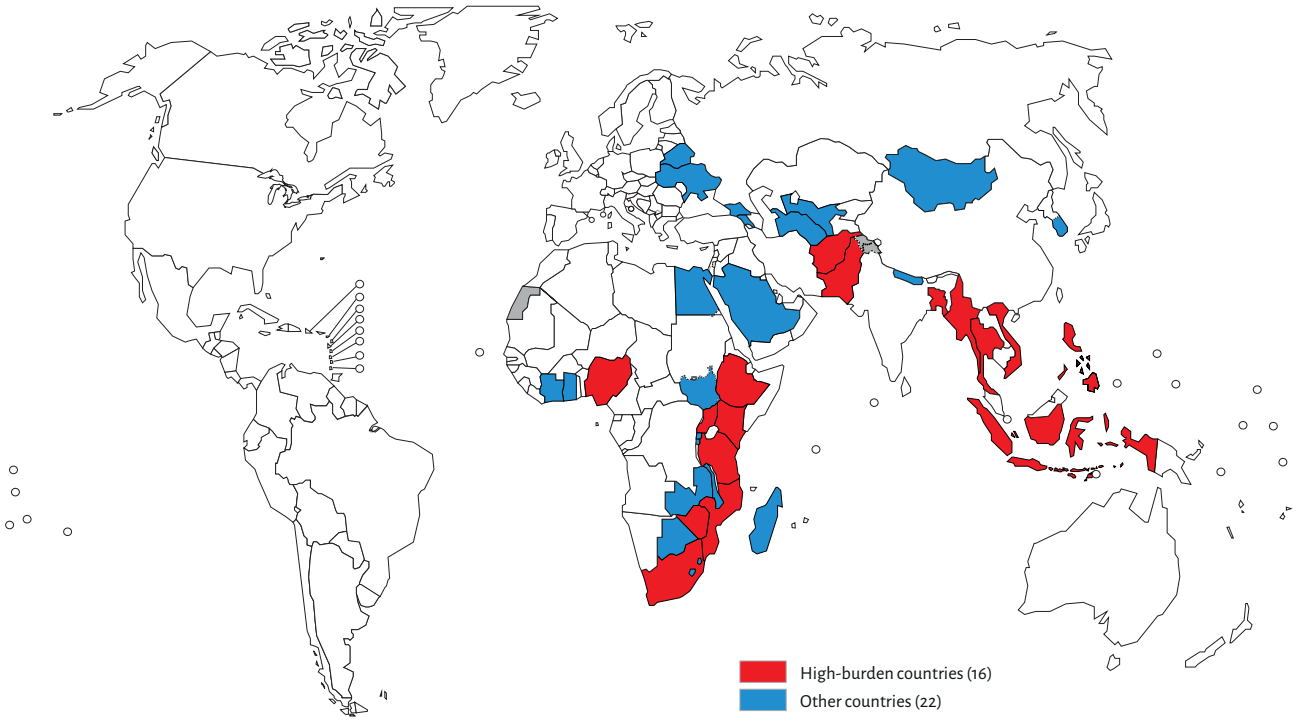
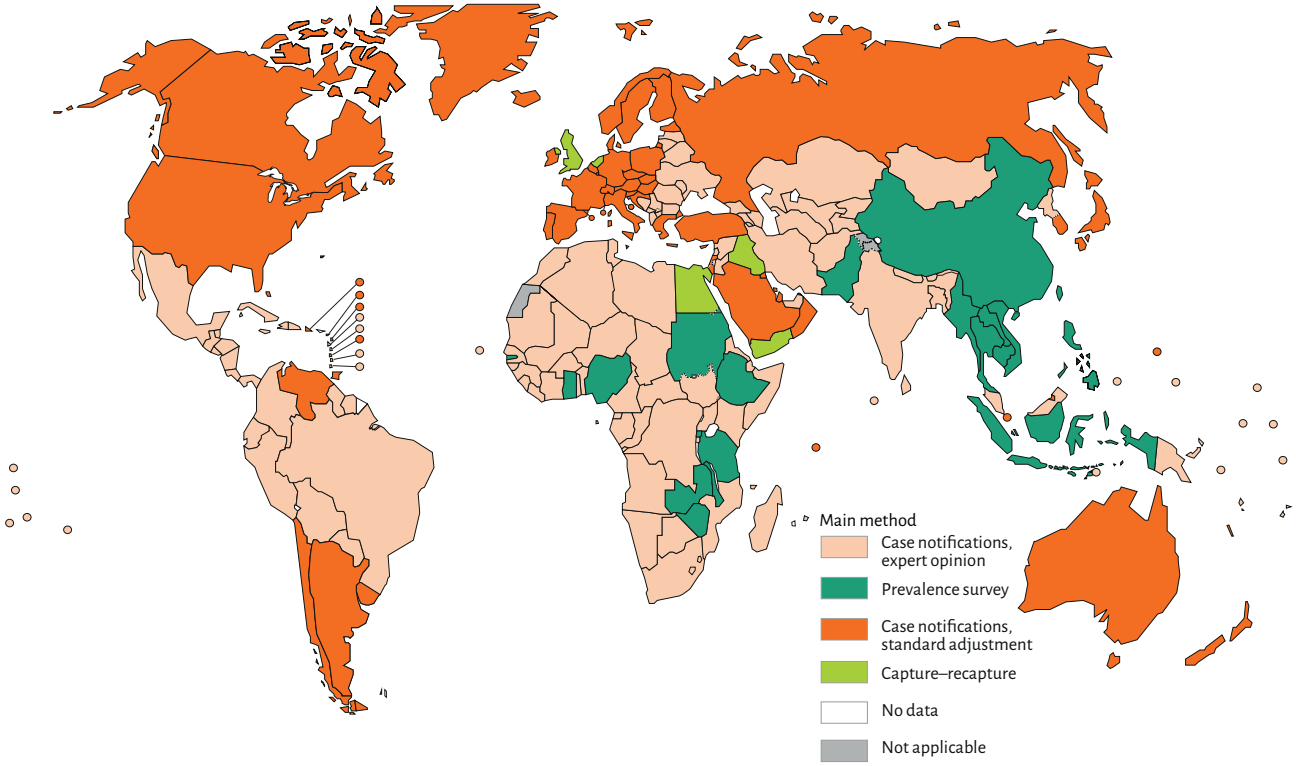


FIGURE 2.2

Main method used to estimate TB incidence[a]



[a] In the first method, case notification data are combined with expert opinion about case detection gaps (under-reporting and under-diagnosis), and trends are estimated using either mortality data, repeat surveys of the annual risk of infection or exponential interpolation using estimates of case detection gaps for three years. For all high-income countries except the Netherlands and the United Kingdom, notifications are adjusted by a standard amount or measure of under-reporting from inventory studies, to account for case detection gaps. For further details about all four methods, see text.

Box 2.3 Low level of under-reporting of detected TB cases in the Republic of Korea

A national case-based and internet-based TB notification system is a key element of the NTP in the Republic of Korea, linked to the initiation of response measures including outbreak investigations, evaluation of contacts and TB case management. The online TB reporting system was established in 2000.[a]

All TB patients who are treated in public health centres are notified to the Korea National TB Surveillance System (KNTSS). In 2006, a national survey found that only 67.6% of patients diagnosed and treated in the private sector were notified, despite a legal framework making notification of TB cases mandatory. Since 2008, the coverage of routine TB surveillance has been systematically assessed using record-linkage of medical records from the National Health Insurance (NHI) system and records from the KNTSS database.[b] National identification numbers are used for record-linkage.

Data on levels of under-reporting of TB case notifications in 2012 and 2013 are presented in **Table B2.3.1**. Under-reporting was defined as failing to report a detected case within 6 months.

TABLE B2.3.1

Under-reporting of detected TB cases in the Republic of Korea

	2012	2013
National health insurance system	36 735	33 800
National TB surveillance system	32 515	31 534
Under-reporting	11.5%	6.7%

Under-reporting to the national TB surveillance system was found to be lower when cases were diagnosed in general hospitals (8%, 2012–2013) compared with private clinics (24%). A regulation is being put in place that makes reimbursement from the national health insurance system conditional upon notification of cases by prescribing physicians, as part of a 5-year plan for TB elimination (2013–2017). In 2011, the national health insurance system covered 90% of medical expenses related to TB, and reimbursement coverage is planned to reach 100% for TB patients in 2016. The new regulation regarding conditional reimbursement and the planned increase in coverage of health insurance to 100% for TB patients should ensure a close to zero level of under-reporting of detected cases in the near future.

[a] WJ Lew, EG Lee, JY Bai et al. An Internet-based surveillance system for tuberculosis in Korea. *Int J Tuberc Lung Dis*, 2006; 10:1241–7.
[b] YS Park, SJ Hong, YK Boo et al. The national status of tuberculosis using nationwide medical records survey of patients with tuberculosis in Korea. *Tuberc Respir Dis (Seoul)*, 2012; 73:48–55.

estimates that was held 31 March–2 April 2015 (**Box 2.1**).[1,2]

In 2014, there were an estimated 9.6 million incident cases of TB (range, 9.1 million–10.0 million)[3] globally, equivalent to 133 cases per 100 000 population (**Table 2.1**, **Table 2.2**). The absolute number of incident cases is falling slowly (**Figure 2.3**), at an average rate of 1.5% per year 2000–2014 and 2.1% between 2013 and 2014. The cumulative reduction in the TB incidence rate 2000–2014 was 18%.

Most of the estimated number of cases in 2014 occurred in Asia (58%) and the African Region (28%);[4] smaller proportions of cases occurred in the Eastern Mediterranean Region (8%), the European Region (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 83% of all estimated incident cases worldwide. The six countries that stand out as having the largest number of incident cases in 2014 were India, Indonesia, China, Nigeria, Pakistan and South Africa; these and the other five countries that make up the top ten in terms of numbers of cases are highlighted in **Figure 2.4**. India, Indonesia and China alone accounted for a combined total of 43% of global cases in 2014.

The 9.6 million incident TB cases in 2014 included 1.1 million–1.3 million (11–13%) among people living with HIV, with a best estimate of 1.2 million (12%) (**Table 2.1**, **Table 2.2**). The proportion of TB cases co-infected with HIV was highest in countries in the African Region (**Figure 2.5**). Overall, 32% of TB cases were estimated to be co-infected with HIV in this region, which accounted for 74% of TB cases among people living with HIV worldwide. In parts of southern Africa, more than 50% of TB cases were co-infected with HIV (**Figure 2.5**).

Following a systematic review of evidence about mortality caused by MDR-TB undertaken in 2013 and consensus about what indicators to use for reporting on the burden of MDR-TB,[5] this report includes updated global estimates of MDR-TB incidence and mortality. The best estimate is that there were 480 000 (range, 360 000–600 000) new cases of MDR-TB worldwide in 2014 (see also **Chapter 4**). This total includes cases of primary and acquired MDR-TB.

The number of incident TB cases relative to population size (the incidence rate) varies widely among countries (**Figure 2.6**, **Figure 2.7**). The lowest rates are found predominantly in high-income countries including most countries in western Europe, Canada, the United States of America, Australia and New Zealand. In these countries, the incidence rate is less than 10 cases per 100 000 population per year. Most countries in the Region of the Americas have rates below 50 per 100 000 population per year and this is the region with

[1] The online technical appendix is available at www.who.int/tb/data.
[2] All background documents are available at www.who.int/tb/advisory_bodies/impact_measurement_taskforce/meetings/consultation_april_2015_tb_estimates_subgroup/en/
[3] "Range" refers here and elsewhere to the 95% uncertainty interval.
[4] Asia refers to the WHO Regions of South-East Asia and the Western Pacific.
[5] See **Box 5.3**, **Chapter 5** in the 2014 global TB report.

TABLE 2.1

Estimated epidemiological burden of TB, 2014. Best estimates are followed by the lower and upper bounds of the 95% uncertainty interval. Numbers in thousands.[a]

	POPULATION	MORTALITY[b]		HIV-POSITIVE TB MORTALITY		PREVALENCE		INCIDENCE		HIV-POSITIVE INCIDENT TB CASES	
Afghanistan	31 628	14	10–18	<0.1	0–0.1	110	56–180	60	53–67	0.3	0.2–0.4
Bangladesh[c]	159 078	81	59–110	0.2	0.1–0.2	640	340–1 000	360	320–410	0.6	0.4–0.7
Brazil	206 078	5.3	4.9–5.7	2.4	1.8–3.2	110	51–180	90	86–95	16	14–17
Cambodia	15 328	8.9	6.3–12	0.8	0.6–1.0	100	87–120	60	54–66	1.8	1.6–2.0
China	1 369 436	38	37–40	0.7	0.5–0.9	1 200	1 100–1 400	930	860–1 000	13	11–16
DR Congo	74 877	52	38–68	6.3	5.0–7.7	400	210–640	240	220–270	34	27–42
Ethiopia	96 959	32	22–43	5.5	4.4–6.8	190	160–240	200	160–240	19	15–23
India	1 295 292	220	150–350	31	25–38	2 500	1 700–3 500	2 200	2 000–2 300	110	96–120
Indonesia	254 455	100	66–150	22	13–32	1 600	1 300–2 000	1 000	700–1 400	63	41–90
Kenya	44 864	9.4	6.7–12	8.1	6.4–10	120	64–190	110	110–110	40	38–42
Mozambique	27 216	18	12–26	37	29–45	150	80–240	150	120–180	85	65–110
Myanmar	53 437	28	20–37	4.1	3.3–5.1	240	190–310	200	180–220	19	15–24
Nigeria	177 476	170	91–280	78	53–110	590	450–740	570	340–870	100	59–160
Pakistan	185 044	48	11–110	1.3	0.8–1.9	630	530–740	500	370–650	6.4	4.4–8.7
Philippines	99 139	10	9.0–11	<0.1	0–0.1	410	360–470	290	250–320	2.5	2.0–3.2
Russian Federation	143 429	16	15–16	1.1	0.8–1.3	160	70–270	120	110–130	5.5	4.5–6.6
South Africa	53 969	24	22–26	72	58–89	380	210–590	450	400–510	270	240–310
Thailand	67 726	7.4	3.9–12	4.5	2.3–7.4	160	110–220	120	61–190	15	7.8–24
Uganda	37 783	4.5	3.2–6.1	6.4	5.0–8.1	60	33–95	61	53–69	28	24–32
UR Tanzania	51 823	30	13–54	28	15–43	270	110–510	170	80–290	62	29–110
Viet Nam	92 423	17	11–23	1.9	1.3–2.5	180	76–330	130	110–150	7	5.7–8.5
Zimbabwe	15 246	2.3	1.4–3.4	5.2	3.2–7.8	44	24–71	42	29–58	25	17–35
High-burden countries	**4 552 704**	**940**	**790–1 100**	**320**	**280–360**	**10 000**	**9 200–12 000**	**8 000**	**7 500–8 500**	**930**	**850–1 000**
AFR	963 361	450	350–560	310	270–350	3 200	2 800–3 600	2 700	2 400–3 000	870	790–950
AMR	981 613	17	16–18	6	5.2–6.8	350	270–440	280	270–290	36	34–38
EMR	635 745	88	43–150	3.2	2.6–4.0	1 000	880–1 200	740	610–890	12	10–15
EUR	907 279	33	33–34	3.2	2.7–3.7	440	330–560	340	320–350	20	18–21
SEAR	1 906 087	460	350–570	62	51–74	5 400	4 400–6 500	4 000	3 700–4 400	210	180–240
WPR	1 845 184	88	81–95	4.9	4.2–5.7	2 100	1 900–2 400	1 600	1 500–1 600	31	28–35
Global	**7 239 269**	**1 100**	**970–1 300**	**390**	**350–430**	**13 000**	**11 000–14 000**	**9 600**	**9 100–10 000**	**1 200**	**1 100–1 300**

[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 and are shown separately in this table.
[c] For Bangladesh, a joint reassessment of estimates of TB disease burden will be undertaken following completion of the national TB prevalence survey.

TABLE 2.2

Estimated epidemiological burden of TB, 2014. Best estimates are followed by the lower and upper bounds of the 95% uncertainty interval. Rates per 100 000 population except where indicated.

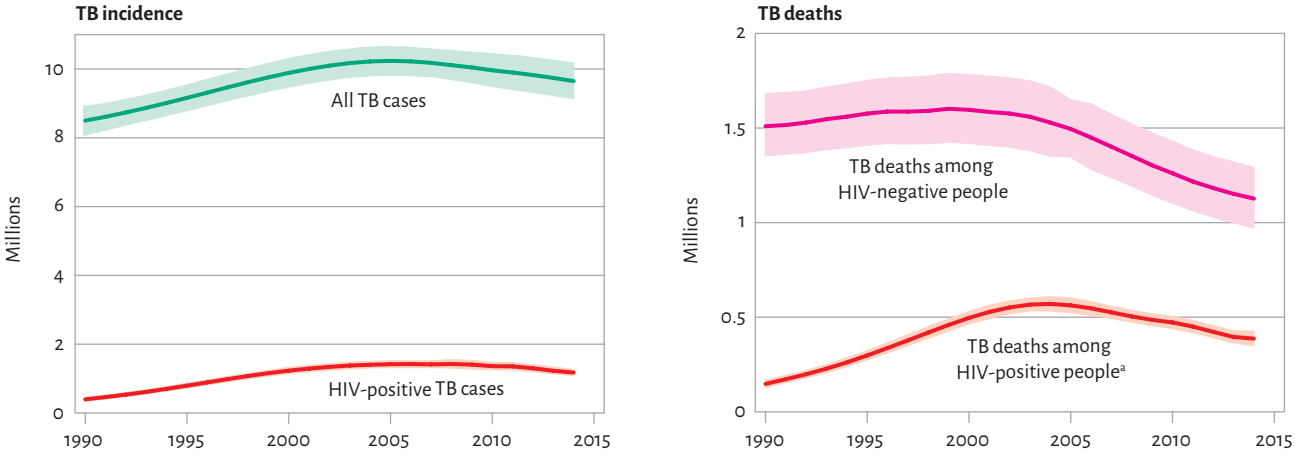
	POPULATION (THOUSANDS)	MORTALITY[a]		HIV-POSITIVE TB MORTALITY		PREVALENCE		INCIDENCE		HIV PREVALENCE IN INCIDENT TB CASES (%)	
Afghanistan	31 628	44	32–57	0.3	0.2–0.3	340	178–555	189	167–212	0.5	0.4–0.7
Bangladesh[b]	159 078	51	37–68	0.1	0–0.1	404	211–659	227	200–256	0.2	0.1–0.2
Brazil	206 078	2.6	2.4–2.7	1.2	0.9–1.6	52	25–89	44	42–46	17	16–19
Cambodia	15 328	58	41–78	5.3	4.1–6.7	668	565–780	390	353–428	3.0	2.8–3.2
China	1 369 436	2.8	2.7–2.9	<0.1	0–0.1	89	78–102	68	63–73	1.4	1.2–1.7
DR Congo	74 877	69	50–90	8.4	6.7–10	532	282–859	325	295–356	14	11–17
Ethiopia	96 959	33	23–44	5.7	4.6–7.0	200	161–243	207	168–250	9.3	8.2–10
India	1 295 292	17	12–27	2.4	2.0–2.9	195	131–271	167	156–179	5.0	4.5–5.4
Indonesia	254 455	41	26–59	8.5	5.2–13	647	513–797	399	274–546	6.2	5.1–7.5
Kenya	44 864	21	15–28	18	14–22	266	142–427	246	240–252	36	34–38
Mozambique	27 216	67	44–96	134	106–165	554	295–893	551	435–680	57	50–63
Myanmar	53 437	53	38–70	7.7	6.1–9.5	457	352–575	369	334–406	9.7	7.9–12
Nigeria	177 476	97	51–156	44	30–61	330	253–417	322	189–488	18	15–22
Pakistan	185 044	26	6.0–61	0.7	0.4–1.0	341	285–402	270	201–350	1.3	1–1.5
Philippines	99 139	10	9.1–11	<0.1	0–0.1	417	367–471	288	254–324	0.9	0.7–1.1
Russian Federation	143 429	11	11–11	0.7	0.6–0.9	109	49–192	84	76–93	4.6	3.8–5.3
South Africa	53 969	44	41–48	134	107–164	696	390–1 090	834	737–936	61	56–66
Thailand	67 726	11	5.7–18	6.6	3.4–11	236	161–326	171	90–276	13	12–14
Uganda	37 783	12	8.4–16	17	13–21	159	87–253	161	141–183	45	42–48
UR Tanzania	51 823	58	26–104	53	30–84	528	215–979	327	155–561	37	32–42
Viet Nam	92 423	18	12–25	2	1.4–2.7	198	83–362	140	116–167	5.4	5–5.9
Zimbabwe	15 246	15	9.5–22	34	21–51	292	158–465	278	193–379	60	55–65
High-burden countries	**4 552 704**	**21**	**17–24**	**6.9**	**6.1–7.8**	**227**	**203–253**	**176**	**165–188**	**12**	**10–13**
AFR	963 361	46	36–58	32	28–36	330	288–375	281	250–313	32	28–37
AMR	981 613	1.7	1.6–1.8	0.6	0.5–0.7	36	28–45	28	27–29	13	12–14
EMR	635 745	14	6.8–23	0.5	0.4–0.6	160	139–183	117	96–140	1.7	1.3–2.2
EUR	907 279	3.7	3.6–3.8	0.3	0.3–0.4	48	36–61	37	35–39	5.9	5.4–6.5
SEAR	1 906 087	24	19–30	3.3	2.7–3.9	286	233–343	211	192–232	5.2	4.3–6.1
WPR	1 845 184	4.8	4.4–5.1	0.3	0.2–0.3	116	104–128	85	80–89	2.0	1.8–2.3
Global	**7 239 269**	**16**	**13–18**	**5.3**	**4.8–5.9**	**174**	**158–190**	**133**	**126–141**	**12**	**11–13**

[a] Mortality excludes deaths among HIV-positive TB cases. Deaths among HIV-positive TB cases are classified as HIV deaths according to ICD-10 and are shown separately in this table.

[b] For Bangladesh, a joint reassessment of estimates of TB disease burden will be undertaken following completion of the national TB prevalence survey.

FIGURE 2.3

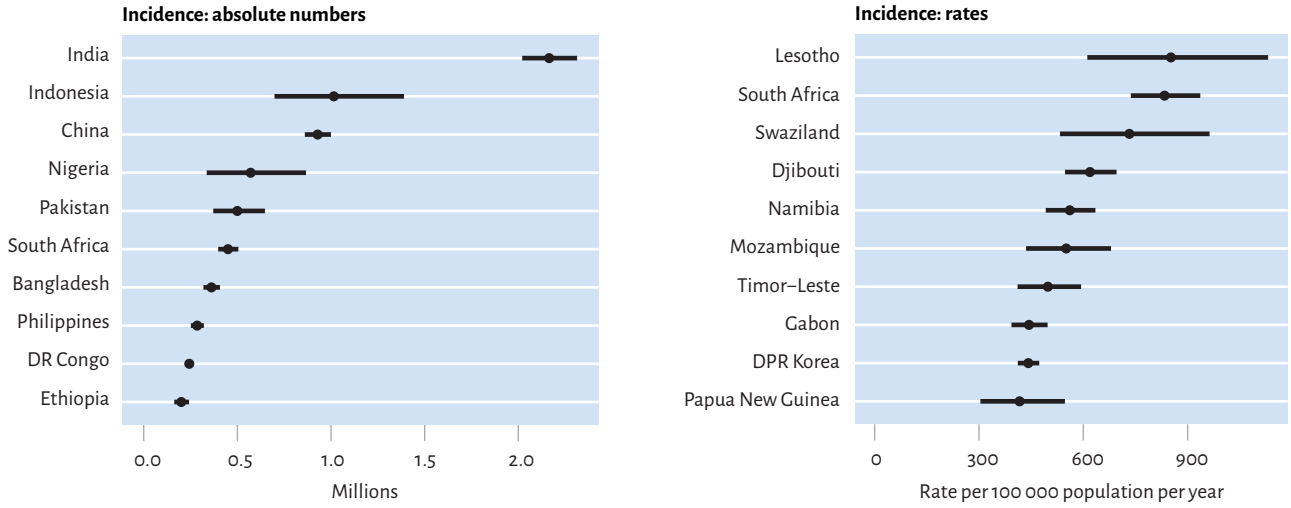
Estimated absolute numbers of TB cases and deaths (in millions per year), 1990–2014



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

FIGURE 2.4

Estimated TB incidence: top-ten countries, 2014. The range shows the lower and upper bounds of the 95% uncertainty interval. The bullet marks the best estimate.



the lowest burden of TB on average. Most of the HBCs have rates of around 150–300 cases per 100 000 population per year (**Table 2.2**, **Figure 2.7**); HBCs with markedly lower rates in 2014 were Brazil, China and the Russian Federation, while rates were above 500 per 100 000 population in Mozambique and South Africa. Other countries in the top ten worldwide in terms of incidence rates in 2014 are shown in **Figure 2.4**.

Globally, the incidence rate was relatively stable from 1990 up until around 2000, and then started to fall (**Figure 2.8**), achieving the MDG target far ahead of the 2015 deadline. The MDG target has also been met in all six WHO regions and in 16 of the 22 HBCs (**Figure 2.9**, **Figure 2.10**, **Table 2.3**).

2.2 TB prevalence

In countries with a relatively high burden of TB (around 100 cases per 100 000 population or more), the prevalence of bacteriologically-confirmed pulmonary TB can be directly measured in nationwide population-based surveys using sample sizes of around 50 000 people. Survey results can be used to produce a national estimate of TB prevalence that includes all forms of TB. The cost of a survey usually ranges from US$ 1 to 4 million, and comprehensive theoretical and practical guidance on survey design, implementation,

TABLE 2.3

2015 targets assessment: global, WHO regions and 22 high-burden countries

INDICATORS AND 2015 TARGETS[a]				
INDICATOR		TB INCIDENCE RATE	TB PREVALENCE RATE	TB MORTALITY RATE
TARGET		INCIDENCE RATE FALLING	50% REDUCTION IN PREVALENCE RATE BY 2015 COMPARED WITH 1990	50% REDUCTION IN MORTALITY RATE BY 2015 COMPARED WITH 1990
GLOBAL				
Global		Met	Almost met	Almost met
WHO REGION				
African (AFR)		Met	Not met	Not met
Americas (AMR)		Met	Met	Met
Eastern Mediterranean (EMR)		Met	Not met	Met
European (EUR)		Met	Not met	Not met
South-East Asia (SEAR)		Met	Met	Met
Western Pacific (WPR)		Met	Met	Met
22 HIGH-BURDEN COUNTRIES				
AFR	DR Congo	Not met	Not met	Not met
	Ethiopia	Met	Met	Met
	Kenya	Met	Not met	Not met
	Mozambique	Not met	Not met	Almost met
	Nigeria	Not met	Not met	Not met
	South Africa	Met	Not met	Not met
	Uganda	Met	Met	Met
	UR Tanzania	Met	Not met	Not met
	Zimbabwe	Met	Not met	Met
AMR	Brazil	Met	Met	Met
EMR	Afghanistan	Not met	Not met	Not met
	Pakistan	Not met	Not met	Met
EUR	Russian Federation	Met	Not met	Not met
SEAR	Bangladesh[b]	Not met	Not met	Not met
	India	Met	Met	Met
	Indonesia	Met	Not met	Not met
	Myanmar	Met	Met	Met
	Thailand	Met	Not met	Almost met
WPR	Cambodia	Met	Met	Met
	China	Met	Met	Met
	Philippines	Met	Met	Met
	Viet Nam	Met	Met	Met

[a] *Met* (**green**) means that the target was achieved before or by the end of 2015. *Not met* (**orange**) means that the target will not be achieved by the end of 2015. *Almost met* (**light green**) means that the reduction was in the range 40–49%, according to the best estimate. Values for 2015 were based on an algorithm that selects the best performing among a family of exponential smoothing via state-space models of the 2005–2014 time-series.

[b] For Bangladesh, a joint reassessment of estimates of TB disease burden will be undertaken following completion of the national TB prevalence survey.

FIGURE 2.5

Estimated HIV prevalence in new and relapse TB cases, 2014

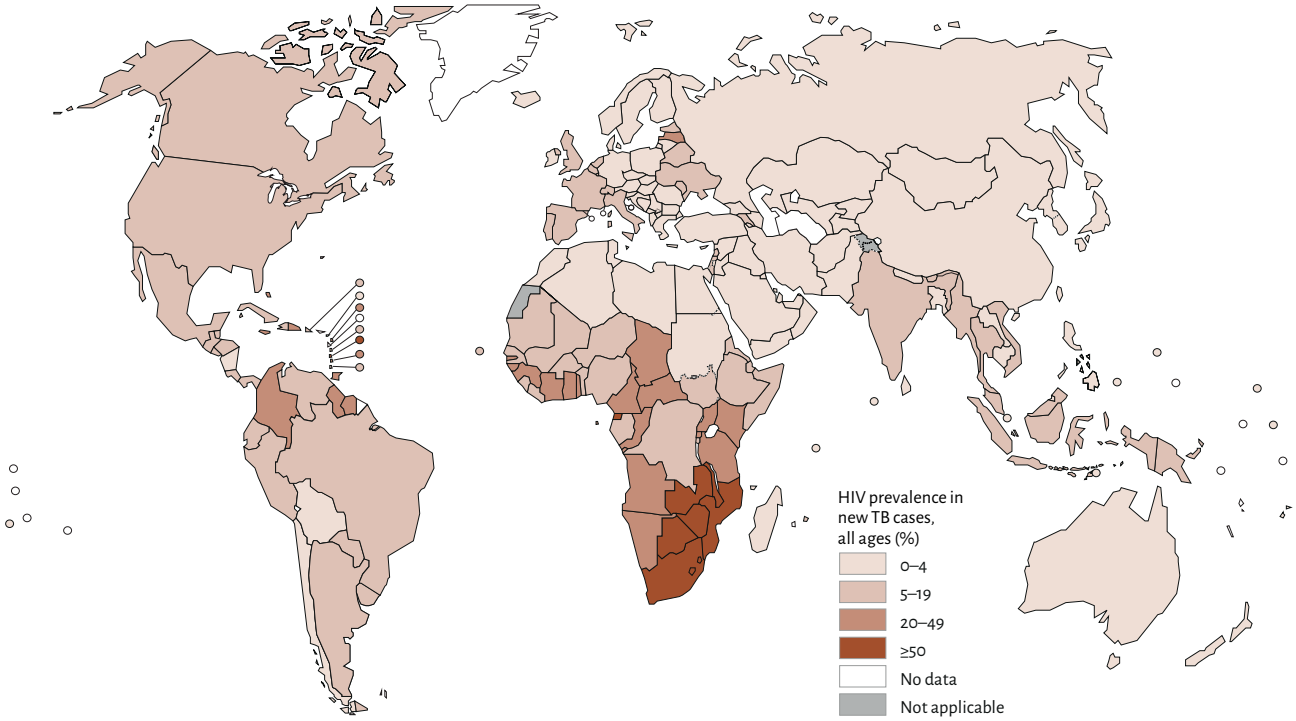


FIGURE 2.6

Estimated TB incidence rates, 2014

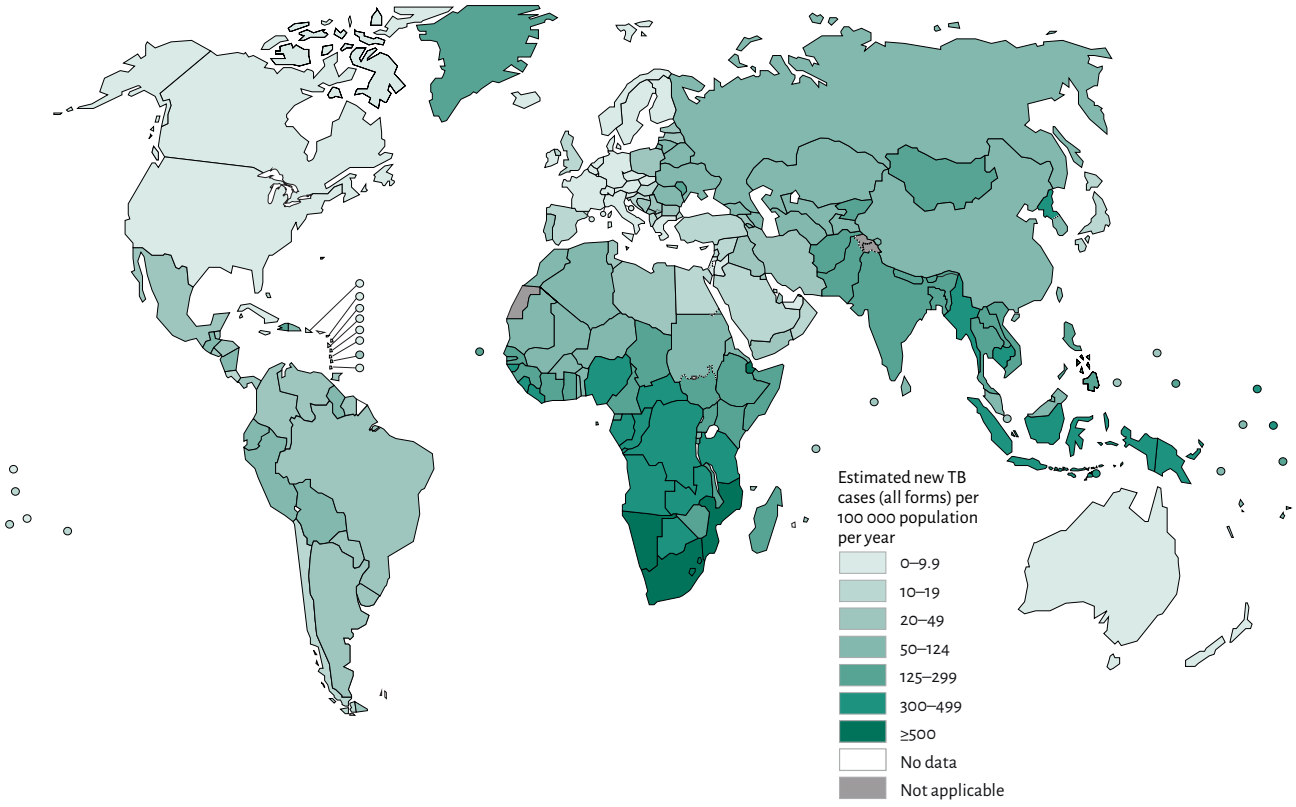
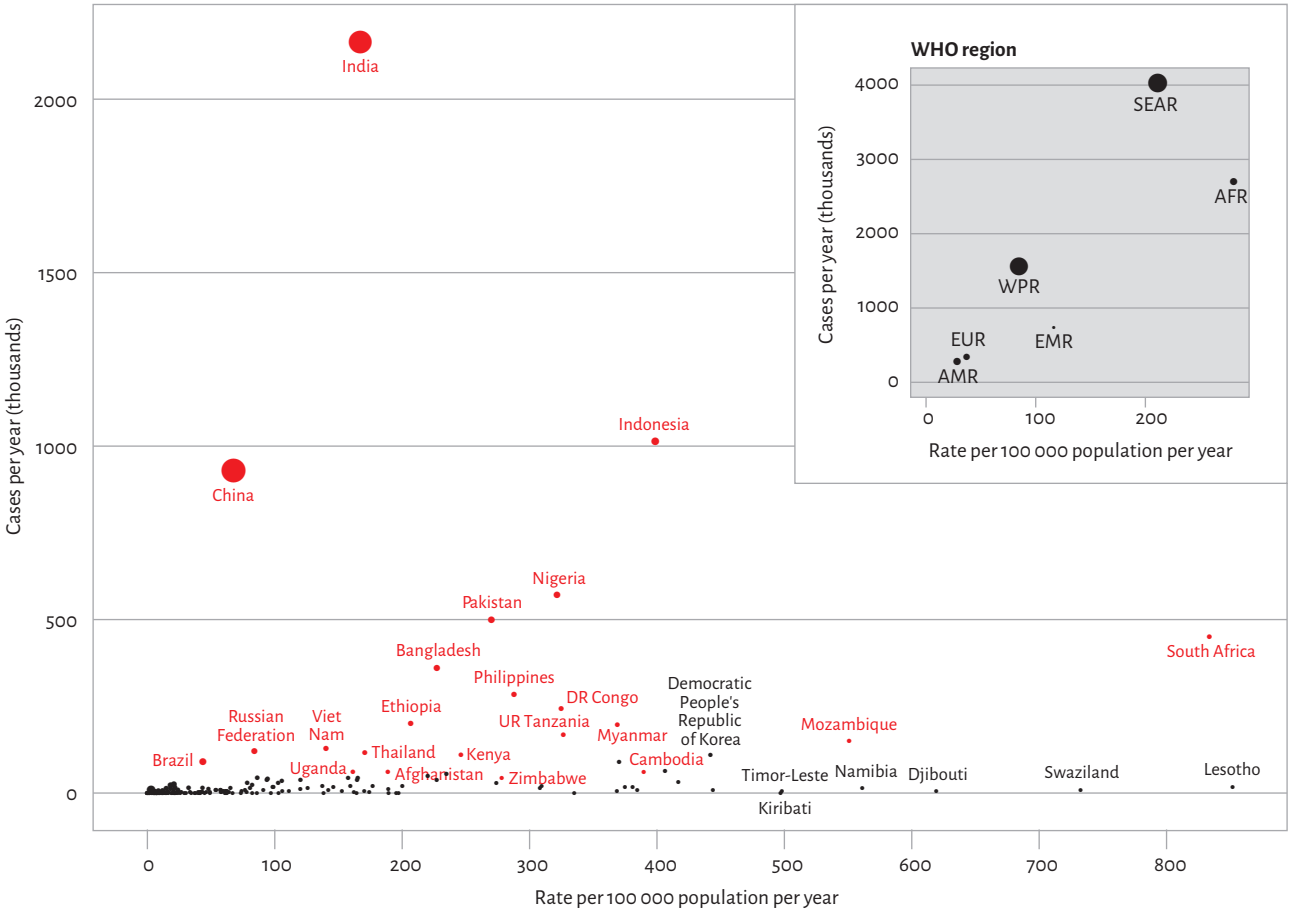


FIGURE 2.7

Global distribution of estimated TB incidence by rate and absolute number, 2014. The size of each bubble is proportional to the size of the country's population. High-burden countries are shown in red.



analysis and reporting of results is available.[1] Repeat surveys conducted about every ten years allow trends in disease burden to be assessed. HBCs that have completed repeat surveys in the last ten years include Cambodia, China, the Philippines and Thailand. Repeat surveys are planned in Myanmar and Viet Nam around 2016–2017; a fourth survey is also planned in the Philippines in 2016. Countries in which surveys have been implemented or are planned in the near future are shown in **Figure 2.11** and **Figure 2.12**. In the 1990s and early 2000s, there was typically no or one survey per year, and all the surveys that were done were in Asia. Between 2009 and 2016, an unprecedented number of national TB prevalence surveys have been or will be conducted, in both Africa and Asia (**Figure 2.12**, **Box 2.1**, **Box 2.2**). The results and lessons learned from one of the most recent surveys, in Indonesia, are highlighted in **Box 2.4**.

In low- and medium-burden countries, sample sizes and costs for surveys become prohibitively large. 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.

Details about the methods used to produce estimates of TB prevalence are provided in the **online technical appendix** and in background documents prepared for the global review of methods used to produce TB burden estimates that was held 31 March–2 April 2015 (**Box 2.1**).[2,3]

There were an estimated 13 million prevalent cases (range, 11 million–14 million) of TB in 2014 (**Table 2.1**), equivalent to 174 cases per 100 000 population (**Table 2.2**). By the end of 2015, it is estimated that the prevalence rate will have fallen 42% globally since 1990, missing the target (**Figure 2.8**, **Table 2.3**). However, two regions met the target before 2015 (the Region of the Americas and the Western Pacific Region) and the South-East Asia Region reached the target (accord-

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

[2] The online technical appendix is available at www.who.int/tb/data.

[3] All background documents are available at www.who.int/tb/advisory_bodies/impact_measurement_taskforce/meetings/consultation_april_2015_tb_estimates_subgroup/en/

Box 2.4 The 2013/2014 national TB prevalence survey in Indonesia: main results, and policy, programmatic and funding implications

A national survey of the prevalence of TB disease in Indonesia was successfully implemented in 2013/2014 under the leadership of the National TB Programme and the National Institute of Health Research and Development. The main objective of the survey was to estimate the prevalence of pulmonary TB (bacteriologically-confirmed) among the general population aged ≥15 years old.

Methods and main results

Survey methods from design through implementation, analysis and reporting of results followed the international recommendations of the WHO Global Task Force on TB Impact Measurement.[a]

All survey participants were screened for symptoms by interview and chest X-ray examination. Participants with any current symptom suggestive of TB or radiological lesion(s) in the lung were requested to submit two sputum specimens (one spot and one early-morning) that were examined by microscopy (AFB) and culture (LJ solid media).

A total of 112 350 people of all ages were enumerated, from 156 clusters around the country. Of these, there were 76 576 eligible individuals aged ≥15 years old. All eligible individuals were invited to participate in the survey, of whom 67 994 (89%) did so. Of those who participated, 15 446 (23%) screened positive and were eligible for sputum examination. A total of 426 TB cases were identified by the survey (**Figure B2.4.1**). The excellent participation rate as well as other survey indicators (for example, very low levels of missing data) show that the survey was implemented to a high standard.

The TB prevalence rate per 100 000 population aged ≥15 years old was estimated to be 257 (95% CI: 210–303) for smear-positive TB, and 759 (95% CI: 590–961) for bacteriologically-confirmed TB. Clear and consistent age and sex differentials were observed for both smear-positive and bacteriologically-confirmed TB, with higher rates among men and older age groups (**Figure B2.4.2**).

The final survey results were used in combination with other sources of information (such as notification data, mortality data from a sample vital registration system and previous national TB prevalence surveys) to update estimates of the burden of TB disease in Indonesia (**Figure B2.4.3**). Both survey results and these updated estimates were discussed and agreed upon in national consensus meetings involving all key stakeholders that were held in September and October 2014.

Lessons learned

The key lessons learned from the survey were:

1. The burden of TB disease in Indonesia is much higher than previously thought.[b] Revised figures for 2013 are an estimated TB incidence rate of 403 (range, 278–550) per 100 000 population and an estimated prevalence (all forms of TB, and including children as well as adults) of 660 (range, 523–813) per 100 000 population. The 2013/2014 survey has provided a more accurate measurement of TB disease burden compared with earlier surveys, since unlike previous surveys it included systematic chest X-ray screening of the entire survey population and bacteriological testing for all those with signs or symptoms suggestive of TB.
2. When analysed alongside results from previous surveys, TB incidence is falling, in line with the MDG target for TB. TB prevalence and mortality are also falling. In addition, the case fatality ratio (the proportion of incident cases that die from TB) is estimated at 11%, considerably better than the global average of 16%.
3. Overall, only about one third of the estimated 1 million incident cases that occur each year are being detected and reported to national authorities.
4. The number of TB patients receiving treatment in public and private hospitals, without linkage or reporting to the national TB programme, was much larger than expected. A high proportion of detected cases (about 50%) had not been reported.
5. A high proportion of people with TB had not been detected at the time of the survey, showing serious delays in TB diagnosis and treatment.

Policy, programmatic and funding implications

The major implications of survey results, some of which require high-level policy action, include:

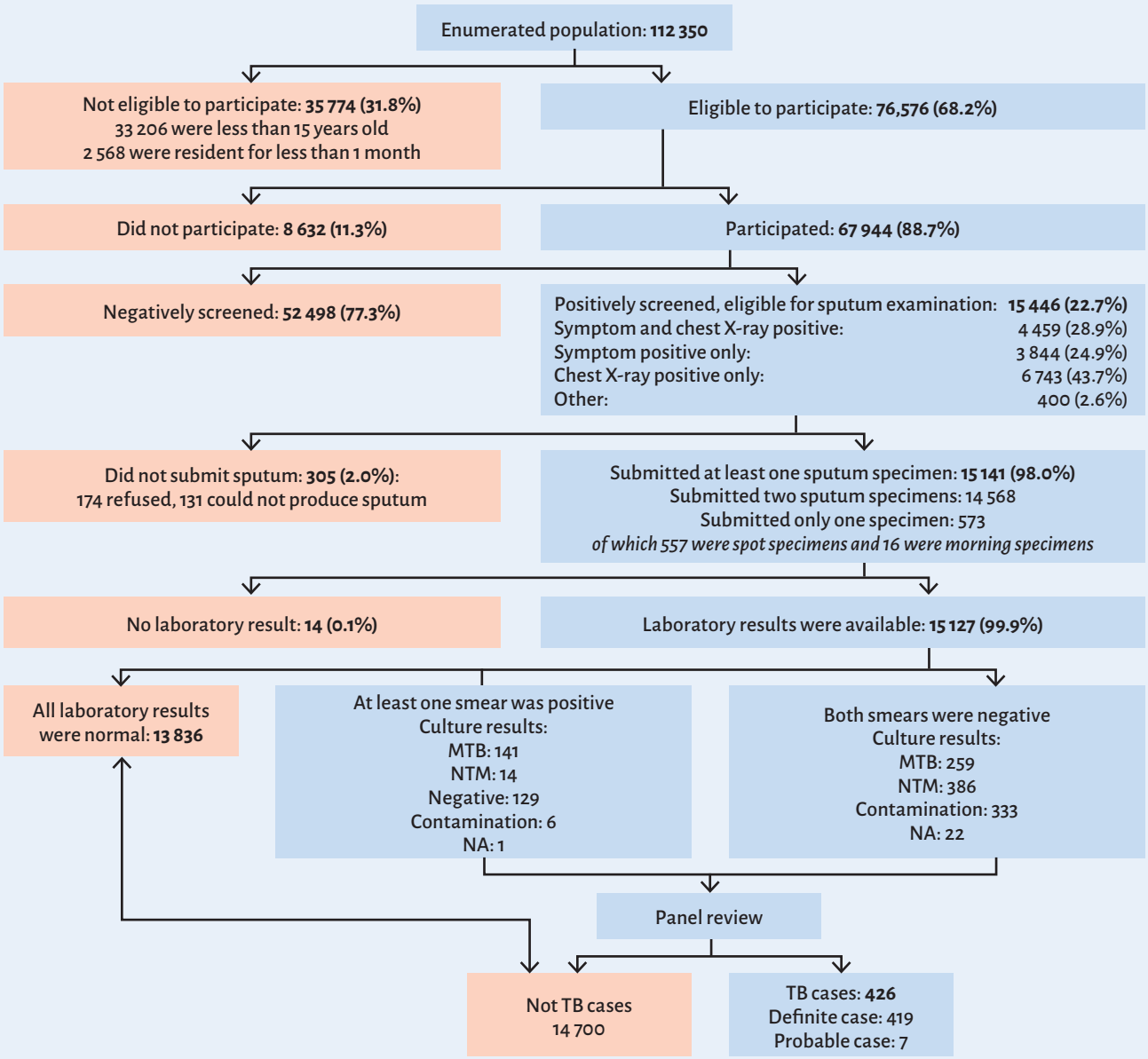
1. TB warrants being one of the top health priorities in Indonesia.
2. Funding needs for TB prevention, diagnosis and treatment are considerably larger than previously thought. Additional resources will need to be mobilized at national, provincial and district levels.
3. Expansion of health insurance coverage is crucial to support high quality TB diagnosis and treatment in public and private hospitals (and in the private sector in general), to ensure that TB disease does not impose a financial burden on patients and their households, and to ensure appropriate cost-recovery for care providers.
4. The current policy of mandatory case notification needs to be strongly enforced to reduce under-reporting of detected cases. This could be facilitated by systems that make it easier for care providers to notify cases, such as a user-friendly electronic surveillance system, and by incentives for reporting (or penalties for not reporting).
5. Screening and diagnostic tools that have a higher sensitivity than current symptom screening and smear microscopy need to be introduced or expanded to help reduce the number of undetected cases in the community, as well as to reduce the possibility of over-diagnosis. Examples include much wider use of chest X-ray screening and rapid molecular diagnostics.
6. Referral mechanisms between health centres and hospitals in both the public and private sectors need to be strengthened and awareness of TB increased throughout the population and among health care workers. These measures will also help to reduce the number of undetected cases in the community.

Conclusions and next steps

The 2013/2014 national survey of the prevalence of TB disease in Indonesia is one of the highest quality national TB prevalence surveys conducted to date, and the importance of the evidence it

FIGURE B2.4.1

Consort diagram of the 2013–2014 national TB prevalence survey in Indonesia



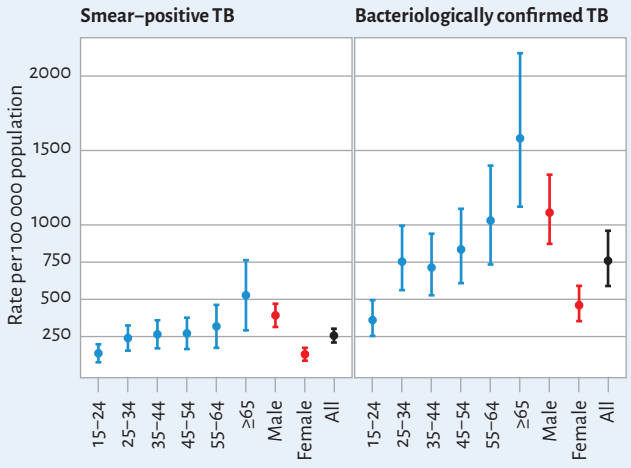
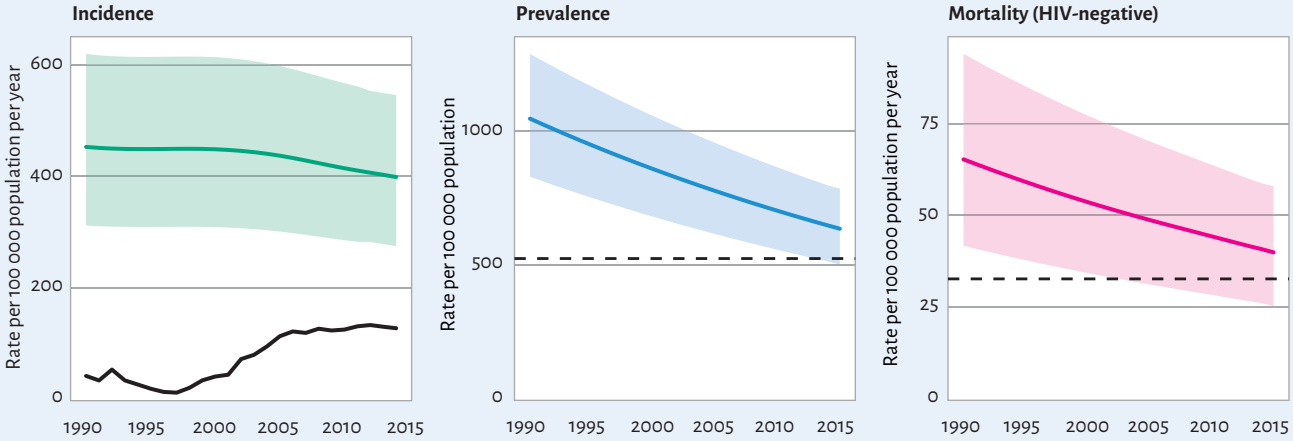


FIGURE B2.4.2

Overall, and age and sex-specific TB prevalence rates as measured in the 2013–2014 national TB prevalence survey in Indonesia, with 95% confidence intervals

FIGURE B2.4.3

Trends in estimated rates of incidence, prevalence and mortality in Indonesia, 1990–2015. Left panel: the incidence rate (**green**) is shown alongside notifications of TB cases (**black**). Centre and right panels: 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.



has produced is clear. Following wide dissemination of findings, results have been used to help develop the national strategic plan 2015–2020 and the preparation of a Concept Note required for financing from the Global Fund. A survey report has been finalized and results will be summarized in a paper for a peer-reviewed journal.

[a] *Tuberculosis prevalence surveys: a handbook*. Geneva: World Health Organization; 2010 (WHO/HTM/TB/2010.17). Available at: http://www.who.int/tb/advisory_bodies/impact_measurement_taskforce/resources_documents/thelimebook/en/

[b] Other examples of countries where a survey has shown that the burden of TB was higher than previously include Laos PDR (2011), Nigeria (2012), Ghana (2013), Malawi (2013) and Zambia (2014).

ing to the best estimate) in 2015 (**Figure 2.13**).[1] TB prevalence is falling in all of the other three regions. Among the 22 HBCs, nine are assessed to have met the target of a 50% reduction from 1990 levels (**Figure 2.14**, **Table 2.3**).

2.3 TB mortality

TB mortality among HIV-negative people can be directly measured using data from national VR systems, provided that these systems have high coverage and causes of death are accurately coded according to the latest revision of the *International classification of diseases* (ICD-10). Sample VR systems covering representative areas of the country (e.g. as in China) provide an interim solution. Mortality surveys can also be used to estimate deaths caused by TB. In 2014, most countries with a high burden of TB lacked national or sample VR systems and few had conducted mortality surveys. 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. 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 this 2015 report, country-specific estimates of TB deaths among HIV-positive people were produced using the Spectrum software that has been used for HIV burden estimates for over a decade.

Until 2008, WHO estimates of TB mortality used VR data for only three countries. This was substantially improved to 89 countries in 2009; however, most of the data were from countries in the European Region and the Region of the Americas, which accounted for less than 10% of the world's TB cases. In 2011, the first use of sample VR data from China and survey data from India enabled a further major improvement to estimates of TB mortality. For the current report, VR data of sufficient coverage and quality were available for 127 countries (**Figure 2.15**) including Indonesia and South Africa for the first time (**Box 2.2**), and survey data were available for two countries (India and Viet Nam). The combined total of 129 countries accounted for 43% of the estimated number of TB deaths globally in 2014. The African Region is the part of the world in which there is the greatest need to introduce or strengthen a vital registration system in which causes of death are classified according to the ICD system.

[1] Values for 2015 were estimated using an algorithm that selects the best performing among a family of exponential smoothing via state-space models of the 2005–2014 time-series.

FIGURE 2.8

Global trends in estimated rates of TB incidence (1990-2014), and prevalence and mortality rates (1990–2015). Left: Estimated incidence rate including HIV-positive TB (**green**) and estimated incidence rate of HIV-positive TB (**red**). Centre and right: 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.

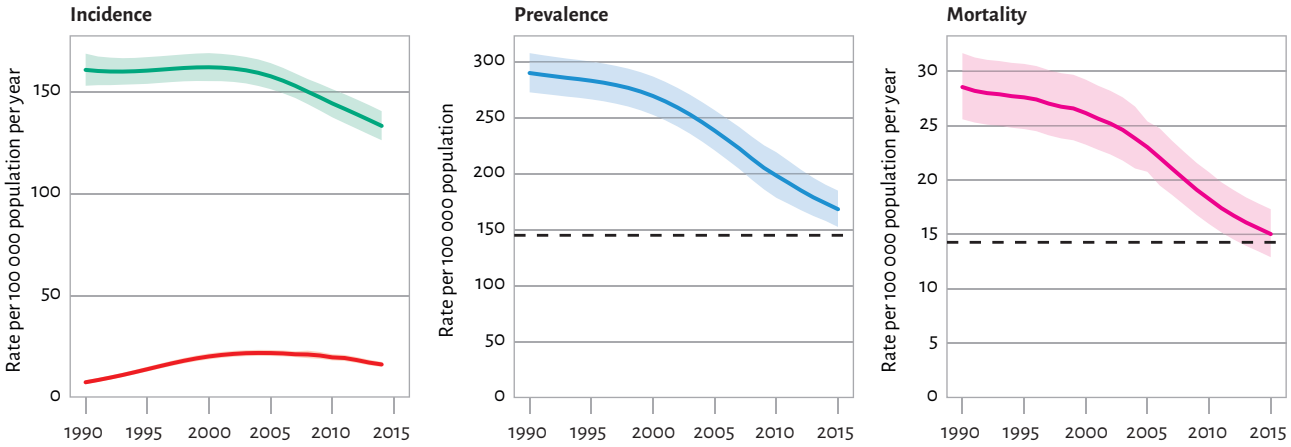


FIGURE 2.9

Estimated TB incidence rates by WHO region, 1990–2014. Estimated TB incidence rates (**green**) and estimated incidence rates of HIV-positive TB (**red**). Shaded areas represent uncertainty bands.

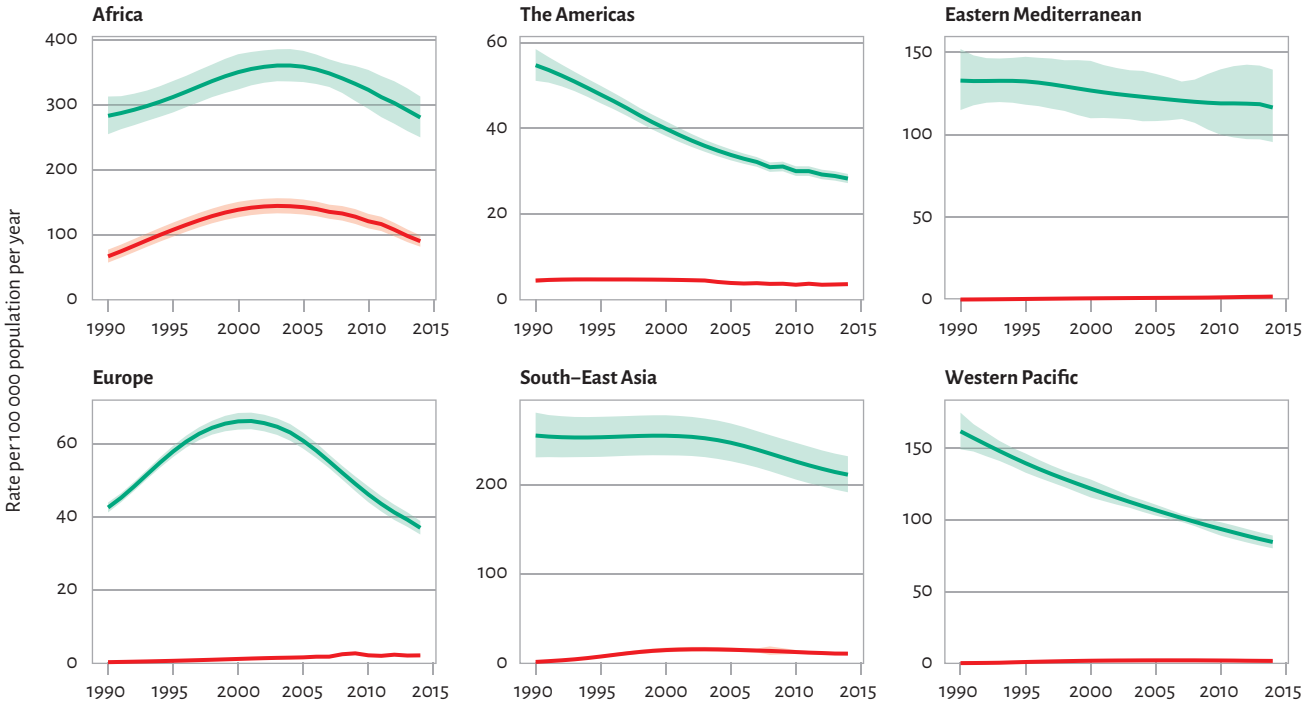
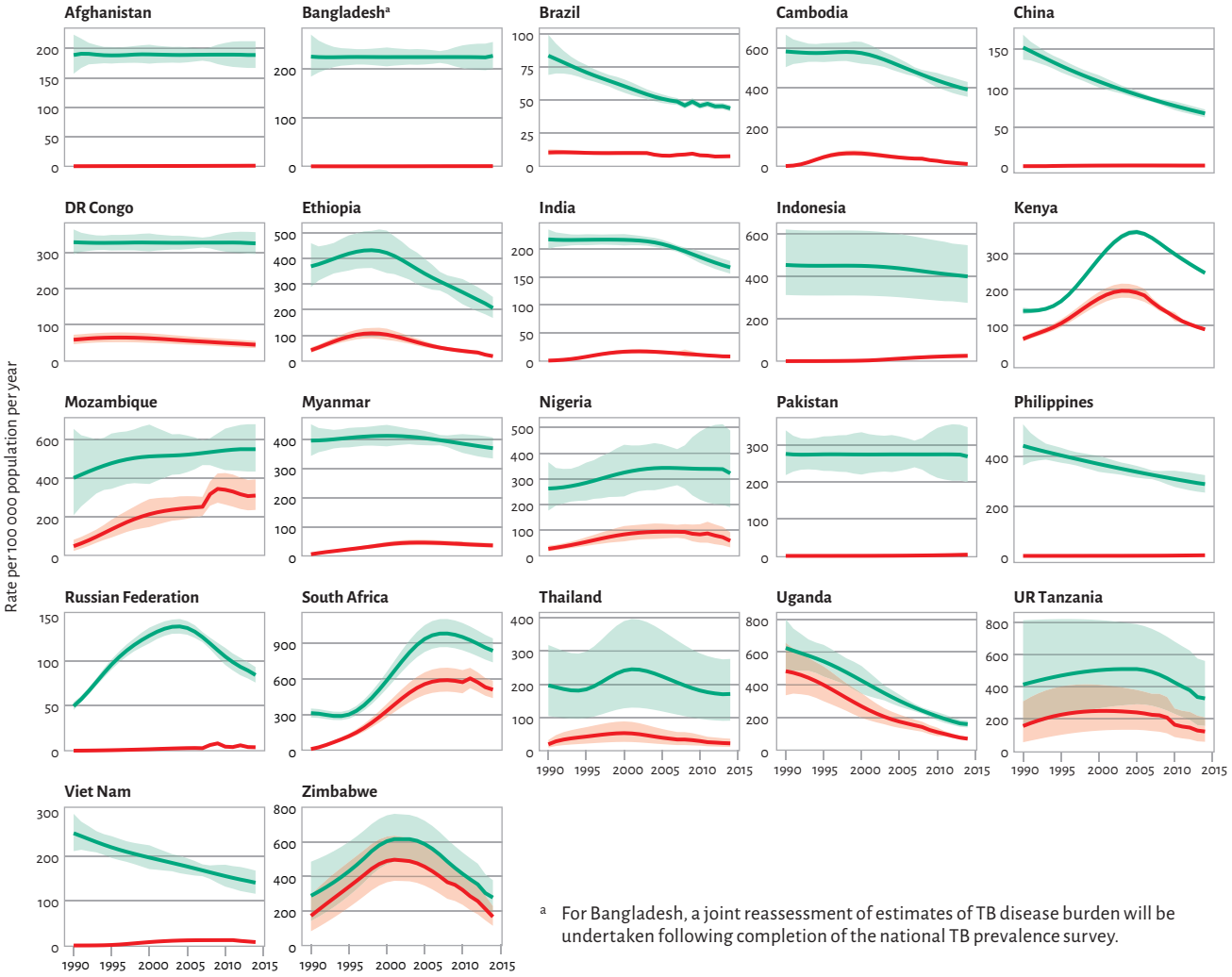


FIGURE 2.10

Estimated TB incidence rates, 22 high–burden countries, 1990–2014. Estimated TB incidence rates (**green**) and estimated incidence rates of HIV–positive TB (**red**). Shaded areas represent uncertainty bands.



[a] For Bangladesh, a joint reassessment of estimates of TB disease burden will be undertaken following completion of the national TB prevalence survey.

Details about the methods used to produce estimates of TB mortality are provided in the **online technical appendix** and in background documents prepared for the global review of methods used to produce TB burden estimates that was held 31 March–2 April 2015 (**Box 2.1**).[1,2]

There were an estimated 1.5 million TB deaths in 2014 (**Table 2.1**, **Figure 2.2**): 1.1 million among HIV-negative people and 390 000 among HIV-positive people (TB deaths among HIV-positive people are classified as HIV deaths in ICD-10).[3] TB ranks alongside HIV as a leading cause of death from an infectious disease (**Figure 2.16a**, **Figure 2.16b**).[4]

Approximately 90% of total TB deaths (among HIV-negative and HIV-positive people) and 80% of TB deaths among HIV-negative people occurred in the African and South-East Asia Regions in 2014. India and Nigeria accounted for about one third of global TB deaths (both including and excluding those among HIV-positive people).

The number of TB deaths (among HIV-negative people) per 100 000 population averaged 16 globally in 2014 (**Table 2.2**) and 21 when TB deaths among HIV-positive people are included. There is considerable variation among countries (**Figure 2.17**), ranging from <1 TB death per 100 000 population (examples include most countries in western Europe, Canada, the United States of America, Australia and New Zealand) to more than 40 deaths per 100 000 population in much of the African Region as well as five HBCs (Afghanistan, Bangladesh, Cambodia, Indonesia and Myanmar).

Globally, the mortality rate (excluding deaths among HIV-

[1] The online technical appendix is available at www.who.int/tb/data.

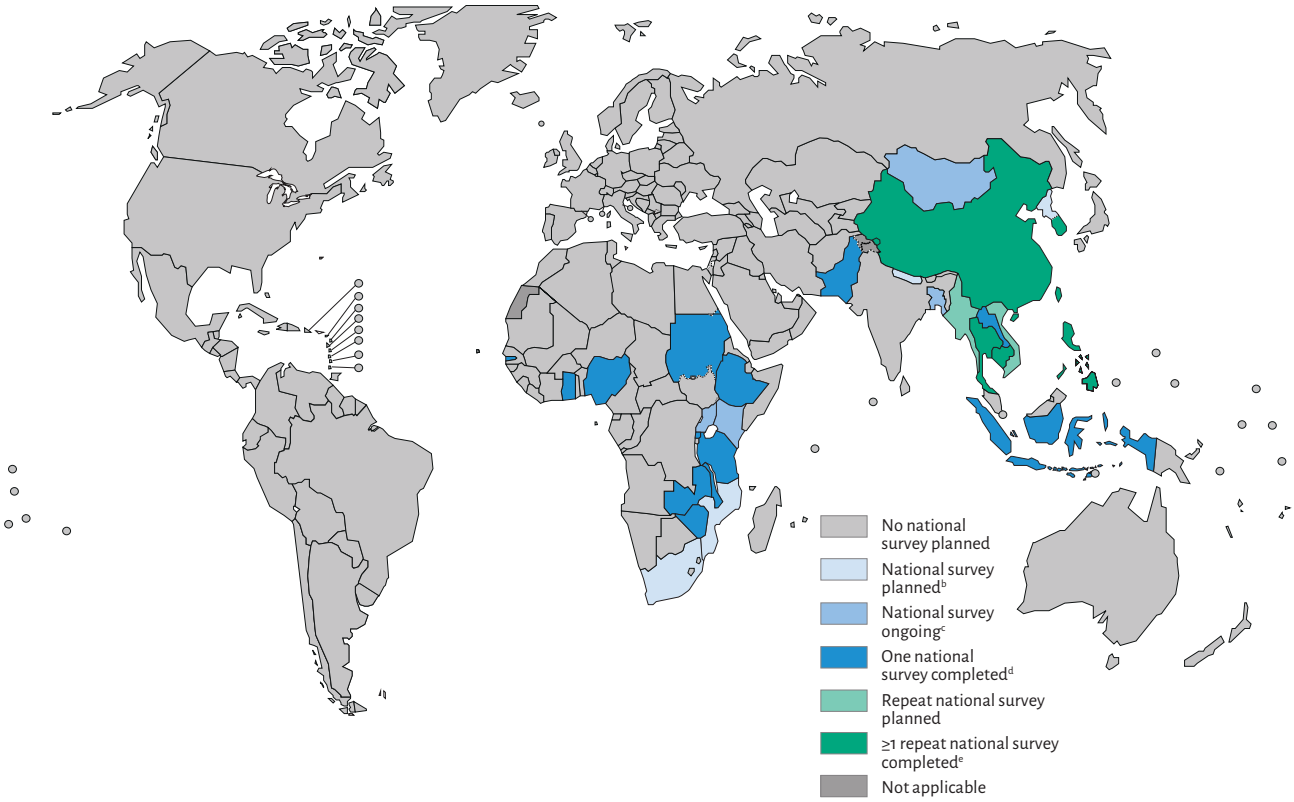
[2] All background documents are available at www.who.int/tb/advisory_bodies/impact_measurement_taskforce/meetings/consultation_april_2015_tb_estimates_subgroup/en/

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

[4] WHO Global Health Observatory data repository, available at http://apps.who.int/gho/data/node.main.GHECOD?lang=en (accessed 27 August 2015).

FIGURE 2.11

Countries in which national population-based surveys of the prevalence of TB disease have been implemented using currently recommended screening and diagnostic methods[a] since 1990 or are planned in the near future: status in August 2015



a Screening methods include field chest X-ray; culture is used to confirm diagnosis.
b A country has submitted at least a draft survey protocol and a budget plan to the WHO Global Task Force for TB Impact Measurement.
c Countries were implementing field operations in August 2015 or were undertaking data cleaning and analysis.
d A survey was conducted in accordance with WHO recommendations as outlined in "Tuberculosis prevalence surveys: a handbook (2011)" and at least a preliminary report has been published.
e A repeat national survey is one in which participants were screened with chest X-ray, and culture examination was used to diagnose TB cases. In the Philippines, a repeat survey is planned in 2016.

FIGURE 2.12

Global progress in implementing national surveys of the prevalence of TB disease, actual (2002–2015) and expected (2016–2017)

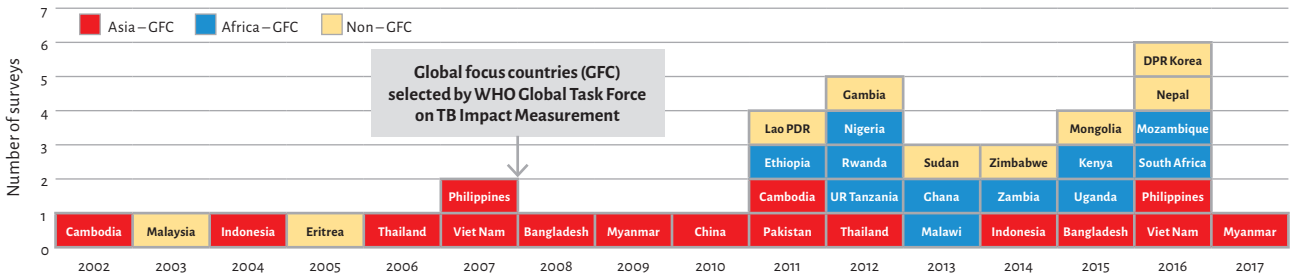


FIGURE 2.13

Estimated TB prevalence rates 1990–2015, 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.

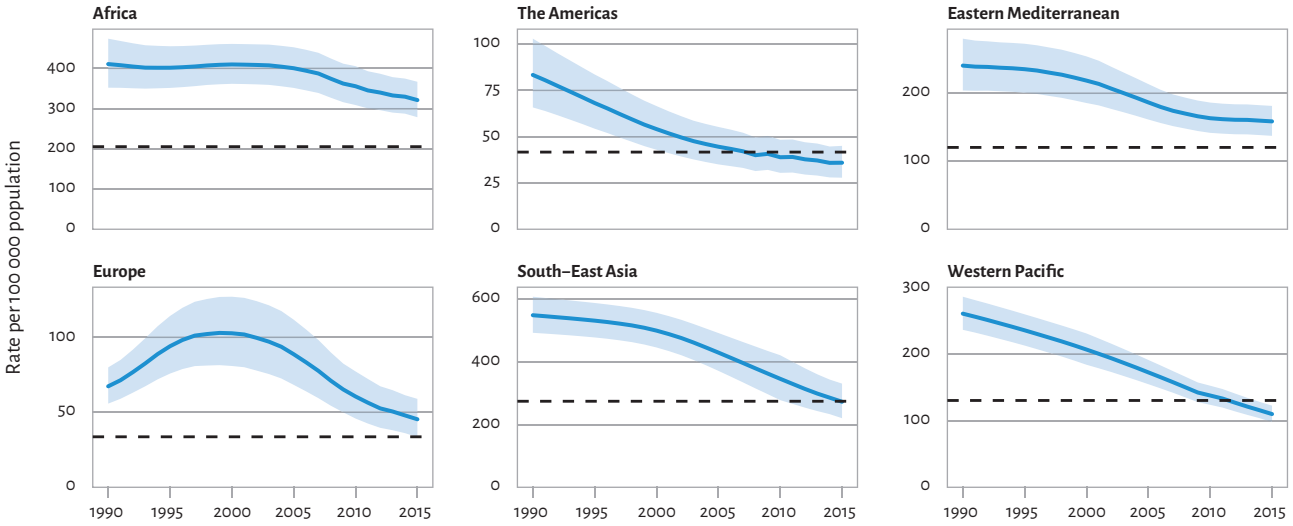
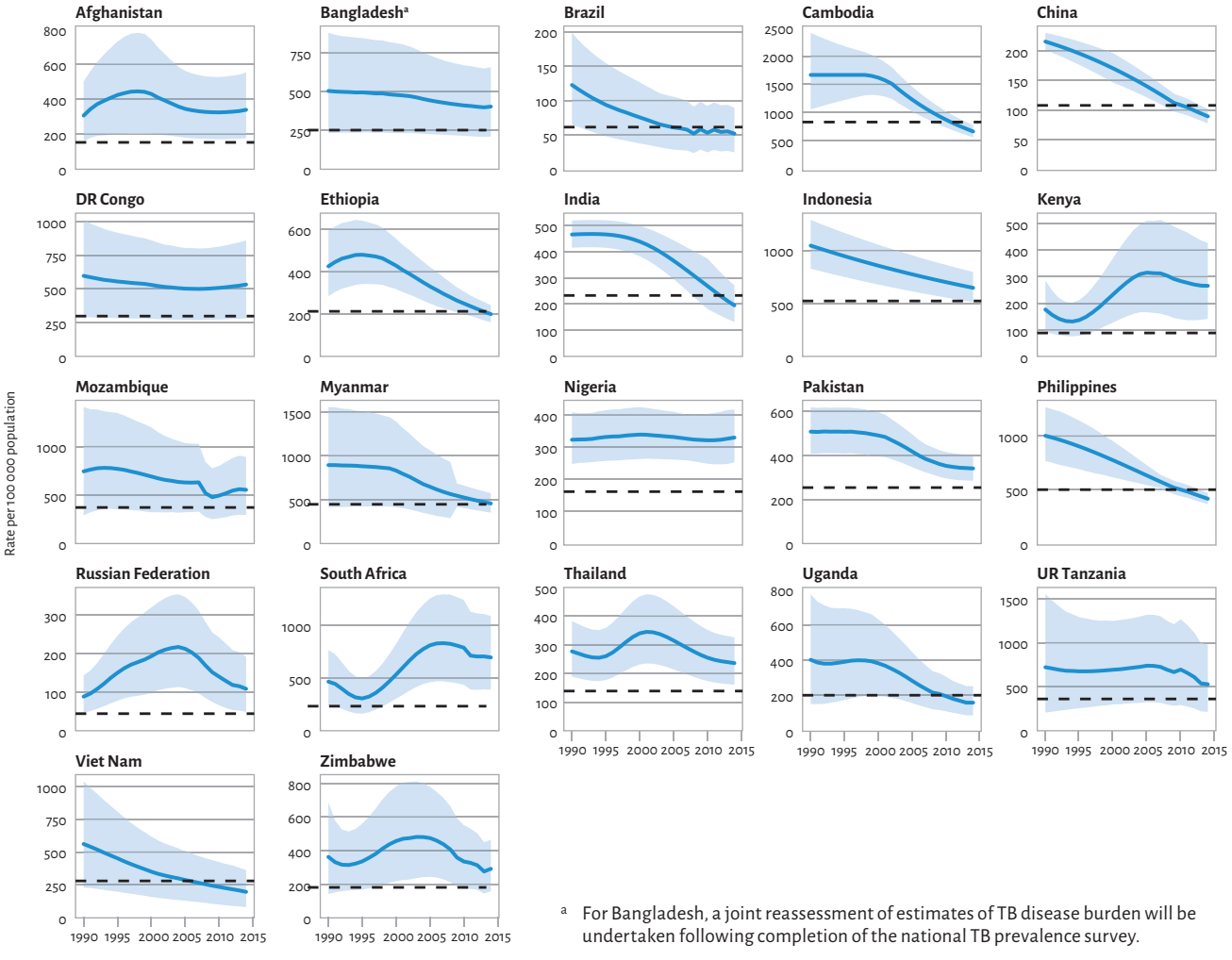


FIGURE 2.14

Estimated TB prevalence rates 1990–2015, 22 high–burden countries. 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.



[a] For Bangladesh, a joint reassessment of estimates of TB disease burden will be undertaken following completion of the national TB prevalence survey.

FIGURE 2.15

Countries (in red) for which TB mortality is estimated using measurements from vital registration systems (n=127) and/or mortality surveys (n=2)

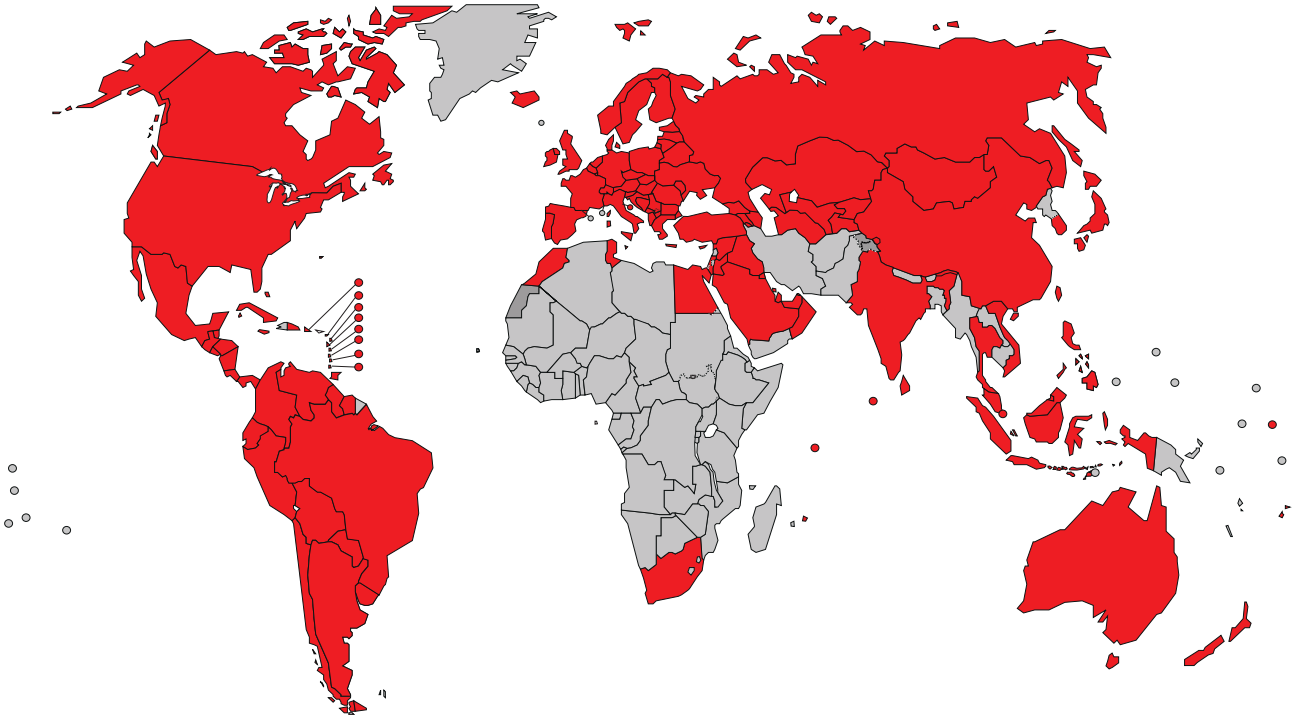


TABLE 2.4

Estimated case fatality ratios (CFRs) in the absence of treatment

CATEGORY OF TB CASE	CFR (95% UNCERTAINTY INTERVAL)
HIV-negative, not on TB treatment	0.43 (0.28–0.53)
HIV-positive, not on TB treatment or ART	0.78 (0.65–0.94)

positive people)[1] fell 47% between 1990 and 2015, narrowly missing the target of a 50% reduction (**Figure 2.8**, **Table 2.3**). However, two WHO regions met the target about ten years in advance of the deadline (the Region of the Americas and the Western Pacific Region), and the Eastern Mediterranean and South-East Asia Regions reached the target (according to the best estimate) by 2015 (**Figure 2.18**).[2] TB mortality has been falling rapidly in the European Region since around 2005, but not fast enough to reach the target given the increase in mortality levels that occurred during the 1990s. In the African Region, mortality is falling but only slowly. Among the 22 HBCs, 11 are assessed to have met the 50% reduction target (**Figure 2.19**, **Table 2.3**).

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

[2] Values for 2015 were estimated using an algorithm that selects the best performing among a family of exponential smoothing via state-space models of the 2005–2014 time-series.

2.3.1 Estimated number of lives saved by TB treatment, 2000–2014

The actual numbers of TB deaths (presented above) can be compared with the number of TB deaths that would have occurred in the absence of TB treatment, to give an estimate of the lives saved by TB interventions. The number of deaths that would have occurred each year in the absence of TB treatment (and without ART provided alongside TB treatment for HIV-positive cases) can be conservatively estimated as the number of estimated incident cases (**section 2.1**) multiplied by the relevant case fatality ratio (**Table 2.4**).[3] Estimates are conservative because they do not account for the impact of TB control or ART on the level of TB incidence, or the indirect, downstream impact of these interventions on future levels of infections, cases and deaths.

Between 2000 and 2014, TB treatment alone saved an estimated 35 million lives among HIV-negative people (**Table 2.5**). Among HIV-positive people, TB treatment supported by ART saved an additional 8.4 million lives.

2.4 Estimates disaggregated by age and sex

This section presents estimates of TB incidence and TB mortality disaggregated by age and sex. Specifically, estimates are shown for men (defined as males aged ≥15 years), women

[3] Further details about methods used to estimate lives saved, including CFRs for different categories of TB case, are provided in the online technical appendix, available at www.who.int/tb/data.

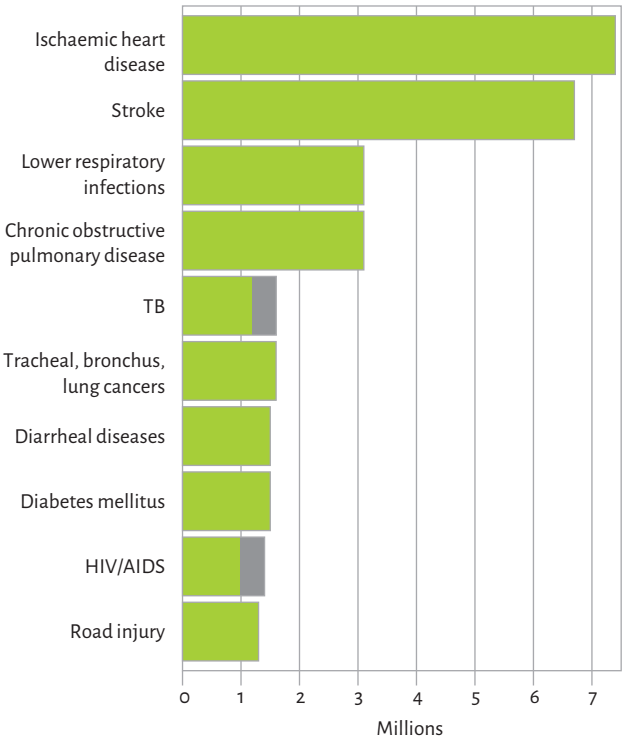
TABLE 2.5

Cumulative number of lives saved by TB and TB/HIV interventions 2000–2014 (in millions), globally and by WHO region. Best estimates are followed by 95% uncertainty intervals.

WHO REGION	HIV-NEGATIVE PEOPLE		HIV-POSITIVE PEOPLE		TOTAL	
	BEST ESTIMATE	UNCERTAINTY INTERVAL	BEST ESTIMATE	UNCERTAINTY INTERVAL	BEST ESTIMATE	UNCERTAINTY INTERVAL
AFR	4.2	3.4–5.1	5.9	5.3–6.5	10.1	9.0–11.2
AMR	1.4	1.2–1.5	0.31	0.28–0.33	1.7	1.6–1.8
EMR	2.6	2.1–3.0	0.06	0.056–0.075	2.6	2.2–3.0
EUR	2.1	1.9–2.4	0.13	0.12–0.14	2.3	2.0–2.5
SEA	15.7	13.7–17.7	1.6	1.4–1.8	17.3	15.3–19.3
WPR	9.2	8.3–10.0	0.29	0.27–0.32	9.5	8.6–10.3
Global	**35.2**	**30.9–39.4**	**8.4**	**7.6–9.2**	**43.5**	**39.2–47.8**

FIGURE 2.16a

Top causes of death worldwide in 2012.[a,b] Deaths from TB among HIV-positive people are shown in grey.[c]



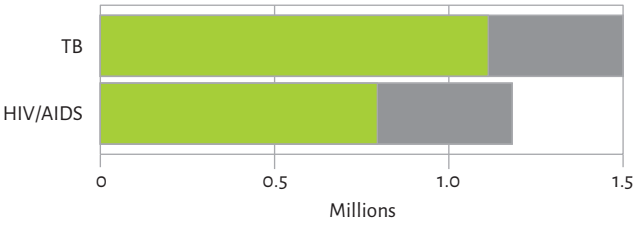
[a] This is the latest year for which estimates for all causes are currently available. See WHO Global Health Observatory data repository, available at http://apps.who.int/gho/data/node.main.GHECOD (accessed 27 August 2015).

[b] For HIV/AIDS, the latest estimates of the number of deaths in 2012 that have been published by UNAIDS are available at www.unaids.org/en/resources/documents/2015/HIV_estimates_with_uncertainty_bounds_1990-2014. For TB, the estimates for 2012 are those published in this report.

[c] Deaths from TB among HIV-positive people are officially classified as deaths caused by HIV/AIDS in the *International classification of diseases*.

FIGURE 2.16b

Estimated number of deaths from HIV/AIDS and TB in 2014. Deaths from TB among HIV-positive people are shown in grey.[a,b]



[a] For HIV/AIDS, the latest estimates of the number of deaths in 2014 that have been published by UNAIDS are available at www.unaids.org/en/resources/documents/2015/HIV_estimates_with_uncertainty_bounds_1990-2014. For TB, the estimates for 2014 are those published in this report.

[b] Deaths from TB among HIV-positive people are officially classified as deaths caused by HIV/AIDS in the *International classification of diseases*.

FIGURE 2.17

Estimated TB mortality rates excluding TB deaths among HIV–positive people, 2014

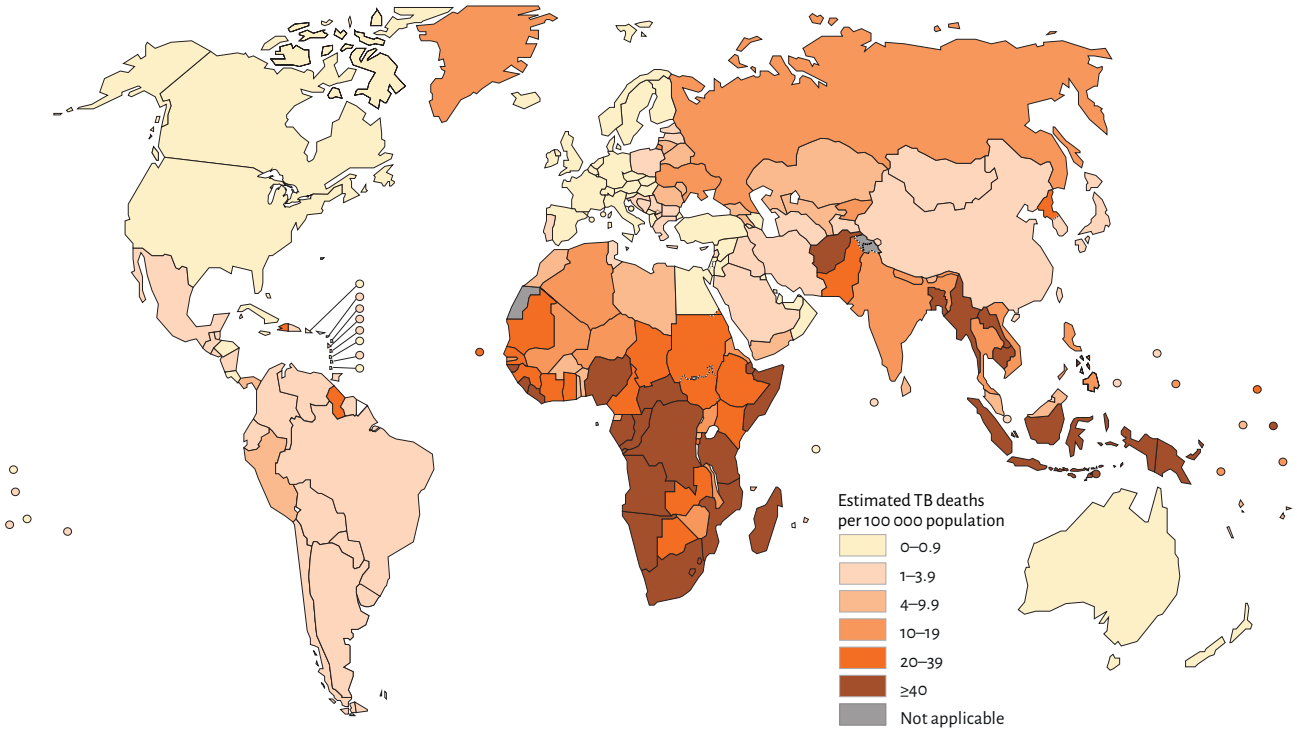


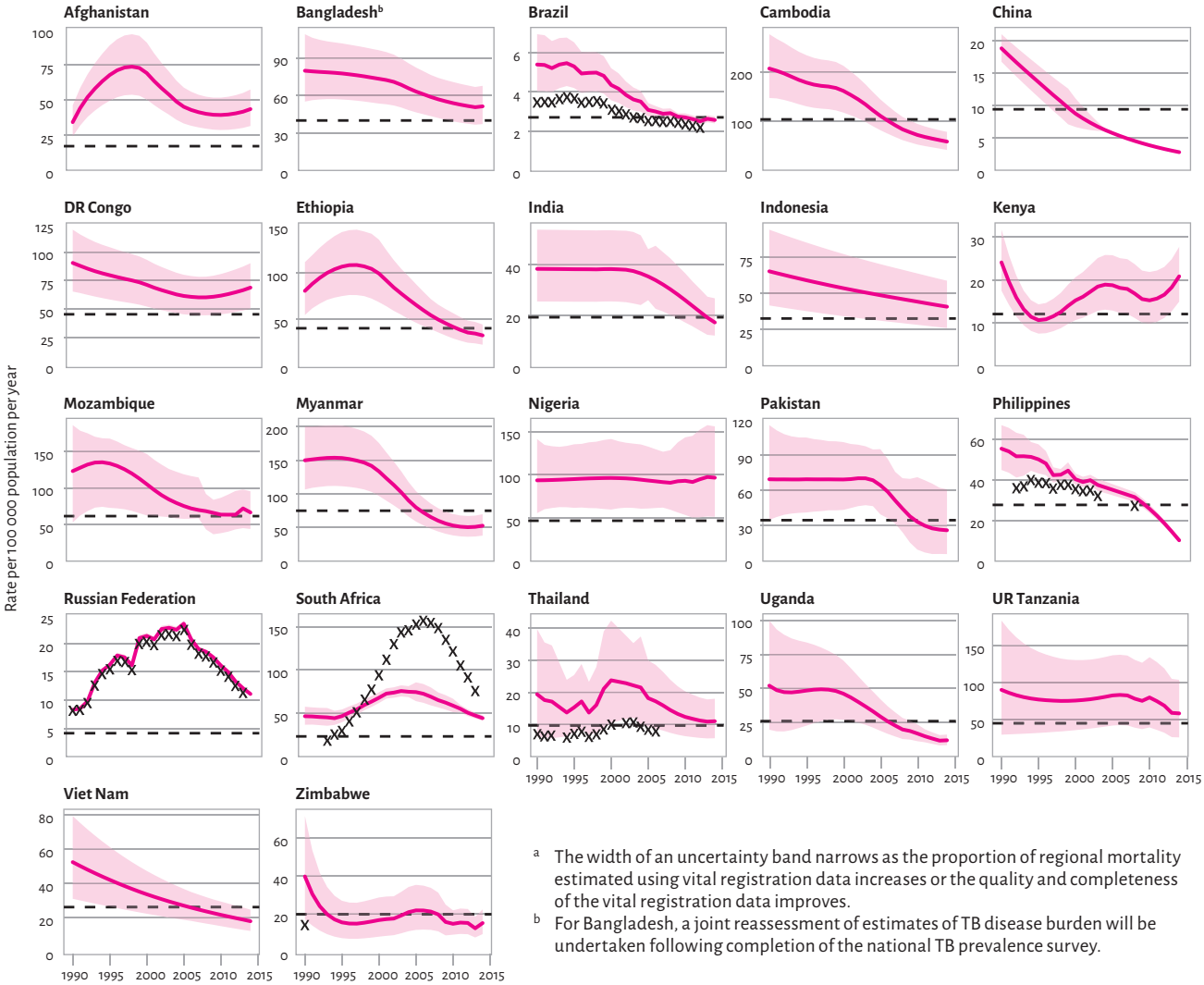
FIGURE 2.18

Estimated TB mortality rates 1990–2015, 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.

[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.

FIGURE 2.19

Estimated TB mortality rates 1990–2015, 22 high–burden countries. Estimated TB mortality excludes TB deaths among HIV-positive people. The horizontal dashed lines represent the Stop TB Partnership target of a 50% reduction in the mortality rate by 2015 compared with 1990. Uncertainty is due to adjustments made to the mortality data from vital registration systems that were reported by countries[a] (mortality data from vital registration systems are represented by the 'x' symbol).



[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.

[b] For Bangladesh, a joint reassessment of estimates of TB disease burden will be undertaken following completion of the national TB prevalence survey.

(defined as females aged ≥15 years) and children (defined as people aged <15 years). The cut-off of 15 years is used because it is consistent with the age categories for which notification data are reported and with the cut-off used in current guidelines to define people eligible to participate in a TB prevalence survey.[1] Details of the methods used to produce disaggregated estimates are provided in the **online technical appendix**.[2]

2.4.1 TB incidence

Estimates of TB incidence among men and women were produced by using notification data combined with the assumption that the men:women ratio of notified cases (1.7 globally)[3] was the same as the ratio for incident cases.[4] In 2014, there were an estimated 5.4 million (range, 5.1–5.8 million) incident cases among men and 3.2 million (range, 3.0–3.4 million) among women.

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

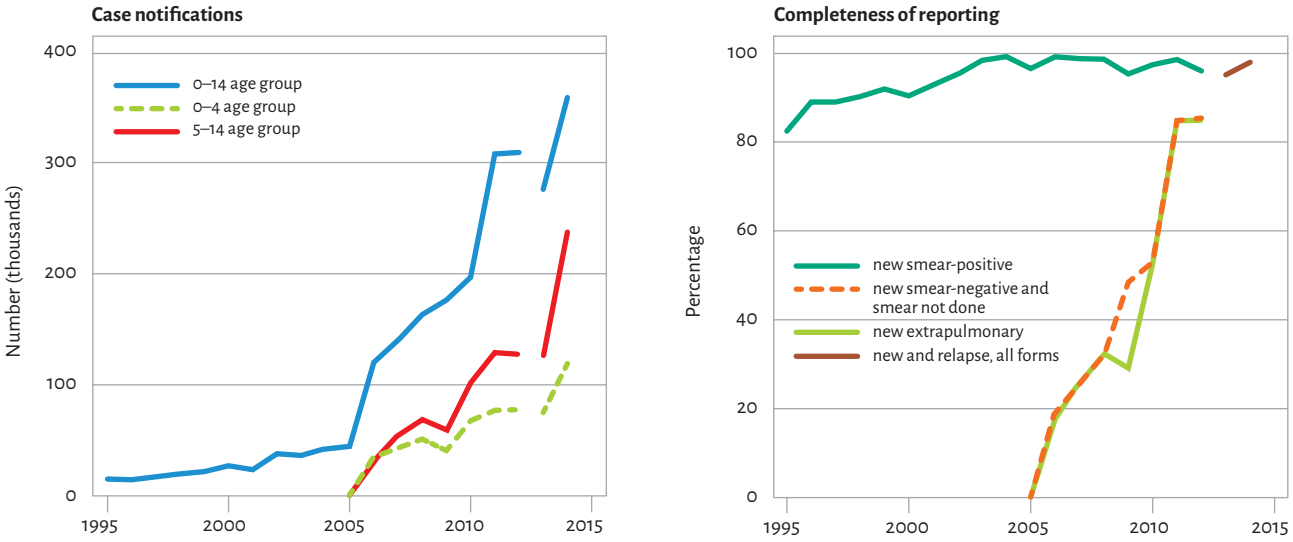
[2] The online technical appendix is available at www.who.int/tb/data.

[3] See also **Table 3.2** in **Chapter 3**.

[4] Evidence from national prevalence surveys of bacteriologically-positive TB consistently show bigger ratios of prevalence to notifications in men than women. This means that the implicit assumption made here, that there is no sex differential in the detection of incident cases, may not be correct. With currently available data, it is not possible to estimate male and female case detection ratios for all countries, but if anything the estimates presented in this chapter are underestimating the share of total TB incidence that is accounted for by men.

FIGURE 2.20

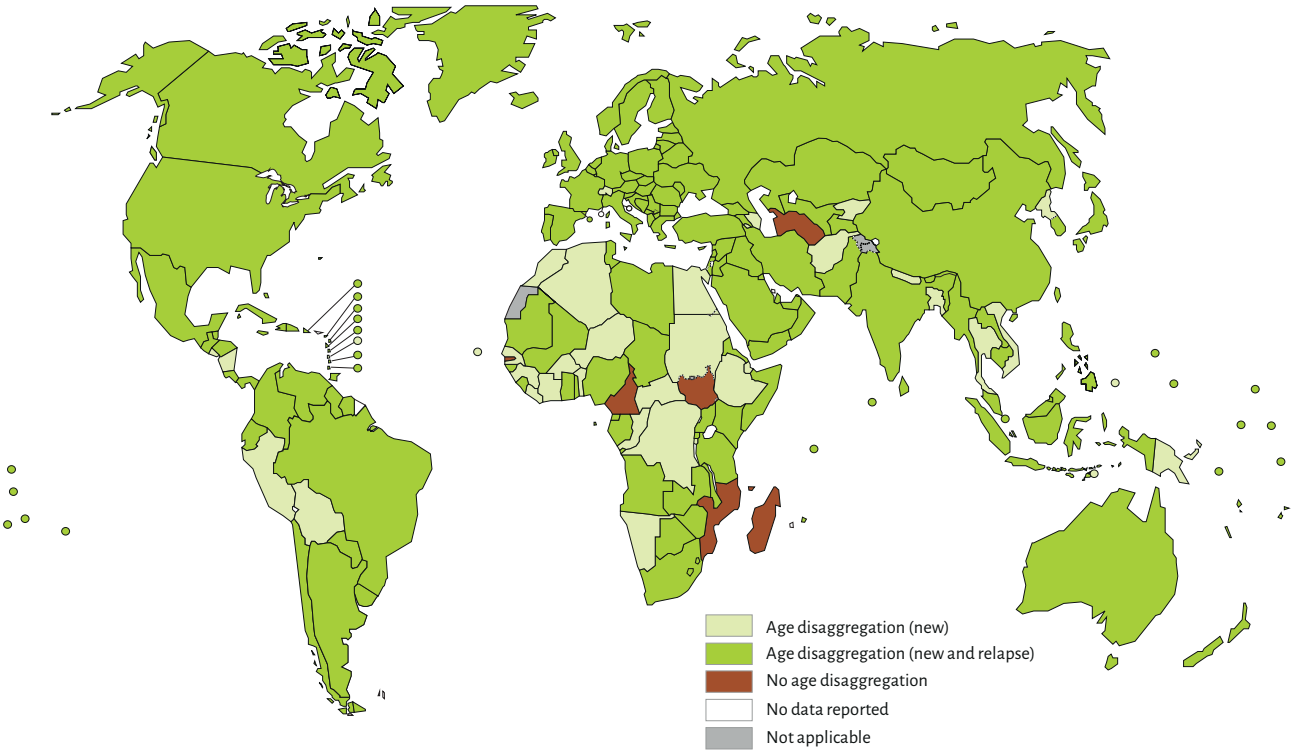
Global progress in reporting of TB cases among children, 1995–2014.[a] Left panel: Number of notifications of cases among children reported to WHO. Right panel: Percentage of case notifications reported to WHO that are age-disaggregated.



[a] Before 2013 childhood case notifications included smear-positive, smear-negative, smear not done and extrapulmonary TB for all new patients. After 2013 (shown as a gap in the graph) childhood case notification include all new and relapse cases irrespective of case type.

FIGURE 2.21

Reporting of new and relapse TB case notifications disaggregated by age, 2014



Box 2.5 Estimating TB incidence among children: challenges, progress to date and next steps

It is well recognized that estimating the incidence of TB in children is difficult and that published estimates vary.[a,b] There are at least four major reasons for this:

1. **TB in children is rarely bacteriologically confirmed.** Direct examination of sputum smears and tuberculin skin testing both suffer from very poor diagnostic performance. TB in children is thus a condition that is usually clinically diagnosed based on a combination of signs and symptoms that are not specific to TB. Case definitions are inconsistent among countries and within countries over time (as a result of changes in medical practice).
2. **Paediatricians who diagnose TB do not always report cases to public health authorities.** Childhood TB is not usually a public health priority and effective linkages between NTPs and the hospitals and clinics where children are usually diagnosed are lacking. Reporting of cases is therefore often incomplete and not supported by a legal framework.
3. **TB cases among children are less likely to be diagnosed in countries with a high burden of TB compared with adults.** Sick children may be evaluated in facilities with little to no capacity to diagnose childhood TB, and diagnostic challenges (the low specificity of clinical signs and symptoms) translate into low access to quality diagnosis and care services.
4. **Different methods have been used to produce estimates.** These include a dynamic model and statistical approaches.

The estimates included in this report are based on combining results from a dynamic model,[c] a statistical approach based on a recent study,[d] and methods previously used by WHO[b] in a statistical ensemble model.[e] Estimates from the dynamic model and statistical approaches using the most updated data for 2014 were found to be similar. This has contributed to a more robust combined estimate compared with those produced using the dynamic model or statistical approaches on their own. In turn, this means that the uncertainty interval from the ensemble approach is narrower than those of estimates produced from each approach used on its own. Nonetheless, the uncertainty interval relative to the best estimate is about twice as large as the relative uncertainty of the overall TB incidence estimate for all ages.

The lack of overlap between the estimate of childhood TB incidence in this report and the one published in the 2014 edition[b] illustrates the difficulties in producing such estimates (explained above) and limitations in the documentation of uncertainty. The estimates in this report use an updated methodological approach recommended by the WHO Global Task Force on TB Impact Measurement (**Box 2.1**, **Box 2.2**). However, even using this approach does not allow all sources of uncertainty, such as uncertainty due to model specification, to be fully quantified in practice.

The variability and lack of stability in recently published estimates of TB incidence among children is concerning. Addressing this challenge requires much greater commitment from national public health authorities to the definition and application of consistent case definitions, to ensuring reporting of cases based on a legal framework and ensuring that children who are close contacts of people with TB are thoroughly investigated using up-to-date national recommendations.

[a] JA Seddon and D Shingadia. Epidemiology and disease burden of tuberculosis in children: a global perspective. *Infect Drug Resist*, 7:153–65, null 2014.
[b] World Health Organization. *Global tuberculosis report 2014*. World Health Organization, Geneva; 2014. (WHO/HTM/TB/2014.08). See particularly **Box 2.5** in **Chapter 2**.
[c] PJ Dodd, E Gardiner, R Coghlan, and JA Seddon. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. *Lancet Glob Health* 2014; 2:e453–9.
[d] HE Jenkins, AW Tolman, CM Yuen et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. *Lancet*, 2014; 383:1572–9.
[e] For details, see the **online technical appendix** to this report at www.who.int/tb/data.

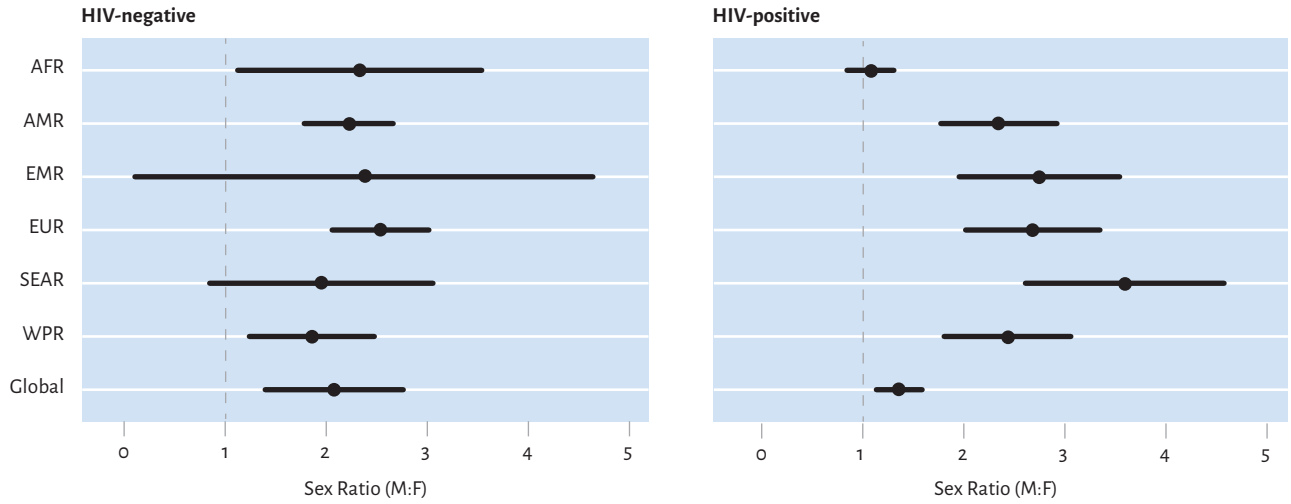
Global progress in reporting of cases among children since 1995 (the first year in which such data were requested for the 0–14 age group) and since 2005 (when further disaggregation for those aged 0–4 and 5–14 was requested) is shown in **Figure 2.20**. By 2014, reporting of age-disaggregated notification data was almost universal (**Figure 2.21**). In 2014, 359 000 new and relapse cases among children were reported, an increase of about 30% compared with 2013. The largest increases were in India (about 30 000) and the Philippines (about 10 000). Cambodia and Myanmar reported age-disaggregated data for the first time.

Producing estimates of TB incidence among children is challenging (**Box 2.5**). However, progress is being made, based on collaborations established in 2013 between WHO and academic groups working on the estimation of TB disease burden among children, as well as recommendations from a global consultation held earlier in 2015 (**Box 2.1**, **Box 2.2**). Methods to estimate TB incidence in children were updated for this report compared with those used to produce estimates published in 2013 and 2014. The updated methods involve use of an ensemble approach in which results from two independent methods are combined. The first method is based on the WHO approach used since 2012, with the modification that child-specific case detection ratios (as opposed to one ratio for all ages) are used according to previously published methods[1] that were updated to use more recent notification data.[2] The second method is a

[1] HE Jenkins, AW Tolman, CM Yuen et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. *Lancet*, 2014; 383:1572–9.
[2] This is in line with WHO suggestions documented in 2014. See Sismanidis C, Law I, Glaziou P,et al. The burden of tuberculosis disease in children. *Lancet*. 2014; 384(9951):1343. doi: 10.1016/S0140-6736(14)61810-9.

FIGURE 2.22

The male:female ratios of TB deaths among adults (aged ≥15 years), globally and by WHO region



dynamic model that uses adult TB prevalence estimates and parameters related to the natural history of TB in children. Global and regional estimates of TB incidence among children using this ensemble approach are shown in **Table 2.6**. The total estimated number of incident cases in 2014 was 1 million, with a CDR of 36%. The African and South-East Asia Regions account for about one third of global cases each.

2.4.2 TB mortality

To produce estimates of TB deaths among HIV-negative adults, mortality data from VR systems disaggregated by age and sex were used. Data were available for 113 countries (all middle or high-income countries). For countries without VR data, estimates were produced using an imputation model that included risk factors known to be associated with TB mortality. This model was used to estimate the ratios of the male to female and child to adult number of TB deaths. TB deaths among HIV-positive people were disaggregated by sex and age using the assumption that the male to female and children to adult ratios are similar to the corresponding ratios of AIDS deaths estimated by UNAIDS.

TB deaths among HIV-negative people

There were an estimated 700 000 TB deaths among HIV-negative men and 340 000 among HIV-negative women in 2014 (**Table 2.7**). The male: female ratio was also above two in all six WHO regions (left panel of **Figure 2.22**). There were an additional 81 000 (range, 69 000–93 000) TB deaths among HIV-negative children, equivalent to 7% of the total number of HIV-negative TB deaths.

TB deaths among HIV-positive people

There were an estimated 190 000 TB deaths among HIV-positive men and 140 000 among HIV-positive women in 2014

TABLE 2.6

Estimated number of incident cases of TB among children in 2014, globally and by WHO region

WHO REGION	NUMBER OF TB CASE NOTIFICATIONS	ESTIMATED TB INCIDENCE	
		BEST ESTIMATE	UNCERTAINTY INTERVAL
AFR	90 523	330 000	290 000–370 000
AMR	10 489	27 000	25 000–29 000
EMR	42 028	80 000	64 000–97 000
EUR	9 898	31 000	28 000–34 000
SEAR	168 310	340 000	310 000–370 000
WPR	37 273	150 000	130 000–170 000
Global	**358 521**	**1 000 000**	**900 000–1 100 000**

TABLE 2.7

Estimated number of TB deaths among HIV-negative adults disaggregated by sex, globally and by WHO region

WHO REGION	WOMEN		MEN	
	BEST ESTIMATE	UNCERTAINTY INTERVAL	BEST ESTIMATE	UNCERTAINTY INTERVAL
AFR	130 000	81 000–170 000	280 000	170 000–400 000
AMR	5 000	4 200–5 800	11 000	9 700–12 000
EMR	26 000	8 600–43 000	55 000	760–110 000
EUR	9 500	7 800–11 000	24 000	22 000–26 000
SEAR	150 000	90 000–210 000	280 000	160 000–400 000
WPR	29 000	21 000–37 000	53 000	43 000–64 000
Global	**340 000**	**270 000–420 000**	**700 000**	**530 000–880 000**

TABLE 2.8

Estimated number of TB deaths among HIV-positive adults disaggregated by sex, globally and by WHO region

WHO REGION	WOMEN		MEN	
	BEST ESTIMATE	UNCERTAINTY INTERVAL	BEST ESTIMATE	UNCERTAINTY INTERVAL
AFR	120 000	110 000–140 000	130 000	94 000–170 000
AMR	1 700	1 500–1 900	3 900	3 200–4 700
EMR	730	550–920	2 000	1 300–2 700
EUR	850	710–980	2 300	1 800–2 800
SEA	13 000	10 000–15 000	45 000	34 000–57 000
WPR	1 300	1 100–1 600	3 300	2 500–4 000
World	**140 000**	**120 000–160 000**	**190 000**	**150 000–230 000**

(**Table 2.8**). Most of these deaths were in the African Region, where the male:female ratio was close to one (right panel of **Figure 2.22**). The male:female ratio in other regions varied from around 2–4, with best estimates of 2.4–3.5. There were an additional 55 000 (range, 50 000–60 000) TB deaths among HIV-positive children, equivalent to 14% of the total number of HIV-positive TB deaths.

The total number of TB deaths among children (136 000, range 115 000–157 000) corresponds to a CFR of 13.6% (compared with 15.5% in adults).

2.5 HBC lists to be used by WHO in the post-2015 era

2.5.1 Background and brief history

The concept of a "high burden country" has become very familiar and widely used in the context of TB. The initial definition of HBCs in 1998 was based on the burden of TB in absolute terms. Its purpose was to allow focused interventions in the countries responsible for 80% of the global burden (measured in terms of the estimated number of incident cases), since progress in these countries would translate into global impact. The concept was subsequently applied to TB/HIV (in 2005) and MDR-TB (in 2008).

The current list of 22 HBCs (featured throughout this chapter) has not changed since 2002, and the HBC lists for TB/HIV and MDR-TB have not been updated since 2009 and 2008, respectively.[1] With the end of the MDGs and Stop TB Strategy in 2015 and the transition to a new era of Sustainable Development Goals (SDGs) and the End TB Strategy (**Chapter 1**), 2015 was the ideal year in which to revisit all three HBC lists and consider their future.

[1] For the TB/HIV list, see **Table 6.1** in **Chapter 6**. For the MDR-TB list, see **Table 4.1** in **Chapter 4**.

2.5.2 Process used to revisit HBC lists and their use post-2015

The process of revisiting HBC lists started with the development of a discussion paper by the Global TB Programme in WHO. This provided a brief history of the current HBC lists, and identified their potential advantages and disadvantages, drawing on input provided from across the WHO TB network, by major global technical and financial agencies, and by individuals who played a leading role in the original establishment and definition of each list. An online survey was then conducted in May 2015, focused on elicitation of feedback about the advantages and disadvantages of the lists, principles and design characteristics related to their use post-2015, and which of four "high-level" options for the use of lists after 2015 was preferred.[2]

Based on feedback received on the discussion paper and the results of the online survey, a proposal was then presented for consideration by WHO's Strategic and Technical Advisory Group for TB (STAG-TB) in June 2015. Full details are available in the discussion paper prepared for the STAG-TB meeting.[3]

2.5.3 Proposal presented to STAG-TB, June 2015

The proposal presented at the June 2015 meeting of STAG-TB can be summarized as follows:

- Three updated lists, for each of TB, MDR-TB and TB/HIV.
- Each list includes 30 countries, defined as the top 20 in terms of absolute numbers of cases, plus the 10 countries with the most severe burden in relative terms that do not already appear in the top 20 ("20+10").
- Two options for defining the "additional top ten" that have a severe burden in relative terms were presented for consideration. The first was to use rates per capita for the TB list, and the proportion of TB cases with MDR-TB and TB/HIV for the other two lists. The second was to use rates per capita for all three lists. It was also recognized that for the additional top ten, a threshold in terms of a minimum number of cases was relevant. The TB list with and without a threshold of 10 000 cases was presented.
- A lifetime of five years for all three lists, 2016–2020.

The STAG-TB recognized the value of HBC lists and endorsed the proposal for three "20+10" lists that would have a lifetime of five years. It was recommended to use rates per capita to define the additional top-ten countries, and to also use a

[2] These were: 1) Discontinue the use of HBC lists; 2) Continue to use three HBC lists (TB, MDR-TB, TB/HIV) but update them using the original criteria; 3) Continue to use three HBC lists (TB, MDR-TB, TB/HIV) but define them using new criteria; 4) Define one HBC list only.

[3] World Health Organization. *Use of high TB burden country lists in the post-2015 era*. Geneva: World Health Organization; 2015. (Discussion paper). Available at: www.who.int/tb/data. This document was updated in August 2015 to reflect the recommendations provided during the STAG-TB meeting and to use the latest estimates of disease burden prepared for this report.

threshold for a minimum number of cases. It was noted that countries with high rates but small numbers of cases are best included as part of regional HBC lists (if such lists are considered useful at that level).

2.5.4 Definition of HBC lists to be used by WHO post-2015, and associated next steps

Following the STAG-TB meeting, the Global TB Programme finalized the definition of the HBC lists to be used by WHO post-2015, as follows:

- Three HBC lists, one for each of TB, MDR-TB and TB/HIV.
- Each list includes 30 countries, defined as the top 20 in terms of absolute numbers and an additional ten that have the highest rates per capita and that are not already part of the top 20.[1] For inclusion in the lists on the basis of rates, countries must also have a minimum of 10 000 incident cases per year (for the TB list) or 1000 cases per year (for the TB/HIV and MDR-TB lists).
- The estimates of TB disease burden used to define the lists are the most up-to-date estimates available in 2015 i.e. those published in this 2015 global TB report.
- The lists will have a lifetime of five years, 2016–2020.

In each list, the resulting list accounts for 86–90% of the global number of cases.

There are two major next steps in 2015. The first is further communication by the Global TB Programme to WHO Member States, technical partners and funding agencies about the final definition of the lists. The second is a meeting to be held on 30 November in association with the international conference on TB and lung diseases (organized by the Union in Cape Town, South Africa). This will focus on implementation of the End TB Strategy (**Chapter 1**) with particular attention to the 30 countries in the new HBC list for TB. Starting in 2016, the new lists of 30 HBCs for TB, TB/HIV and MDR-TB will be used by WHO, including in the next edition of the global TB report.

[1] Some countries with the highest numbers in absolute terms also rank in the top ten in terms of rates.

CHAPTER 3

TB case notifications and treatment outcomes

Key facts and messages

2015 is a landmark year in global monitoring of TB case notifications and treatment outcomes by WHO: it is twenty years since a system for annual collection of these data from all countries was established in 1995. Between 1995 and 2014, data compiled via this system show that a cumulative total of 78 million cases of TB were notified to WHO and 66 million TB patients were successfully treated.

In 2014, 6.3 million cases of TB were notified by national tuberculosis programmes (NTPs) and reported to WHO: just over 6 million individuals were newly diagnosed in 2014 and 261 000 were previously diagnosed TB patients whose treatment regimen was changed.

In 2014, most notified TB cases were adults. Children (aged <15 years) accounted for 6.5% of notified cases, ranging from 3.4% in the Western Pacific Region to 9.5% in the Eastern Mediterranean Region. The male:female ratio of notified cases across all age groups was 1.7 globally, ranging from 1.0 in the Eastern Mediterranean Region to 2.1 in the Western Pacific Region.

Among pulmonary TB cases, 58% were bacteriologically confirmed (as opposed to clinically diagnosed) in 2014; this was unchanged from 2013.

For the first time since 2007, there was a noticeable increase in global TB notifications in 2014 (these had stabilized at around 5.7–5.8 million new and relapse cases for 2007–2013). The increase is explained by a 29% increase in notifications in India, linked to the introduction of a policy of mandatory notification, a new web-based and case-based reporting system that has been rolled out nationwide and greater engagement of the country's large private health sector. India accounted for 27% of global TB notifications in 2014, followed by China (14%).

The private health sector, providers of health services in the public sector that are not directly linked to NTPs and community workers or volunteers can make important contributions to the notification and treatment of TB cases. For example, 12% of notifications in India were from the private sector in 2014, and 55% of notifications in China were from public hospitals outside the NTP network. In six of 41 countries that reported data, more than 50% of notifications were from community referrals in areas where community engagement activities were in place.

Globally, notifications of newly diagnosed TB cases in 2014 represented 63% (95% uncertainty interval, 60–66%) of estimated incident cases. The best estimate of the gap between notifications of new episodes of TB (new and relapse cases) and incident cases was 3.6 million cases.

Two factors explain gaps between notifications and estimated incidence. The first is under-reporting of diagnosed TB cases: for example, of cases detected and treated in the private sector. The second is under-diagnosis. Reasons for under-diagnosis include poor access to health care and failure to detect cases when people with TB visit health care facilities. Intensified efforts, such as those already being made in India, are needed to ensure that all cases are detected, notified to national surveillance systems, and treated according to international standards.

Globally in 2013, the treatment success rate for new cases of TB was 86%. Improvement in treatment outcomes is needed in the Region of the Americas and the European Region, where treatment success rates in 2013 were 75% and 76%, respectively.

The management of latent TB infection (LTBI) is a critical component of the new post-2015 End TB Strategy, and WHO issued guidance for upper-middle and high-income countries with an incidence rate of less than 100 per 100 000 population in 2015. In many of these countries, LTBI policies are in place and detection and treatment is being provided. However, there are also policy-practice gaps that need to be addressed and systems for routine recording and reporting of data need to be improved.

Routine recording and reporting of the numbers of TB cases diagnosed and treated by national TB programmes (NTPs) and monitoring of treatment outcomes was one of the five components of the global TB strategy (DOTS) launched by WHO in the mid-1990s; this remained a core element of its successor, the Stop TB Strategy (2006–2015), and is part of the new End TB Strategy (**Chapter 1**). With the standard definitions of cases and treatment outcomes recommended by WHO and associated recording and reporting framework as a foundation, the number of people diagnosed and treated for TB and associated treatment outcomes is routinely monitored by NTPs in almost all countries, which in turn report these data to WHO in annual rounds of global TB data collection (**Chapter 1**). 2015 is a landmark year in global monitoring of TB case notifications and treatment outcomes by WHO: it is twenty years since a system for annual collection of these

data from all countries was established in 1995. Between 1995 and 2014, data compiled via this system show that a cumulative total of 78 million cases of TB were notified to WHO and 66 million TB patients were successfully treated.[1]

This chapter has six parts. **Section 3.1** summarizes the total number of people diagnosed with TB and notified by NTPs in 2014; these numbers are also disaggregated by case type, age and sex. **Section 3.2** presents and discusses the specific contribution to total case notifications of public–public and public–private mix (PPM) initiatives. **Section 3.3** highlights the role of community engagement in TB detection and treatment. **Section 3.4** presents trends in notifications between 1990 and 2014 and compares these with trends in estimated TB incidence. The ratios of notified to estimated incident cases (an indicator known as the case detection rate or CDR) are provided for selected years. **Section 3.5** describes the latest data on treatment outcomes (for cases registered for treatment in 2013) as well as treatment outcomes achieved in selected years since 1995. **Section 3.6**, the final part of the chapter, introduces a new topic to the global TB report: policy and practices related to treatment of latent TB infection (LTBI). This is a core component of the End TB Strategy, which covers the period 2016–2035 (**Chapter 1**).

3.1 Case notifications in 2014 by type of disease, age and sex

Box 3.1 lists the definitions of TB cases recommended by WHO as part of an updated recording and reporting framework issued in March 2013,[2] and that were used in the 2014 and 2015 rounds of global TB data collection. These updated definitions were necessary to accommodate diagnosis using Xpert MTB/RIF and other WHO-endorsed molecular tests (**Chapter 5**), as well as offering an opportunity to improve aspects of the previous (2006) framework, such as inclusion of more comprehensive reporting of TB cases among children.

Notifications of TB cases in 2014 are summarized globally, for the six WHO regions and for the 22 high TB-burden countries (HBCs) in **Table 3.1**. In 2014, 6.3 million people with TB were notified to NTPs and reported to WHO. Of these, just over 6 million had a new episode of TB (shown as the total of new and relapse cases) and 261 000 had already been diagnosed with TB but their treatment was changed to a retreatment regimen.

For the first time since 2007, there was a noticeable increase in global TB notifications in 2014, which had previously stabilized at 5.7–5.8 million new and relapse cases for the seven years from 2007–2013 (**Figure 3.1**). The increase is mostly explained by a 29% increase in notifications in India, linked to the introduction of a policy of mandatory notification, a new web-based and case-based reporting system that has been rolled out nationwide, and greater engagement of the country's large private health sector. India accounted for 27% of global TB notifications in 2014 (**Box 3.2**, **Figure 3.3**), up from 22% in 2013. The South-East Asia and Western Pacific Regions (which include India and China, respectively) together accounted for 63% of notifications of new and relapse cases globally, and the African Region for 21%. The other three regions accounted for relatively small proportions of cases. Among pulmonary TB cases, 58% were bacteriologically confirmed (as opposed to clinically diagnosed) in 2014; this was unchanged from 2013.

In both the Eastern Mediterranean and Western Pacific regions, the TB epidemic is a markedly ageing one, with a progressive increase in the notification rate with age and a peak among those aged ≥65 years old (**Figure 3.4**). A similar pattern is evident in the South-East Asia Region. Elsewhere, and most noticeably in the African Region, notification rates in 2014 peaked in younger adults.

Most countries are now able to report notifications disaggregated by both age and sex (**Table 3.2**). In 2014, adults accounted for most of the notified cases. Children (aged <15 years) accounted for only 6.5% of notifications, although this ranged from 3.4% in the Western Pacific Region to 9.5% in the Eastern Mediterranean Region. The global male:female sex ratio was 1.7, but among HBCs this ratio varied from 0.7 in Afghanistan to 3.0 in Viet Nam. Variation among countries in the child:adult and male:female ratios of cases may reflect real differences in epidemiology, differential access to or use of health care services linked to the NTP, and/or differential reporting practices. Evidence from recent national TB prevalence surveys shows that the male:female ratio for bacteriologically-confirmed TB among adults is typically around 2–3 in Asian countries and 1–2 in Africa, and that the ratio of prevalent to notified cases is systematically higher among men than women (suggesting that women with TB have a higher chance of being notified).[3,4]

3.2 Contribution of public–public and public–private mix initiatives to TB case notifications and treatment support in 2014

Ensuring proper diagnosis, standardized treatment and prompt notification of all TB cases to NTPs requires collaboration with the full range of health care providers. Engaging all care providers in TB care and control is component four of the Stop TB Strategy and part of pillar two (of three) of the post-2015 End TB Strategy (**Chapter 1**).

In recent years, many countries have made considerable progress in scaling up PPM initiatives. However, demon-

[1] These figures are for new and relapse cases. See **Box 3.1** for case definitions.

[2] *Definitions and reporting framework for tuberculosis – 2013 revision*. Geneva, World Health Organization; 2013 (WHO/HTM/TB/2013.2). Available at: www.who.int/tb/publications/definitions.

[3] Onozaki I, Law I, Sismanidis C et al. National tuberculosis prevalence surveys in Asia 1990–2012: an overview of results and lessons learned. *Trop Med Int Health* 2015; 20(9):1128–1145. doi: 10.1111/tmi.12534. Epub 2015 Jun 7.

[4] WHO and partners are preparing a paper summarizing results from recent prevalence surveys in Africa. It is anticipated that this will be published in 2016.

Box 3.1 WHO definitions of TB cases recommended for use since March 2013 and that were used in the 2014 and 2015 rounds of global TB data collection[a]

Bacteriologically confirmed case of TB A patient from whom a biological specimen is positive by smear microscopy, culture or WHO-approved rapid diagnostic test (such as Xpert MTB/RIF). All such cases should be notified, regardless of whether TB treatment is started.

Clinically diagnosed case of TB A patient who does not fulfil the criteria for bacteriologically confirmed TB but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. This definition includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extrapulmonary cases without laboratory confirmation. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

Case of pulmonary TB Any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Miliary TB is classified as pulmonary TB because there are lesions in the lungs. Tuberculous intra-thoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitute a case of extrapulmonary TB. A patient with both pulmonary and extrapulmonary TB should be classified as a case of pulmonary TB.

Case of extrapulmonary TB Any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. abdomen, genitourinary tract, joints and bones, lymph nodes, meninges, pleura, skin.

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

Retreatment case of TB A patient who has been treated for one month or more with anti-TB drugs in the past. Retreatment cases are further classified by the outcome of their most recent course of treatment into four categories.

1. *Relapse* patients have previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).
2. *Treatment after failure* patients have previously been treated for TB and their most recent course of treatment failed i.e. they had a positive sputum smear or culture result at month 5 or later during treatment.
3. *Treatment after loss to follow-up* patients have previously been treated for TB and were declared 'lost to follow-up' at the end of their most recent course of treatment.
4. *Other previously treated* patients are those who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.

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.

Case of rifampicin-resistant TB (RR-TB) A patient with TB that is resistant to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, whether mono-resistance, multidrug resistance, polydrug resistance or extensive drug resistance.

[a] *Definitions and reporting framework for tuberculosis – 2013 revision*. Geneva, World Health Organization, 2013 (WHO/HTM/TB/2013.2). Available at www.who.int/tb/publications/definitions.

FIGURE 3.1

Global trends in absolute number of notified TB cases (black) and estimated TB incidence (green), 1990–2014.
Case notifications include new and relapse cases (all forms).

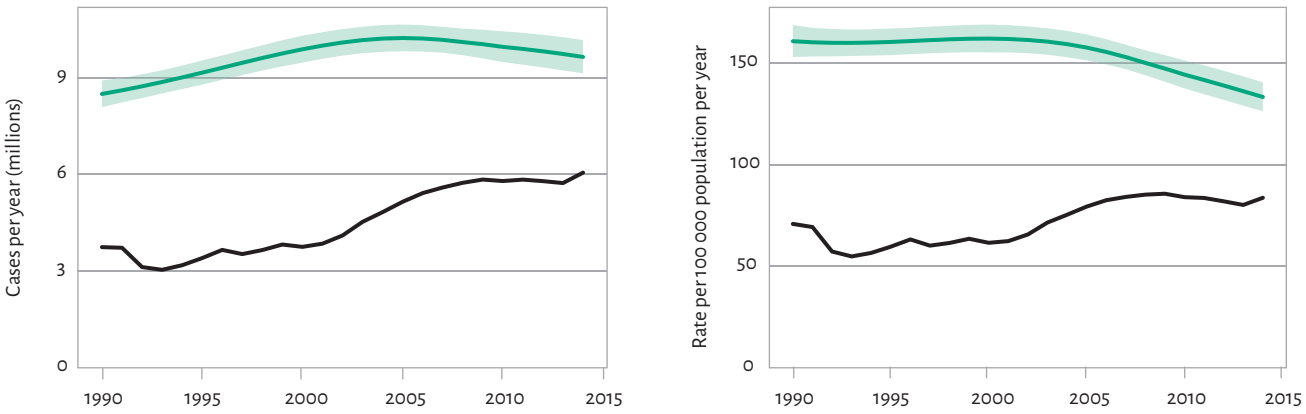


TABLE 3.1

Case notifications, 2014

	TOTAL NOTIFIED	NEW AND RELAPSE[a]	RETREATMENT EXCLUDING RELAPSE	NEW OR PREVIOUS TREATMENT HISTORY UNKNOWN			RELAPSE			PERCENTAGE OF PULMONARY CASES BACTERIOLOGICALLY CONFIRMED
				PULMONARY BACTERIOLOGICALLY CONFIRMED	PULMONARY CLINICALLY DIAGNOSED	EXTRAPULMONARY	PULMONARY BACTERIOLOGICALLY CONFIRMED	PULMONARY CLINICALLY DIAGNOSED	EXTRAPULMONARY	
Afghanistan	32 712	31 746	966	14 737	8 573	7 227	1 209			65
Bangladesh	196 797	191 166	5 631	106 767	42 832	37 406	2 989	863	309	72
Brazil	81 512	73 970	7 542	41 120	17 801	9 479	3 602	1 488	480	70
Cambodia	43 738	43 059	679	12 168	11 286	18 310	445	709	141	51
China	826 155	819 283	6 872	235 704	526 106	32 348	25 125			33
DR Congo	116 894	115 795	1 099	75 631	13 494	19 566	4 298	1 892	914	84
Ethiopia	119 592	119 592		40 087	41 575	37 930				49
India	1 683 915	1 609 547	74 368	754 268	343 032	275 502	124 679	112 066		66
Indonesia	324 539	322 806	1 733	193 321	101 991	19 653	6 449	1 391	1	66
Kenya	89 294	88 025	1 269	34 997	30 872	14 640	3 569	2 947	1 000	53
Mozambique	58 270	57 773	497	24 430	23 455	6 276	1 542	2 070		50
Myanmar	141 957	138 352	3 605	42 608	70 305	16 108	5 276	3 650	405	39
Nigeria	91 354	86 464	4 890	49 825	29 460	4 764	2 415		0	64
Pakistan	316 577	308 417	8 160	122 537	120 350	57 463	7 420	426	221	52
Philippines	267 436	243 379	24 057	92 991	139 950	4 161	6 277			41
Russian Federation	136 168	102 340	33 828	37 296	40 894	8 763	7 982	6 753	652	49
South Africa	318 193	306 166	12 027	155 473	106 482	33 522	7 430	2 693	566	60
Thailand	71 618	67 722	3 896	34 394	21 115	10 244	1 969	0	0	63
Uganda	46 171	44 187	1 984	26 079	11 854	4 180	1 499	468	107	69
UR Tanzania	63 151	61 571	1 580	23 583	23 380	13 600	1 008			51
Viet Nam	102 087	100 349	1 738	49 938	25 179	18 118	7 114			69
Zimbabwe	32 016	29 653	2 363	11 224	13 151	3 909	1 369			49
High-burden countries	**5 160 146**	**4 961 362**	**198 784**	**2 179 178**	**1 763 137**	**653 169**	**223 666**	**137 416**	**4 796**	**56**
AFR	1 342 400	1 300 852	41 548	635 560	399 155	212 057	39 782	11 217	3 081	62
AMR	228 476	215 243	13 233	127 864	40 746	32 501	10 193	2 918	1 021	76
EMR	465 677	453 393	12 284	183 630	151 696	103 959	12 368	866	874	56
EUR	321 421	266 058	55 363	112 416	76 759	39 175	23 935	11 483	2 290	61
SEAR	2 580 605	2 482 074	98 531	1 188 654	632 418	389 819	152 498	117 970	715	64
WPR	1 375 572	1 335 816	39 756	449 845	734 179	103 085	44 354	3 037	1 316	40
Global	**6 314 151**	**6 053 436**	**260 715**	**2 697 969**	**2 034 953**	**880 596**	**283 130**	**147 491**	**9 297**	**58**

Blank cells indicate data not reported.

[a] New and relapse includes cases for which the treatment history is unknown.

strating progress in terms of the contribution of non-NTP public and private sector providers to total case notifications requires systematic recording of the source of referral and place of TB treatment locally, and reporting and analysis of aggregated data nationally. In many countries, data related to the contribution of private sector providers are still not collected or reported through routine monitoring systems, although there are excellent examples of how this can be done (**Box 3.2**).

The available data show that the approach to and contribution of PPM varies across countries, and is related to the number and type of health care providers. **Table 3.3a** shows ten prominent examples of countries (including HBCs) where public-public mix interventions contributed between 11% and 55% of total notifications in 2014. **Table 3.3b** presents ten prominent examples of countries (including HBCs) where public-private mix interventions contributed between 12% and 46% of total case notifications.

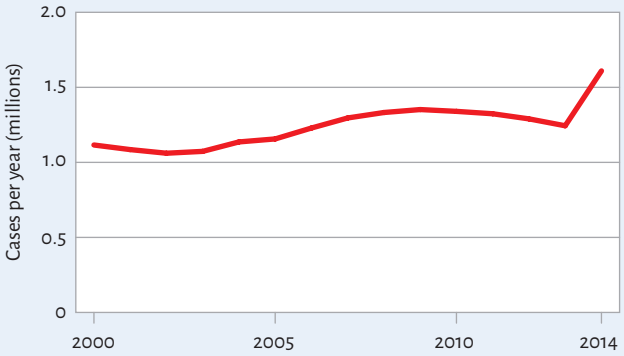
Box 3.2 Substantial increases in TB notifications in India 2013–2014 – the role of mandatory notification and e-health interventions

The number of new and relapse TB cases notified in India reached 1.61 million in 2014, a 29% increase compared with 1.24 million in 2013 (**Figure B3.2**). This substantial increase is due to better reporting of detected cases to national authorities (as opposed to an increase in the underlying TB incidence), which can be explained by three major factors:

- The introduction of a policy of mandatory notification of TB cases in May 2012;[a]
- The launch of a new web-based system (Nikshay) for case-based notification by the Central TB Division (CTD) and the National Informatics Centre in June 2012;[b]
- Increased and intensified efforts to engage with the private sector by the Revised National Tuberculosis Control Programme (RNTCP), which have been facilitated by Nikshay.

FIGURE B3.2

Case notifications in India, 2000–2014



Mandatory notification was introduced in recognition of the fact that while the private sector provides treatment for approximately 50% of TB patients,[c] most of these cases were not being reported to the RNTCP.

Nikshay was introduced as part of efforts to facilitate reporting of TB cases, including those treated in the private sector. The system is available for reporting of cases by both public and private health care facilities. It is accessible via android-based smartphones and a web-portal, both of which facilitate the process of notifying cases. Since its rollout nationwide by the end of 2012, reporting from the private sector has grown and data quality has improved. By June 2015, more than 4.6 million TB patients had been reported by over 40 000 public and over 90 000 private health care facilities, with about 5 000 TB cases being added to the system each day. Nikshay has also eliminated the time previously taken to transmit laboratory results to treatment sites and peripheral units.

Nikshay captures data that are important for both programme management and clinical care. These include details of who notified a TB case, who provides direct observation of treatment (DOT), patient transfers, and contact tracing, as well as demographic and clinical details of the individual TB patient such as age, sex, HIV status, bacteriology and drug-susceptibility test results, and treatment outcomes. This has allowed the RNTCP to generate reports consistent with updated definitions of case definitions and treatment outcomes recommended by WHO since 2013 (**Box 3.1**). This includes age and sex-disaggregated data for all new and relapse cases, which could not be produced using the old reporting system. The CTD uses five variables to avoid entry of duplicate records in Nikshay. The greater granularity of the data being recorded in Nikshay is also allowing better forecasting of TB drug requirements for children and adults, and provides information on the nutritional status of patients.

To support the introduction and implementation of Nikshay, online videos in English and Hindi were used to train frontline workers, and mobile-phone short messaging services (SMS) were used to ensure regular contact of users with programme managers at all levels. Managers can now receive reports on case-finding, sputum conversion and treatment outcome via SMS. Patients – half of whom have a mobile number entered in the system – also benefit from SMS reminders for visits related to follow-up of treatment. Traditional paper-based and aggregated quarterly reporting will be phased out in 2016, and reporting will be entirely through Nikshay.

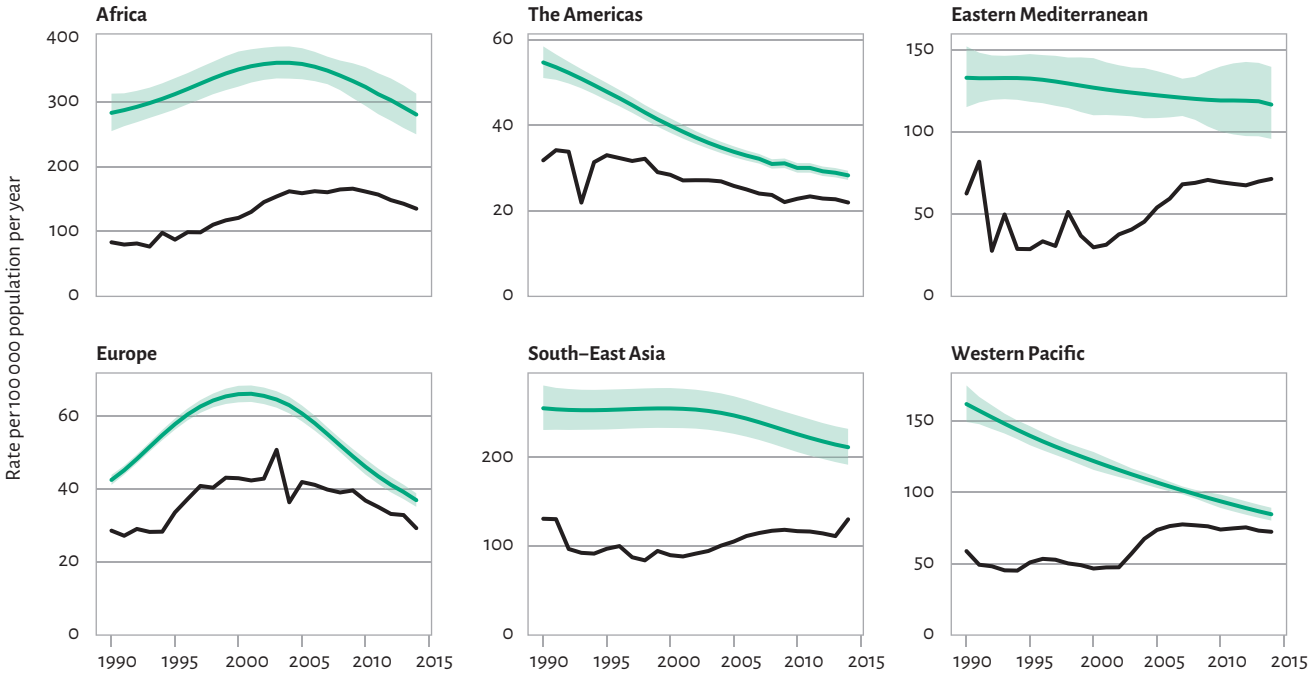
In the next phase of Nikshay's development, the aim is to capture geospatial data to enable spatial surveillance, and to use and record bar-codes on medication boxes for drug supply chain and inventory management. Linking up with other electronic services may also allow electronic payments to patients and providers, and access to the national unique identification number (Aadhaar)[d] and related social support schemes for TB patients.

The cities of Mumbai, Patna and Mehsana already provide good examples of how digital technologies are helping the RNTCP to reach out to providers who are involved in TB care but who have previously been outside the reach of national surveillance. In these settings, private providers can phone call centres free of charge to ensure free anti-TB medications for their patients. Patients receive "e-vouchers" for standardized medications, which they can redeem at no charge at private chemists. Call centres also issue reminders to patients for follow-up visits via telephone calls and SMS. This digital system is linked with the RNTCP, so that programme staff receive alerts and can take actions as necessary. Incentives for notification are paid to providers electronically, as are payments for laboratory tests. e-Learning tools have also been introduced to facilitate the dissemination of the 'Standards for TB Care in India', and e-Learning techniques have also been useful for rapid, large-scale training of staff on the use of the call centres.

[a] http://pib.nic.in/newsite/erelease.aspx?relid=83486
[b] http://nikshay.gov.in/AboutNikshay.htm
[c] Satyanarayana S, Nair SA, Chadha SS, et al. From where are tuberculosis patients accessing treatment in India? Results from a cross-sectional community based survey of 30 districts. *PLoS One* 2011; 6: e24160
[d] https://resident.uidai.net.in/

FIGURE 3.2

Case notification and estimated TB incidence rates by WHO region, 1990–2014. Regional trends in case notification rates (new and relapse cases, all forms) (**black**) and estimated TB incidence rates (**green**). Shaded areas represent uncertainty bands.



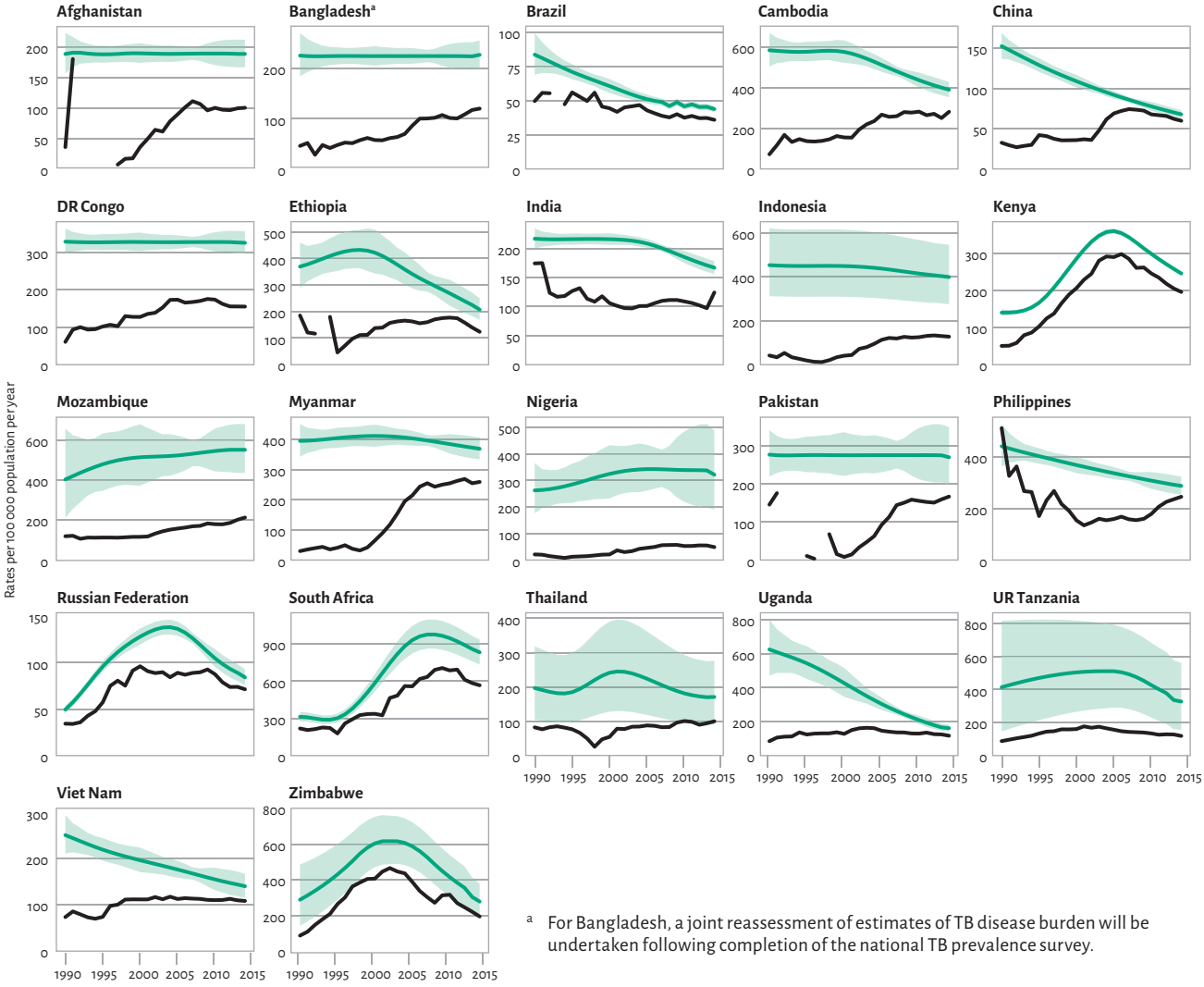
In China, a large proportion of people with TB seek care from public hospitals, and various models of hospital engagement exist. In 2014, public hospitals contributed 55% of all notified TB cases. A web-based system for reporting of communicable diseases has played a key role in ensuring that TB cases detected in public hospitals outside the NTP network are notified. Medical college hospitals in India, speciality lung hospitals and general hospitals in Indonesia, hospitals owned by social security organizations in Peru and other Latin American countries, and the hospitals of health insurance organizations in Egypt are other examples of public health care providers that are making important contributions to TB case notifications. In 2014, public sector medical college hospitals in India alone reported 176 000 TB cases. Given that health centres and hospitals are often managed by different departments within ministries of health and that ministries such as those for education, social welfare, defence or justice can also be involved in providing health services, implementing public-public mix approaches is essential in many parts of the world.

Public-private mix approaches are necessary in countries with a large private sector, including most HBCs in the South-East Asia and Western Pacific regions and an increasing number of countries in the African Region, where the private medical sector is growing rapidly. The steep rise in TB case notifications from private sector care providers in India between 2013 and 2014 (from 85 000 to 195 000 in 2014) is particularly impressive. Further details are provided in **Box 3.2**. A large increase of more than 30% in notifications from the private sector in Pakistan between 2013 and 2014 is also a notable achievement. Both countries have made concerted efforts to increase notifications of detected cases by the private sector, and these are now paying off.

The private health sector in Africa is often considered insignificant in terms of its contribution to provision of TB care. Data from Kenya, Malawi and Nigeria show that this is not always the case. In 2014 as in 2013, almost one in five cases notified in Malawi was reported by a private care provider, even though TB drugs are generally not available in private pharmacies (unlike in Kenya and Nigeria). Most of the contributions to TB case notifications in Malawi are referrals of people with TB signs and symptoms to the public sector by the front-line, community-based private health care providers. These often include clinical officers, nurses and traditional healers. Engaging such front-line care providers, including drug shops and pharmacies, facilitates early case detection. The Malawi example should prompt other countries that have not previously considered PPM to be of importance to revisit their strategies. In all settings, PPM interventions should also be designed to help not only detection of TB cases, but also early detection by providers where care is often sought first.

FIGURE 3.3

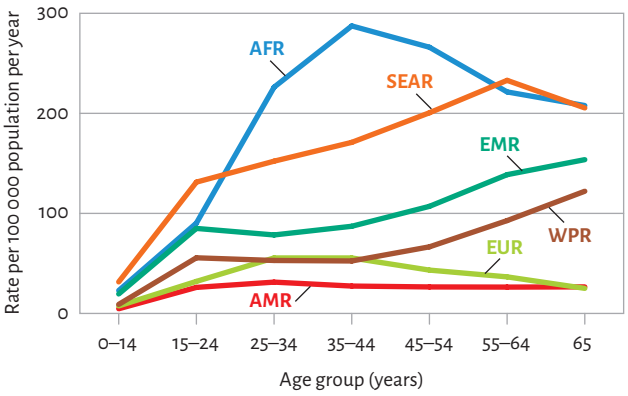
Case notification and estimated TB incidence rates, 22 high-burden countries, 1990–2014. Trends in case notification rates (new and relapse cases, all forms) (black) and estimated TB incidence rates (**green**). Shaded areas represent uncertainty bands.



[a] For Bangladesh, a joint reassessment of estimates of TB disease burden will be undertaken following completion of the national TB prevalence survey.

FIGURE 3.4

Regional TB notification rates by age, 2014[a]



[a] Countries not reporting cases in these categories are excluded. Cases included make up 87% of reported cases and exclude the following high–burden countries: Afghanistan, Ethiopia, Mozambique and Thailand.

3.3 Community contributions to TB notifications and treatment support

Despite the best efforts of health systems, about one third of people who develop TB globally are still either not diagnosed, or their cases are not reported (see **section 3.5**). Difficulty in accessing health facilities is one of the reasons why people with TB may not be diagnosed, and can also have a negative impact on treatment adherence. Access to health care can be affected by social and political factors (such as stigma and discrimination, and the availability of cross-border services for migrants), and economic barriers (for example, the cost of transport). The role of community engagement in contributing to TB prevention, diagnosis and treatment, especially where people with TB have poor access to formal health services, is therefore well-recognized. Fostering such community participation has been an explicit component of the Stop TB Strategy and a "strong coalition with civil society

TABLE 3.2

Notifications of new and relapse TB cases by age and sex, 2014

	0–14 YEARS	≥15 YEARS	AGE UNKNOWN	% AGED <15 YEARS	MALE/ FEMALE RATIO
Afghanistan*	4 454	18 856	7 227	19	0.7
Bangladesh*	6 262	180 743	0	3.3	1.5
Brazil	2 368	71 602	0	3.2	2.1
Cambodia	12 050	31 009		28	1.2
China	4 164	815 119	0	0.5	2.3
DR Congo*	3 438	71 901	292	4.6	1.3
Ethiopia*	15 917	103 675	0	13	1.2
India	95 709	1 513 838		5.9	1.9
Indonesia	23 170	299 636	0	7.2	1.4
Kenya	8 448	80 846	0	9.5	1.5
Mozambique				–	–
Myanmar	36 301	101 987	64	26	1.6
Nigeria	5 463	85 891	0	6.0	1.5
Pakistan	27 245	281 172	0	8.8	1.0
Philippines	12 191	46 965	38 422	21	1.8
Russian Federation	3 195	98 433	712	3.1	2.3
South Africa	31 977	274 189	0	10	1.3
Thailand*	119	34 275	0	0.3	2.5
Uganda	3 316	40 871		7.5	1.8
UR Tanzania	6 463	55 108	0	10	1.5
Viet Nam*	144	49 785		0.3	3.0
Zimbabwe	2 290	27 363		7.7	1.3
High-burden countries	**304 684**	**4 283 264**	**46 717**	**6.6**	**1.7**
AFR	90 523	963 808	2 298	8.6	1.4
AMR	10 489	198 350	1 935	5.0	1.7
EMR	42 028	399 043	7 945	9.5	1.0
EUR	9 898	250 946	719	3.8	2.0
SEAR	168 310	2 248 065	19 394	7.0	1.8
WPR	37 273	1 063 252	38 422	3.4	2.1
Global	**358 521**	**5 123 464**	**70 713**	**6.5**	**1.7**

Blank cells indicate data that could not be reported for the age categories shown.
– indicates values that cannot be calculated.
* New cases only.

TABLE 3.3a

Contribution of public-public mix[a] to notifications of TB cases in selected countries, 2014

COUNTRY	NUMBER OF TB CASES NOTIFIED BY NON-NTP PUBLIC SECTOR CARE PROVIDERS	TOTAL NUMBER OF TB CASES NOTIFIED	CONTRIBUTION OF NON-NTP PUBLIC SECTOR CARE PROVIDERS TO TOTAL CASE NOTIFICATIONS (%)
China	458 356	826 155	55
Côte d'Ivoire	2 279	23 750	9.5
Egypt	1 375	7 467	18
El Salvador	1 016	2 220	46
India	189 857	1 683 915	11
Indonesia	57 586	324 539	18
Iraq	2 748	8 341	33
Peru	8 164	31 461	26
Sri Lanka	4 457	9 473	47
Yemen	3 390	9 693	35

[a] Includes all contributions from non-NTP providers of care in the public sector, including public hospitals, public medical colleges, prisons/ detention centres, military facilities, railways and public health insurance organizations.

TABLE 3.3b

Contribution of public-private mix[a] to notifications of TB cases in selected countries, 2014

COUNTRY	NUMBER OF TB CASES NOTIFIED BY PRIVATE SECTOR CARE PROVIDERS	TOTAL NUMBER OF TB CASES NOTIFIED	CONTRIBUTION OF PRIVATE SECTOR CARE PROVIDERS TO TOTAL NOTIFICATIONS (%)
Bangladesh	22 960	196 797	12
Ethiopia	16 876	119 592	14
India	194 992	1 683 915	12
Iran	3 093	10 395	30
Iraq	3 803	8 341	46
Kenya	18 200	89 294	20
Malawi	3 500	17 723	20
Myanmar	25 978	141 957	18
Nigeria	13 031	91 354	14
Pakistan	55 254	316 577	17

[a] Private sector providers include private individual and institutional providers, corporate/business sector providers, mission hospitals, nongovernmental organizations and faith-based organizations.

Box 3.3 Definitions of key terms and indicators used to monitor community engagement

Community-based TB activities. These cover a wide range of activities that contribute to the detection, referral and treatment of people with drug-susceptible, drug-resistant and HIV-associated TB. They are conducted outside the premises of formal health facilities (e.g. hospitals, health centres and clinics) in community-based structures (e.g. schools, places of worship, congregate settings, markets) and homesteads. Community health workers and community volunteers carry out community-based TB activities, depending on the national and local context.

Community health workers. These are people with some formal education who have been given training to contribute to community-based health services, including TB prevention and patient care and support. Their profile, roles and responsibilities vary greatly among countries, and their time is often compensated by incentives in kind or in cash.

Community volunteers. These are people who have been systematically sensitized about TB prevention and care, either through a short, specific training scheme or through repeated, regular contact sessions with professional health workers.

Core indicators for routine monitoring of community-based TB activities

In 2013, three core indicators were defined and agreed by WHO and partners. These are:

1. *Percentage of TB notifications from community referrals.* This indicator measures the proportion of notified TB patients (all forms of TB) who were referred by a community health worker or community volunteer.
2. *Percentage of registered TB patients who received treatment support in the community.* This indicator measures the proportion of TB patients who were supported during treatment by a community health worker or community volunteer.
3. *Percentage of registered TB patients who received treatment support in the community who were successfully treated.* This indicator measures the proportion of TB patients who received treatment support from a community health worker or community volunteer during their TB treatment and who were successfully treated.

organizations and communities" is one of the four principles underpinning the End TB Strategy (**Chapter 1**). Establishing and strengthening collaboration with nongovernmental and other civil society organizations to scale up community-based TB activities, and enhancing their role in the design and implementation of national TB strategic plans, are important.

Accurate monitoring of the contributions of communities to TB notifications and treatment support requires standard definitions of key concepts and indicators, and standardized systems for recording and reporting of data. These were developed in 2013 and are shown in **Box 3.3**. Data for the three core indicators were collected for the first time in 2013, with a focus on 13 countries in the African and South-East Asia regions that were known to be recording and reporting such information. In 2014, data collection was expanded and 22 countries from the same two regions reported data. Based on these two years of experience, data collection was expanded in the 2015 round of global TB data collection to cover the European, Eastern Mediterranean and Western Pacific regions. Following consultations with WHO staff in Regional and Country Offices, a total of 69 countries were targeted for reporting of data. Of these, 41 reported data for at least one of the three core indicators; 34 (83%) reported data on the percentage of TB patients who received treatment support in the community, and 30 (73%) reported data on the percentage of TB notifications that originated from community referrals.

A summary of the contribution of communities to TB notifications and treatment support is provided in **Table 3.4**. About one third (14/41) of countries reported nationwide coverage of community engagement in case notification, and 41% (17/41) reported nationwide coverage of community-based treatment support. In areas where community-based referral activities were in place, the percentage of notified TB patients accounted for by community referrals ranged from 2% in Myanmar and Sri Lanka to 73% in Cambodia. The proportion of TB patients receiving community-based treatment support ranged from 2% in Malaysia, Romania and Sierra Leone to 100% in Kenya, Pakistan and Tajikistan.

Reporting of the treatment success rate among TB patients who received treatment support in the community has continued to be a challenge. Among the 41 countries that reported data related to community engagement, only 26 (41%) reported information for this indicator. Even in these countries, there are concerns with the accuracy of the reported data. For example, while the general tendency was for treatment outcomes to improve between 2013 and 2014 among patients receiving treatment support from a community volunteer or community health worker, there were large year-to-year changes in some countries that appeared implausible. Intensified efforts are needed to improve the accuracy of data for this indicator, and/or to revisit its status as a core indicator. For example, it may be more appropriate to assess this indicator as part of a periodic evaluation, rather than through routine reporting. This is being considered by WHO as part of wider efforts to develop expanded guidance on community engagement.

It is also important to note that there are countries in which community-based TB activities are a routine com-

Box 3.4 The ENGAGE-TB approach: progress and highlights to date

The ENGAGE-TB approach aims to integrate community-based TB activities into the work of nongovernmental organizations and other civil society organizations that were previously not engaged in TB prevention, diagnosis and treatment. Pilot projects were started in 2012 with funding from the Bristol-Myers Squibb Foundation Secure the Future in five countries: the Democratic Republic of the Congo, Ethiopia, Kenya, South Africa and the United Republic of Tanzania. In Ethiopia, TB activities were integrated into maternal and child health activities and cervical cancer screening. In Kenya, they were integrated into maternal and child health activities and livelihood initiatives. In the other three countries, they were integrated into HIV programmes.

By the end of 2014, the total population covered by the pilot projects had reached 8 million and 24 previously unengaged nongovernmental organizations had started to implement community-based TB activities. In pilot areas, community referrals of people with signs and symptoms suggestive of TB contributed 5–68% of notified TB patients in 2013 and 2014, and 20–89% of all TB patients had benefited from community-based treatment support during the same period.

ponent of TB services, but where it is not yet possible to quantify this contribution. For example, Zimbabwe has recently finalized revisions to its national monitoring and evaluation system and will be able to report data on community contributions starting in 2016. In the near future, it is also anticipated that Malawi will incorporate routine reporting of community contributions within the existing monitoring and evaluation system.

In addition to improving the documentation and reporting of community-based TB activities, efforts to engage nongovernmental organizations that have previously not been involved in TB prevention, diagnosis and treatment have continued using the ENGAGE-TB approach.[1] In addition to five focus countries (the Democratic Republic of the Congo, Ethiopia, Kenya, South Africa and the United Republic of Tanzania), five additional countries have now integrated the ENGAGE-TB approach into their national strategies and mobilized funding for its implementation. These are Burkina Faso, Côte d'Ivoire, Malawi, Namibia and Zimbabwe. Progress made to date in the original five countries is described in **Box 3.4**.

3.4 Trends in case notifications 1990–2014 and estimates of the case detection rate

Globally, the number of TB cases newly diagnosed and notified per 100 000 population remained relatively stable between 1990 and 2000, rose sharply between 2000 and 2008, and then fell slowly from 2009 to 2013 (**Figure 3.1**). In terms of absolute numbers, there was an increase from 1995 to 2000, a more pronounced increase from 2000 to 2008 and then very little change from 2008 to 2013 (**Figure 3.1**). Between 2013 and 2014, these patterns changed, with a clear upward increase in terms of rates and absolute numbers. This change is driven by an increase in the South-East Asia Region (**Figure 3.2**), which itself reflects the large increase in notifications (of 366 000 cases) in India between 2013 and 2014 (**Figure 3.3**, **Box 3.2**).

Globally and in all WHO regions, a clear gap exists between the numbers of notified cases and the estimated numbers of incident cases. However, this gap has narrowed in the last 15 years, especially in the Eastern Mediterranean and Western Pacific regions and to a lesser extent in the South-East Asia Region (**Figure 3.2**). Trends in the 22 HBCs are shown in **Figure 3.3**; for other countries these trends are illustrated in country profiles that are available online.[2]

The case detection rate (CDR)[3] for TB is an indicator that is included within the Millennium Development Goals (MDG) framework. 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 cases of TB that year. The CDR is expressed as a percentage; it gives an approximate[4] indication of the proportion of all incident TB cases that are actually diagnosed and reported to NTPs or national surveillance systems.

The best estimate of the CDR for all forms of TB globally in 2014 was 63% (range, 60–66%), up from 48–52% in 2005 and 36–40% in 1995 – the year in which the DOTS strategy began to be introduced and expanded (**Table 3.5**).[5] The best estimate of the global gap between notifications (of new episodes of TB i.e. new and relapse cases) and incident cases in 2014 was 3.6 million cases.

At regional level, the highest CDRs in 2014 were estimated to be in the Region of the Americas (best estimate 77%; range, 75–81%), the Western Pacific Region (best estimate 85%; range, 81–90%) and the European Region (best estimate 79%; range, 75–83%). The other regions had estimated CDRs of 43–75%, with best estimates in the range 48–62%.

[1] http://www.who.int/tb/people_and_communities/en/

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

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

[4] 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.

[5] The ranges represent 95% uncertainty intervals. There is uncertainty in estimates of the CDR because of uncertainty in estimates of TB incidence (the denominator).

TABLE 3.4

Community contributions to TB case notifications and treatment support for TB patients (all forms) in 41 countries,[a] 2013–2014. Data are for the basic management units (BMUs) that reported data.

COUNTRIES	CONTRIBUTION TO TB NOTIFICATIONS, 2014			CONTRIBUTION TO TREATMENT ADHERENCE SUPPORT, 2013		
	TOTAL TB NOTIFICATIONS (ALL FORMS) FROM COMMUNITY REFERRALS IN 2014		GEOGRAPHIC COVERAGE OF DATA REPORTING BY BMUs	TB PATIENTS (ALL FORMS) WHO RECEIVED TREATMENT ADHERENCE SUPPORT IN THE COMMUNITY IN 2013		GEOGRAPHIC COVERAGE OF DATA REPORTING BY BMUs
	NUMBER	% OF BMU NOTIFICATIONS		NUMBER	% OF ALL TB PATIENTS	
Afghanistan	1 088	7	661/722	1 089	13	336/722
Bangladesh	79 477	61	478/880		Not available	
Botswana		Not available		5 316	63	27/27
Bulgaria	229	15	22/22		Not available	
Burkina Faso	299	5	86/86	1 569	39	30/86
Burundi	796	11	17/17	1 335	18	17/17
Cambodia	14 115	73	43/93		Not available	
Côte d'Ivoire	8 165	36	151/184	7 785	29	134/184
DR Congo	12 649	57	95/516	7 202	49	95/516
Eritrea	102	4	69/69		Not available	
Ethiopia	14 399	38	364/957	11 314	22	760/957
Georgia	28	82	3/77		Not available	
Ghana	326	16	49/216	11 392	73	216/216
Guinea[b]	1 307	11	55/465	1 307	12	55/465
India	19 713	3	1 200/3 394	726 069	52	3 394/3 394
Indonesia	8 707	11	47/511	4 218	14	27/511
Kenya	3 535	9	798/3 320	78 813	100	3 046/3 320
Lesotho		Not available		9 649	90	17/34
Madagascar	5 914	52	72/215	382	5	72/215
Malaysia		Not available		84	2	15/146
Mongolia	351	8	32/32	731	16	32/32
Mozambique[b]	2 868	5	323/323	5 656	11	251/323
Myanmar	1 304	2	171/354	1 605	5	165/354
Namibia		Not available		6 463	63	31/34
Nepal	457	3	75/75	363	19	5/75
Nigeria		Not available		55 995	56	774/774
Pakistan		Not available		231 557	100	1 137/1 306
Republic of Moldova		Not available		3 308	78	57/57
Romania		Not available		320	2	177/177
Rwanda	1 188	20	515/515	2 889	48	515/515
Sao Tome and Principe	109	69	1/1		Not available	
Senegal	1 011	10	76/76	891	7	76/76
Sierra Leone	3 065	40	170/170	187	2	170/170
South Africa[c]	928	0.3	Not available		Not available	
Sri Lanka	85	2	26/26	1 637	18	26/26
Tajikistan	883	14	109/109	6 495	100	109/109
Timor-Leste		Not available		244	7	18/18
Uganda		Not available		26 044	55	117/117
UR Tanzania	10 416	18	168/168	49 412	75	168/168
Uzbekistan[b]	7 191	64	4 278/4 516	20 812	96	4 433/4 516
Viet Nam		Not available		100 721	99	815/815

[a] Twenty-eight countries did not submit data for either indicator: Algeria, Angola, Armenia, Azerbaijan, Benin, Bhutan, Cameroon, Cape Verde, Central African Republic, Chad, Congo, Gabon, Gambia, Guinea-Bissau, Kiribati, Liberia, Malawi, Mali, Mauritania, Niger, Philippines, Sudan, Swaziland, Thailand, Togo, Turkey, Zambia and Zimbabwe.

[b] The proportion of patients receiving treatment support in the community was calculated using the total cohort (all BMUs) of TB patients starting treatment in 2013 as the denominator. Data disaggregated by BMU were not reported.

[c] The proportion of notifications that came from community referrals was calculated using the total cohort (all BMUs) of TB patients notified in 2014 as the denominator. Data disaggregated by BMU were not reported.

TABLE 3.5

Estimates of the case detection rate for new and relapse cases %, 1995–2014.[a] Best estimates are followed by the lower and upper bounds of the 95% uncertainty interval

	1995		2000		2005		2010		2014	
Afghanistan	–	–	19	18–21	47	44–51	53	48–59	53	47–60
Bangladesh	21	20–23	26	24–28	38	36–41	45	41–50	53	47–60
Brazil	79	73–85	73	67–80	84	79–90	82	78–86	82	78–86
Cambodia	24	22–26	27	25–30	52	49–56	65	59–70	72	66–80
China	33	31–35	33	31–35	75	71–79	87	81–94	88	82–95
DR Congo	31	29–33	39	36–42	53	50–56	53	49–57	48	43–52
Ethiopia	11	9.3–13	33	27–40	48	41–57	66	55–80	60	49–73
India	59	56–61	49	47–51	48	47–50	59	55–62	74	70–80
Indonesia	4	2.9–5.8	8.9	6.5–13	26	19–37	30	22–44	32	23–46
Kenya	62	60–64	72	70–74	81	79–82	82	80–84	80	78–82
Mozambique	23	18–32	23	17–31	30	25–36	33	27–40	39	31–49
Myanmar	10	9.3–11	16	14–17	53	50–56	66	61–72	70	64–78
Nigeria	4.3	3.4–5.7	6.5	4.9–9.1	13	11–18	16	11–24	15	10–26
Pakistan	3.9	3.3–4.6	2.9	2.4–3.6	34	29–40	56	45–73	62	48–83
Philippines	42	39–46	42	38–46	47	44–51	58	52–65	85	76–97
Russian Federation	60	56–64	75	70–80	65	62–69	84	77–92	85	77–94
South Africa	59	53–67	58	51–65	60	53–68	73	65–82	68	61–77
Thailand	41	26–78	23	14–43	39	24–74	56	34–100	59	36–110
Uganda	23	19–27	30	25–37	48	43–55	62	55–70	72	64–83
UR Tanzania	28	16–62	32	20–61	31	20–54	31	20–58	36	21–77
Viet Nam	34	30–38	57	50–65	64	58–71	71	61–84	77	65–94
Zimbabwe	61	44–92	67	54–86	66	54–83	76	59–100	70	51–100
High-burden countries	**34**	**33–36**	**35**	**33–36**	**48**	**46–50**	**57**	**54–60**	**62**	**58–66**
AFR	28	26–30	34	32–37	44	41–47	50	46–55	48	43–54
AMR	69	66–72	71	68–74	76	74–79	76	73–79	77	75–81
EMR	22	19–24	23	20–27	44	39–50	58	50–69	61	51–75
EUR	58	57–60	65	63–67	69	67–72	80	76–84	79	75–83
SEAR	38	35–42	35	32–39	43	39–46	52	47–57	62	56–68
WPR	36	35–38	38	36–40	69	66–71	79	75–83	85	81–90
Global	**37**	**36–39**	**38**	**36–40**	**50**	**48–52**	**58**	**55–61**	**63**	**60–66**

– 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. The lower and upper bounds are defined as the 2.5th and 97.5th centiles of outcome distributions produced in simulations.

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 2014 (>80%) were estimated to be in Brazil, China, the Philippines and the Russian Federation. The lowest rates, with best estimates of 50% or less, were in the Democratic Republic of the Congo, Indonesia, Mozambique, Nigeria and the United Republic of Tanzania.

There are two major reasons for a gap between notifications and estimated incidence. The first is underreporting of diagnosed TB cases, for example because private sector providers fail to notify cases. This is one of the reasons for a relatively low CDR in Indonesia (see also **Box 2.4**, **Chapter 2**). The second is under-diagnosis of people with TB for reasons such as poor access to health care and failure to recognize TB signs and symptoms and test for TB when people do present to health care facilities. A good example is Nigeria, where the 2012 national TB prevalence survey suggested that this is a major reason for the low CDR.[1] It should also be acknowledged that the estimates of TB incidence are uncertain, and the gap between the estimated number of incident cases and

[1] World Health Organization. *Global tuberculosis report* 2014. Geneva: World Health Organization; 2014 (WHO/HTM/TB/2014.08). See pp10–11.

Box 3.5 Definitions of treatment outcomes for new and relapse cases recommended for use since March 2013 and that were used in the 2014 and 2015 rounds of global TB data collection[a]

Cured A pulmonary TB patient with bacteriologically-confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.

Completed treatment A TB patient who completed treatment without evidence of failure but with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.

Died A TB patient who died from any cause during treatment.

Failed A TB patient whose sputum smear or culture is positive at month five or later during treatment.

Lost to follow-up A TB patient who did not start treatment or whose treatment was interrupted for two consecutive months or more.

Not evaluated A TB patient for whom no treatment outcome is assigned. This includes cases 'transferred out' to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.

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 cases registered in the calendar year 2012). This group forms the denominator for calculating treatment outcomes. The sum of the patients included in the above treatment outcome categories should equal the number of cases registered. It should be highlighted that in the new definitions recommended since March 2013 **any patient found to have drug-resistant TB and placed on second-line treatment should be removed from the drug-susceptible TB outcome cohort**. This means that management of the standard TB register and of the second-line TB treatment register needs to be coordinated to ensure proper accounting of the outcomes of treatment (see also **Chapter 4**).

[a] *Definitions and reporting framework for tuberculosis – 2013 revision*. Geneva, World Health Organization, 2013 (WHO/HTM/TB/2013.2). Available at www.who.int/tb/publications/definitions.

the number of notifications could be under- or over-stated.

Intensified efforts are needed to ensure that all cases are detected, notified to national surveillance systems, and treated according to international standards. Progress towards the goal of universal health coverage, implementation of PPM initiatives such as those described in **section 3.2**, and ensuring that there is an effective regulatory framework that includes mandatory notification of cases are all essential to reduce underreporting and under-diagnosis, and constitute part of the End TB Strategy (**Chapter 1**). The current status of progress towards universal health coverage from a financing perspective is discussed further in **Chapter 7**.

3.5 Treatment outcomes

The definitions of TB treatment outcomes for new and relapse cases of TB that are recommended by WHO as part of an updated recording and reporting framework issued in March 2013, and used in the 2015 round of global TB data collection, are shown in **Box 3.5**.[1] Most of these cases (97% globally) have drug-susceptible TB, but in some parts of the world, especially countries of the former Soviet Union, more than 20% of new and relapse cases have MDR-TB (Chapter 4). Universal access to drug susceptibility testing, as called for in the End TB Strategy (**Chapter 1**), is required to ensure that all people with TB receive appropriate treatment.

Data on treatment outcomes for new and relapse cases of TB are shown for the world, the six WHO regions and the 22 HBCs in **Table 3.6** and **Figure 3.5**. Globally, the treatment success rate for the 5.4 million new and relapse cases that were treated in the 2013 cohort was 86%. It is impressive that as the size of the global treatment cohort grew from 1.0 million in 1995 to 4.2 million in 2005 and 5.4 million in 2013, the treatment success rate first improved and has subsequently been sustained at a high level.

Among the six WHO regions, the highest treatment success rates were in the Western Pacific Region, the South-East Asia Region and the Eastern Mediterranean Region. The treatment success rate was 79% in the African Region. The lowest treatment success rates were in the Region of the Americas and the European Region (both 75%). In the Region of the Americas, treatment outcomes would probably be considerably improved if the number of patients in the "not evaluated" category could be reduced. In the European Region, rates of treatment failure, death and loss to follow-up, as well as the proportion of patients without a documented treatment outcome, all need to be reduced. One explanation for the poor outcomes in this region may be that the proportion of new and relapse cases that have drug-resistant TB is high (**Chapter 4**). All cases need to be tested for susceptibility to first-line drugs, and those with rifampicin-resistant and MDR-TB enrolled on second-line rather than first-line regimens.

Most of the 22 HBCs have reached or exceeded a treatment success rate of 85%. Improvements are still needed in

[1] Treatment outcomes for people diagnosed with rifampicin-resistant and MDR-TB are presented in **Chapter 4**.

TABLE 3.6

Treatment success for all new and relapse[a] cases (%) and cohort size (thousands), 1995–2013

a. Treatment success (%)

	1995	2000	2005	2010	2011	2012	2013
Afghanistan	–	85	90	86	88	88	88
Bangladesh	71	81	90	91	91	92	93
Brazil	17	71	72	72	73	72	72
Cambodia	91	91	91	89	94	94	93
China	93	93	92	95	95	95	95
DR Congo	74	78	85	89	87	88	87
Ethiopia	61	80	78	77	89	91	89
India	25	34	87	89	89	88	88
Indonesia	91	87	89	89	88	86	88
Kenya	75	80	81	86	87	86	86
Mozambique[b]	39	75	79	85	–	87	88
Myanmar	67	82	83	88	88	89	87
Nigeria	49	79	75	81	85	86	86
Pakistan	70	74	82	90	92	91	93
Philippines	60	88	89	90	87	88	90
Russian Federation	65	68	67	66	65	69	68
South Africa	58	63	69	53	77	77	78
Thailand	64	69	71	83	82	81	81
Uganda	44	63	73	68	73	77	75
UR Tanzania	73	78	83	89	88	90	91
Viet Nam	89	92	92	92	93	91	89
Zimbabwe	53	69	66	76	80	81	80
High-burden countries	**53**	**67**	**85**	**86**	**88**	**88**	**88**
AFR	60	71	74	73	79	81	79
AMR	50	76	75	73	75	75	75
EMR	79	81	82	88	89	87	91
EUR	67	75	77	74	73	76	75
SEAR	33	50	87	89	89	88	88
WPR	80	90	90	92	93	92	92
Global	**57**	**69**	**84**	**84**	**87**	**86**	**86**

b. Cohort size (thousands)

	1995	2000	2005	2010	2011	2012	2013
Afghanistan		3.1	10	26	26	29	31
Bangladesh	11	38	119	150	148	165	184
Brazil	46	34	78	78	71	75	77
Cambodia	4.4	15	34	40	37	38	36
China	131	214	788	877	856	885	842
DR Congo	16	36	65	109	92	105	112
Ethiopia	5.1	30	39	152	91	45	44
India	265	349	1 071	1 229	1 209	1 288	1 244
Indonesia	3	52	244	296	314	329	326
Kenya	6.5	28	98	90	82	98	81
Mozambique	11	13	18	20		21	23
Myanmar	7.9	17	73	127	135	137	136
Nigeria	9.5	16	35	78	84	90	92
Pakistan	0.8	4.1	117	256	255	111	289
Philippines	90	50	81	162	190	214	216
Russian Federation	0.05	3.6	74	94	89	90	83
South Africa	28	86	259	338	292	328	321
Thailand	20	23	49	48	49	58	66
Uganda	15	14	21	40	43	26	45
UR Tanzania	20	24	59	59	59	62	64
Viet Nam	38	53	55	88	89	104	102
Zimbabwe	9.7	14	43	46	40	38	35
High-burden countries	**739**	**1 119**	**3 430**	**4 403**	**4 252**	**4 337**	**4 475**
AFR	178	365	886	1 220	1 103	1 142	1 165
AMR	129	111	187	200	191	202	201
EMR	46	64	226	386	391	242	432
EUR	34	42	221	255	244	251	241
SEAR	318	512	1 639	1 980	1 986	2 114	2 101
WPR	296	360	1 030	1 240	1 233	1 344	1 298
Global	**1 001**	**1 453**	**4 188**	**5 280**	**5 146**	**5 295**	**5 437**

Blank cells indicate data not reported.

– indicates values that cannot be calculated.

[a] Cohorts before 2012 include new cases only. For the 2012 and 2013 cohorts, 14 and 16 high-burden countries respectively included both new and relapse cases, as recommended in the revised recording and reporting framework issued by WHO in 2013 (see Definitions and reporting framework for tuberculosis 2013 revision. Geneva, World Health Organization, 2013 (WHO/HTM/TB/2013.2). Available at www.who.int/tb/publications/definitions.

[b] Treatment outcomes in Mozambique are for new pulmonary bacteriologically-confirmed cases only. Introduction of monitoring of outcomes for other cases was started in 2015.

Box 3.6 Outcomes of TB treatment by HIV status[a]

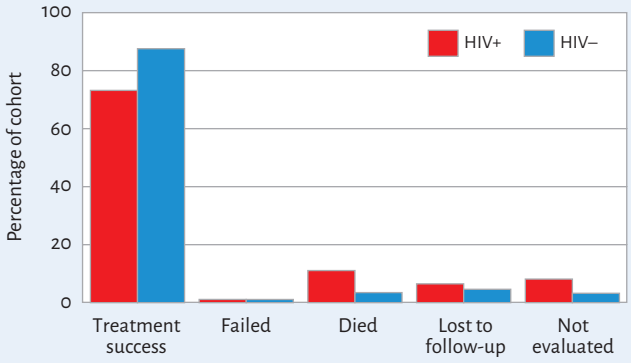
In the 2015 round of global TB data collection, 140 countries reported treatment outcomes for the 2013 patient cohort that were disaggregated by HIV status. This was an increase from 133 countries that reported such data for 2012. These 140 countries included 22 of the 41 high TB/HIV burden countries (listed in **Table 6.1** of **Chapter 6**) and collectively accounted for 71% (n= 397 000) of the HIV-positive TB patients reported by NTPs in 2013, similar to the level of 2012 (70%).

Overall, the treatment success rate in 2013 was worse for HIV-positive TB patients (73%) compared with HIV-negative TB patients (88%), similar to levels in 2012 (**Figure B3.6**). The difference was smaller in the African region (75% and 84%, respectively). There were large differences in the European and Eastern Mediterranean Regions, where the treatment success rates among HIV-positive TB patients were only 47% and 60% respectively, compared with 80% and 91% among HIV-negative patients. The treatment success rate in the European Region were much worse than in 2012 (47% versus 57%), mainly reflecting data for Ukraine. This country accounted for 80% of the HIV-positive TB patients for whom treatment outcomes in 2013 were reported, but did not report data in 2012. More encouragingly, the treatment success rate for HIV-positive TB patients in the Western Pacific Region was substantially better in 2013 compared with 2012 (73% vs 57%).

Globally, the proportion of TB patients who died during treatment remained more than three times higher among HIV-positive TB patients (11% versus 3.5%). In the African Region, HIV-positive TB patients were almost twice as likely to die compared with HIV-negative TB patients (9.8% versus 5.1%). Differentials were larger in the European Region (21% versus 6.6%) and the Eastern Mediterranean Region (17% versus 1.8%). The proportion of patients categorized as lost to follow-up, who may also have died of TB, was also higher for those who were HIV-positive (6.5% versus 4.6%), similar to levels in 2012. The proportion of HIV-positive TB patients for whom the treatment outcome was not evaluated was relatively similar globally (8.1% compared with 7.6% of HIV-negative TB patients), although there was a noticeable drop in the Western Pacific Region (from 30% of patients in 2012 to 12% in 2013). This is the main explanation for the large improvement in the treatment success rate for HIV-positive TB patients in this region.

FIGURE B3.6

Outcomes of TB treatment by HIV status, 2013



[a] Countries with no treatment outcome data for HIV-positive TB patients were excluded from the analysis.

Brazil, the Russian Federation, South Africa, Thailand, Uganda and Zimbabwe.

Treatment outcomes in 2013 were worse among HIV-positive TB patients compared with HIV-negative TB patients (**Box 3.6**). Further efforts are needed to narrow this gap.

3.6 Detection and treatment of latent TB infection

Latent TB infection (LTBI) is defined as the presence of immune responses to *Mycobacterium tuberculosis* antigens without clinical evidence of active TB. Most people with LTBI have no signs or symptoms of TB disease and are not infectious. However, they are at risk of developing active TB disease and becoming infectious. The lifetime risk of TB disease for a person with documented LTBI is estimated at 5–15%, with the majority of cases occurring within the first five years after initial infection.[1]

The risk of LTBI reactivation can be reduced by preventive treatment. WHO has issued global recommendations on the treatment of LTBI for people living with HIV and for children aged less than 5 years old who are close contacts of a TB case.[2,3] Most recently, WHO has issued guidelines on the management of LTBI that are targeted at upper-middle and high-income countries with an estimated incidence rate of less than 100 per 100 000 population.[4] In these countries, systematic testing and treatment of LTBI is recommended for a wider range of risk groups: people living with HIV, adult as well as child contacts of pulmonary TB cases, patients with silicosis, patients initiating anti-tumour necrosis factor (TNF) treatment, patients on dialysis, and transplant patients (**Table 3.7**).

The management of LTBI is a critical component of the new post-2015 End TB Strategy (**Chapter 1**), and is one of the interventions that can help countries to achieve the ambi-

[1] Getahun H, Matteelli A, Chaisson RE, Raviglione M. Latent Mycobacterium tuberculosis infection. *New Engl J Med*. 2015;372(22):2127–35.

[2] World Health Organization. *Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings*. Geneva: World Health Organization; 2011.

[3] World Health Organization. *Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle income countries*. Geneva: World Health Organization; 2012.

[4] World Health Organization. *Guidelines on the management of latent tuberculosis infection*. Geneva: World Health Organization; 2015. Available at: http://www.who.int/tb/publications/ltbi_document_page/en/

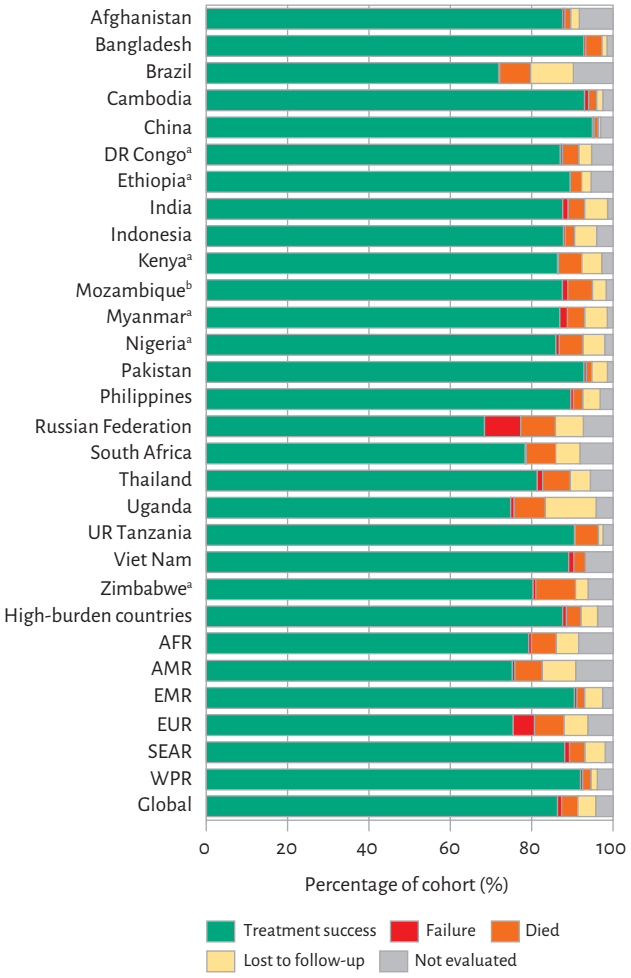
TABLE 3.7

WHO recommendations for the management of latent TB infection, by country group

COUNTRY GROUP	AT RISK POPULATIONS	TESTING ALGORITHM	TREATMENT OPTIONS
High-income and upper middle-income countries with an estimated TB incidence rate of less than 100 per 100 000 population	Strongly recommended for the following risk groups: 1) People living with HIV; 2) Adults and children who are household or close contacts of pulmonary TB cases; 3) Clinical indications – patients with silicosis; patients initiating anti-TNF treatment; patients on dialysis; transplant patients.	Exclude active TB using TB investigations. A positive IGRA or TST test result is required to diagnose LTBI.	6 months daily isoniazid 9 months daily isoniazid 3 months weekly rifapentine plus isoniazid 3 to 4 months daily isoniazid plus rifampicin 3 to 4 months daily rifampicin
Resource-limited and other middle-income countries with an estimated TB incidence rate of more than 100 per 100 000 population	1) People living with HIV; 2) Children under 5 years of age who are household contacts of a TB case.	Exclude active TB using TB investigations. An LTBI test is not required prior to LTBI treatment, but is encouraged for people living with HIV. IGRA should not replace TST.	6 months daily isoniazid

FIGURE 3.5

Treatment outcomes for new and relapse cases, 2013, globally, for the six WHO regions and 22 high-burden countries



[a] Treatment outcomes are for new cases only.
[b] Treatment outcomes in Mozambique are for new pulmonary bacteriologically-confirmed cases only. Introduction of monitoring of outcomes for other cases was started in 2015.

tious targets of a 90% reduction in the TB incidence rate and a 95% reduction in TB deaths by 2035, compared with 2015 levels. LTBI management can also contribute to TB elimination, especially in low TB incidence settings. In this context, country preparedness for the programmatic implementation of LTBI management (including addressing well-recognized challenges such as treatment adherence) is of growing priority and importance. A two-pronged approach is required, in which: (1) treatment for LTBI is provided in all countries to people living with HIV and children aged less than 5 years old who are household or close contacts of a TB case; and (2) treatment for LTBI is provided to additional risk groups in upper-middle and high-income countries with an incidence rate of less than 100 per 100 000 population.

Data on the treatment of LTBI among people living with HIV are already collected routinely, with data presented in this report (**Chapter 6**). In 2014 and 2015, WHO expanded data collection related to LTBI through discussions during regional meetings of NTP managers (or their equivalent) and other national stakeholders in four WHO regions, and by conducting a special survey of existing policy and practices in upper-middle income and high-income countries with an incidence rate of less than 100 per 100 000 population (shown in **Figure 3.6**). The main results are summarized below.

FIGURE 3.6

The 113 upper-middle-income and high-income countries with an estimated incidence rate of less than 100 per 100 000 population that are the primary audience for 2015 WHO guidelines on the management of latent TB infection

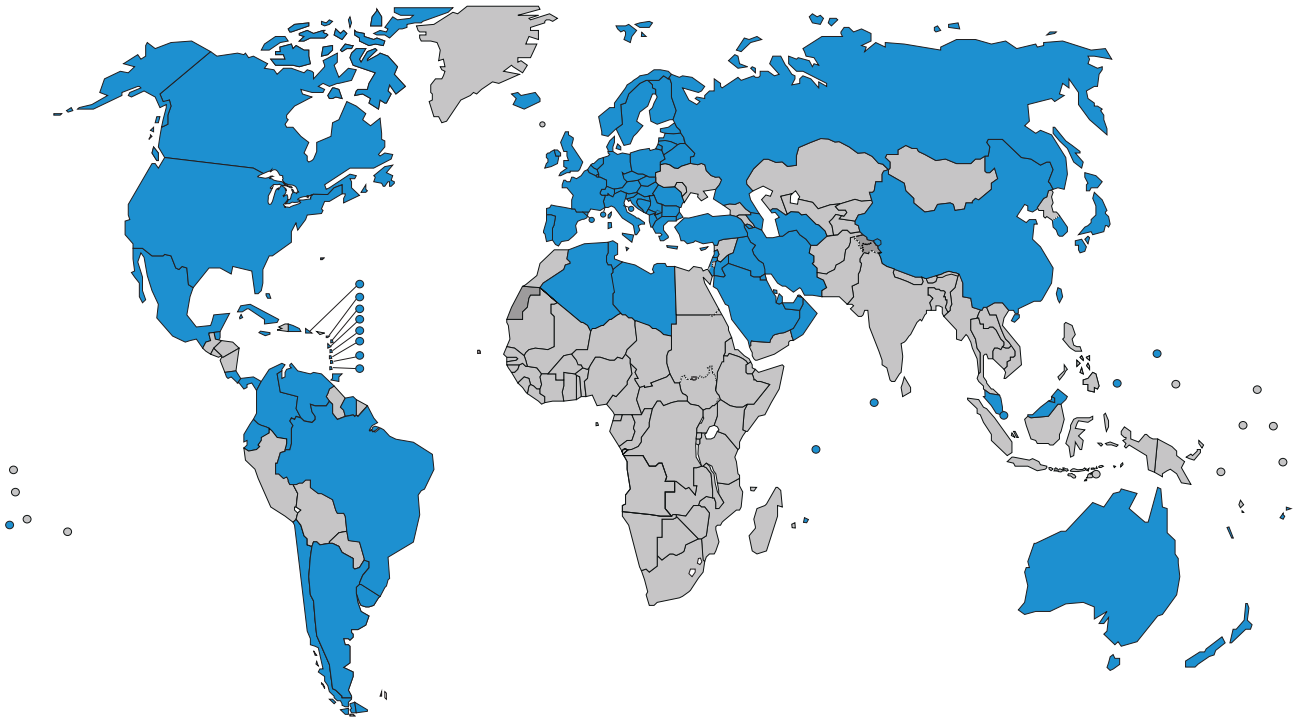
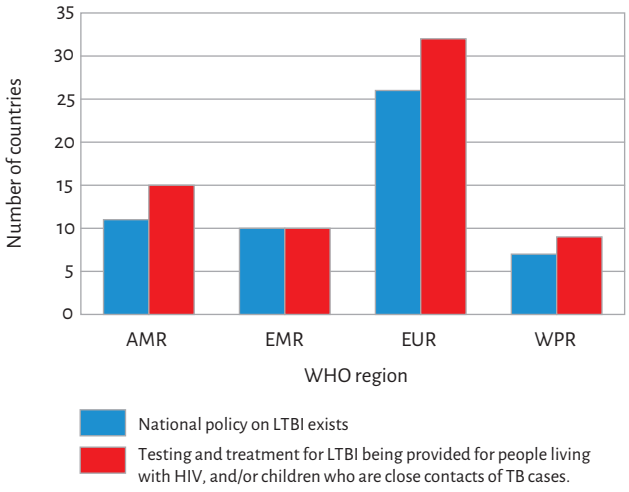


FIGURE 3.7

Reported policies and practices for latent TB infection (LTBI) in upper-middle-income and high-income countries with an estimated incidence rate of less than 100 per 100 000 population, four WHO regions[a]



[a] Two countries in the African Region (Algeria and Seychelles) were included in the survey, both of which reported that they had national policies on LTBI and were providing LTBI testing and treatment for people living with HIV and/or children who are close contacts of TB cases. One country in the South-East Asia Region (Maldives) was invited to participate in the survey but no response was received.

3.6.1 Results from a survey of LTBI policy and practice in upper-middle and high-income countries with an incidence rate of less than 100 per 100 000 population

Data were reported by 74 (69%) of the 108 countries invited to participate in the survey.[1] Among these countries, 76% (56/74) had a national policy on LTBI but a higher number (68/74, 92%) were providing testing for LTBI and preventive treatment for people living with HIV and/or children who were contacts of TB cases. This demonstrates a gap between policy and practice, which existed in three of four WHO regions (**Figure 3.7**). Systematic testing and treatment for LTBI in other risk groups for whom it is recommended was reported by only a few countries.

Testing for LTBI and exclusion of active TB

Of the 68 countries implementing systematic testing and treatment of LTBI in at least one at-risk population, 30 (44%) relied only on the tuberculin skin test (TST); the other 38 countries used both TST and interferon-gamma release assays (IGRAs) to test for LTBI.[2] TST was the only test used in most countries in the Eastern Mediterranean Region (70%, 7/10) and the Americas (73%, 11/15). Both tests were common-

[1] Five countries or territories with very small populations and numbers of TB cases were not included in the survey: Bermuda, Monaco, San Marino, Turks and Caicos Islands, US Virgin Islands.

[2] In the remaining six countries, specific at-risk populations were not identified.

ly used in the European Region (81%, 25/31). Shortages of TST were reported by 34 countries.

To exclude active TB prior to starting treatment for LTBI, most countries (62%, 42/68) used a combination of clinical screening for TB symptoms and a chest X-ray; this is consistent with WHO recommendations. A further 24 countries used these methods but supplemented them with additional diagnostic tests including smear microscopy, culture, and molecular testing. The remaining country used only clinical symptoms to exclude active TB.

Treatment regimens

In just over half of the 68 countries (35/68, 51%), the only option for LTBI treatment was a daily regimen of isoniazid for six or nine months. Rifamycin-containing regimens were used in other countries, but to date the shortest and simplest regimen (a weekly dose of rifapentine plus isoniazid for 12 weeks) had been adopted by only five of these countries.

Recording and reporting

Recording and reporting gaps were evident in many countries. Of the 40 countries providing testing and treatment for LTBI for people living with HIV, only 21 had a system for recording and reporting data. Of the 53 countries providing LTBI to children aged less than five who were household or close contacts of TB cases, 33 had a system for recording or reporting data. A monitoring and evaluation framework for LTBI is being developed by WHO and is expected to be available in 2016.

Key messages and conclusions

Overall, the survey shows that intensified efforts are needed to ensure that national LTBI policies are in place, as a foundation for programmatic management of LTBI using standardised approaches. Such policies should prioritize and target population groups with the highest risk of progression to active disease in whom the benefits of preventive treatment outweigh the potential risks. Efforts are needed to promote the use of short treatment regimens, such as weekly rifapentine plus isoniazid for 12 weeks, which would have potential benefits in terms of acceptability, adherence, and tolerability compared to the standard isoniazid regimen. Systems for routine collection and analysis of data are required in all countries and shortages in the supply of TST must be addressed.

CHAPTER 4

Drug-resistant TB

Key facts and messages

Drug-resistant TB poses a major threat to control of TB worldwide. By the end of 2014, data on anti-TB drug resistance were available for 153 countries, accounting for more than 95% of the world's population and estimated TB cases. Eighty of these countries have continuous surveillance systems, while the others rely on epidemiological surveys.

In 2014, the first-ever drug resistance surveys were completed in the Democratic People's Republic of Korea (North Hwanghae Province), Iraq, Papua New Guinea (four provinces), Turkmenistan and Ukraine; repeat surveys were completed in Iran, Lesotho, Morocco and Senegal. In mid-2015, drug resistance surveys were ongoing in 13 countries. These included the first nationwide surveys in the Democratic Republic of the Congo, India and Sudan.

Globally, an estimated 3.3% (95% CI: 2.2–4.4%) of new cases and 20% (95%CI: 14–27%) of previously treated cases have MDR-TB; these levels have remained virtually unchanged in recent years. In 2014, there were an estimated 480 000 (range: 360 000–600 000) new cases of MDR-TB worldwide, and approximately 190 000 (range: 120 000–260 000) deaths from MDR-TB. Among patients with pulmonary TB who were notified in 2014, an estimated 300 000 (range: 220 000–370 000) had MDR-TB. More than half of these patients were in India, China and the Russian Federation.

Extensively drug-resistant TB (XDR-TB) has been reported by 105 countries. On average, an estimated 9.7% (95% CI: 7.4–12%) of people with MDR-TB have XDR-TB.

There was major progress in coverage of drug susceptibility testing (DST) between 2013 and 2014. Worldwide, 12% of new bacteriologically-confirmed TB cases and 58% of previously treated TB patients were tested for drug resistance in 2014, up from 8.5% and 17% respectively in 2013 (representing proportional increases of 43% and 223%, respectively). Coverage was highest in the European Region (97% of new cases). In the South-East Asia and Western Pacific regions combined, two-thirds of previously treated cases underwent testing.

Globally in 2014, 123 000 patients with MDR -TB or rifampicin-resistant tuberculosis (RR-TB) were notified, of whom about 75% lived in the European Region, India, South Africa or China. This was equivalent to 41% of the 300 000 notified TB patients who were estimated to have MDR-TB in 2014. The number of notified MDR/RR-TB cases in 2014 was almost the same as in 2013. A major diagnostic gap has therefore persisted, and was worst in the Western Pacific Region where detected cases represented 19% of estimated cases. The figure for China was 11%.

People with MDR-TB or RR-TB are eligible for second-line treatment with MDR-TB regimens. A total of 111 000 people were started on MDR-TB treatment in 2014, an increase of 14% compared with 2013. The ratio of enrolled to notified MDR/RR-TB cases was 90% globally, and >90% in 15 high MDR-TB burden countries as well as the European Region and the Region of Americas. The ratio was <60% in 3 high MDR-TB burden countries: China (49%), Myanmar (44%) and Nigeria (53%).

The 2015 treatment success target of ≥75% for MDR-TB patients was reached by 43 of the 127 countries and territories that reported outcomes for the 2012 cohort. Only three high MDR-TB burden countries (Estonia, Ethiopia, and Myanmar) achieved a treatment success rate of ≥75%. Globally, only 50% of patients on MDR-TB treatment were successfully treated, largely due to high rates of mortality and loss to follow-up.

Despite progress in responding to the challenge of drug-resistant TB, serious detection and treatment gaps remain. Intensified efforts to close these gaps are urgently required.

Drug-resistant TB continues to threaten global TB control and remains a major public health concern in many countries. The first part of this chapter (**section 4.1**) summarizes the progress made in the global coverage of surveillance of anti-TB drug resistance, using the most recent data gathered from epidemiological surveys and continuous surveillance systems, with a focus on multidrug-resistant TB (MDR-TB)[1] and extensively drug-resistant TB (XDR-TB).[2] The second part of this chapter presents an assessment of global and national progress in diagnosing and treating rifampicin-resistant (RR-TB) and MDR-TB (**section 4.2**).

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 153 countries worldwide (79% of 194 WHO Member States).

[1] Defined as resistance to at least rifampicin and isoniazid, the two most powerful first-line anti-TB drugs.

[2] XDR-TB is defined as MDR-TB plus resistance to at least one fluoroquinolone and a second-line injectable.

This number includes 80 countries that have continuous surveillance systems based on routine diagnostic drug susceptibility testing (DST) of all TB patients, and 73 countries that rely on epidemiological surveys of representative samples of patients. Over the past two decades, all 22 high TB and/or 27 high MDR-TB burden countries (for a total of 36 countries) have either established a continuous surveillance system or conducted at least one survey to monitor drug resistance. Progress towards achieving global coverage of drug resistance surveillance data is shown in **Figure 4.1**.

Continuous surveillance for MDR-TB, based on routine DST of TB patients and systematic collection and analysis of data, is the most effective approach to monitor trends in drug resistance. The number of countries that can rely on data generated by continuous surveillance systems is increasing, following major efforts to scale up the availability of culture and DST services. In the past two years, an additional 10 countries established high quality continuous surveillance systems to monitor drug resistance in new and previously treated TB cases. Several countries of the eastern European and central Asian regions, where proportions of MDR-TB among TB cases are the highest, have established high quality surveillance systems to monitor drug resistance. These are Belarus, Estonia, Georgia, Kazakhstan, Latvia, Lithuania, the Russian Federation (at subnational level) and Tajikistan.

Surveys conducted every five years represent the most common approach to investigating the burden of drug resistance in resource-limited settings where routine DST is not accessible to all TB patients, due to lack of laboratory capacity or resources. In 2014, the first-ever drug resistance surveys were completed in the Democratic People's Republic of Korea (North Hwanghae Province), Iraq, Papua New Guinea (four provinces), Turkmenistan and Ukraine; repeat surveys were completed in Iran, Lesotho, Morocco and Senegal.

Of the 36 high TB and/or MDR-TB burden countries, 26 have generated drug resistance data through epidemiological surveys. Nearly half of these (14 countries) have conducted surveys recently, between 2010 and 2014. These are Afghanistan (Central region), Azerbaijan, Bangladesh, Kyrgyzstan, Myanmar, Nigeria, Pakistan, the Philippines, Tajikistan, Thailand, Uganda, Ukraine, Uzbekistan and Viet Nam. Three countries have not completed a survey since the mid-1990s: the Democratic Republic of the Congo, Kenya and Zimbabwe. However, a national survey is currently being implemented in all three of these countries.

Six high TB and/or MDR-TB burden countries (Afghanistan, Brazil, the Democratic Republic of the Congo, India, Indonesia and the Russian Federation) still rely on drug resistance surveillance data gathered from sub-national areas only. This situation will improve in the near future. In 2014, Brazil launched a large nationwide sentinel system to monitor drug resistance. The Democratic Republic of the Congo and India are currently conducting national surveys, and in Indonesia the first-ever nationwide drug resistance survey is

FIGURE 4.1

Global coverage of surveillance data on drug resistance, 1994–2015

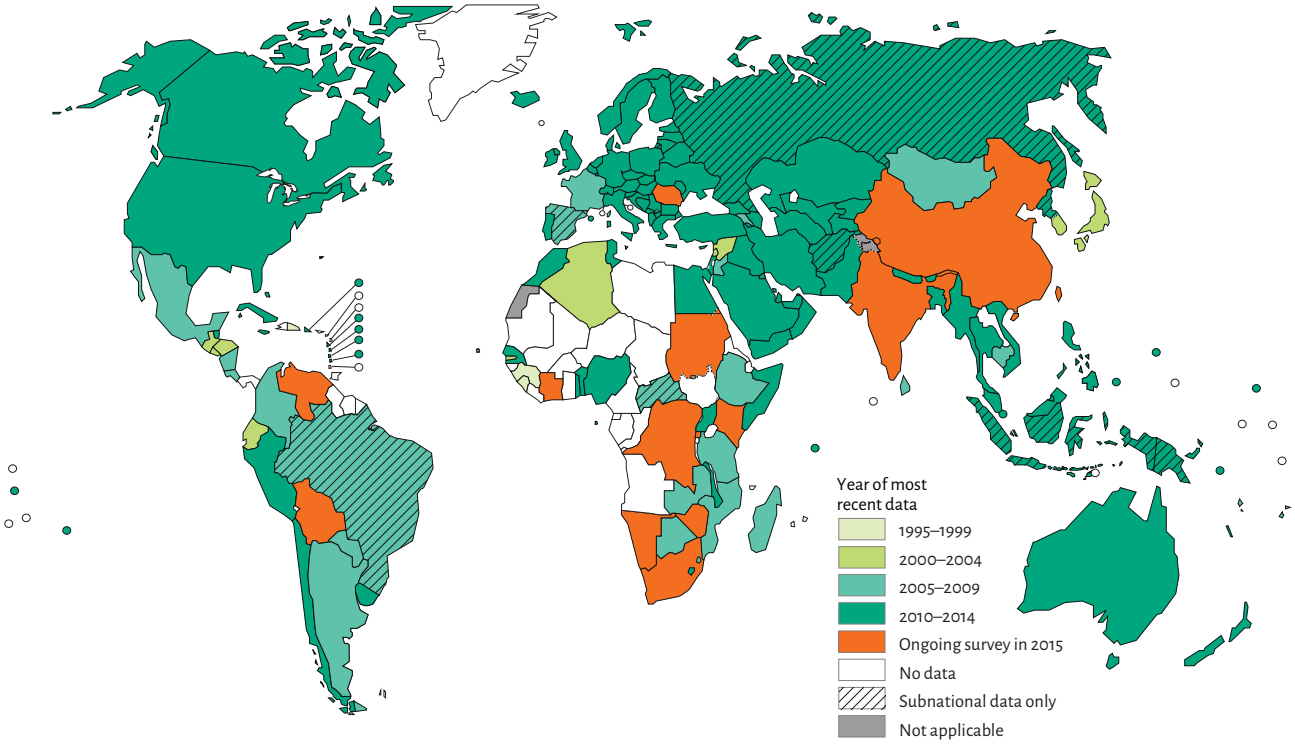


TABLE 4.1

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

	ESTIMATED % OF NEW TB CASES WITH MDR-TB[a]	95% CONFIDENCE INTERVAL	ESTIMATED % OF RE-TREATMENT TB CASES WITH MDR-TB[a]	95% CONFIDENCE INTERVAL
Armenia	9.4	7.0–12	43	38–49
Azerbaijan	13	10–16	28	22–37
Bangladesh	1.4	0.7–2.5	29	24–34
Belarus	34	32–36	69	66–72
Bulgaria	2.3	1.3–3.8	23	17–31
China	5.7	4.5–7.0	26	22–30
DR Congo[b]	2.2	0.3–4.1	11	6.2–16
Estonia	19	14–27	62	42–79
Ethiopia	1.6	0.9–2.8	12	5.6–21
Georgia	12	10–13	39	35-44
India	2.2	1.9–2.6	15	11–19
Indonesia	1.9	1.4–2.5	12	8.1–17
Kazakhstan	26	25–27	58	57–59
Kyrgyzstan	26	23–31	55	52–58
Latvia	8.2	5.8–11	30	21–40
Lithuania	14	12–16	49	43–55
Myanmar	5.0	3.1–6.8	27	15–39
Nigeria	2.9	2.1–4.0	14	10–19
Pakistan	3.7	2.5–5.0	18	13–23
Philippines	2.0	1.4–2.7	21	16–29
Republic of Moldova	24	21–26	62	59–65
Russian Federation	19	14–25	49	40–59
South Africa	1.8	1.4–2.3	6.7	5.4–8.2
Tajikistan	8.1	6.9–9.4	52	47–57
Ukraine	22	20–24	56	50–61
Uzbekistan	23	18–30	62	53–71
Viet Nam	4.0	2.5–5.4	23	17–30
High MDR-TB burden countries	**3.8**	**2.2–5.4**	**22**	**13–31**
AFR	2.1	0.5–3.7	11	6.7–16
AMR	2.4	1.3–3.5	11	6.5–16
EMR	3.2	2.3–4.1	18	12–25
EUR	15	10–20	48	43–53
SEAR	2.2	1.9–2.6	16	14–18
WPR	4.4	2.5–6.3	22	18–25
Global	**3.3**	**2.2–4.4**	**20**	**14–27**

[a] Best estimates are for the latest available year.
[b] The estimates for DR Congo are indirect estimates based on data from countries in the same epidemiological region.

scheduled for implementation in 2016. The remaining countries should consider conducting nationwide drug resistance surveys in the short term to better understand the burden of MDR-TB and to guide the planning of diagnostic, treatment and care services.

In mid-2015, drug resistance surveys were ongoing in 13 countries. These included the first-ever nationwide surveys in the Democratic Republic of the Congo, India and Sudan; and repeat surveys in Bolivia, China, Côte d'Ivoire, Kenya, Namibia, Romania, Rwanda, Venezuela, South Africa and Zimbabwe.

Central and Francophone Africa remain the parts of the world where drug resistance surveillance data are most lacking, largely as a result of weak laboratory infrastructure. These countries should consider conducting drug resistance surveys using Xpert MTB/RIF to at least obtain a nationally representative estimate of the proportion of TB patients with rifampicin resistance.

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

Globally in 2014, there were an estimated 3.3% (95% CI: 2.2–4.4%) of new cases and 20% (95%CI: 14–27%) of previously treated cases with MDR-TB (**Table 4.1**). These estimates are essentially unchanged from those published in recent global TB reports.

The proportions of new and previously treated TB cases with MDR-TB at the country level are shown in **Figure 4.2** and **Figure 4.3**, and for the 27 high MDR-TB burden countries also in Table 4.1. Eastern European and central Asian countries continue to have the highest levels of MDR-TB. Among new cases, the proportions with MDR-TB were highest in Belarus, Estonia, Kazakhstan, Kyrgyzstan, the Republic of Moldova, the Russian Federation, Ukraine and Uzbekistan. Among previously treated TB cases, the proportions with MDR-TB were highest in Belarus, Estonia, Kazakhstan, Kyrgyzstan, the Republic of Moldova, Tajikistan, Ukraine and Uzbekistan. In the Russian Federation, even though the average proportion of previously treated cases with MDR-TB does not exceed 50%, the proportion is well above 50% in several Federal Subjects.

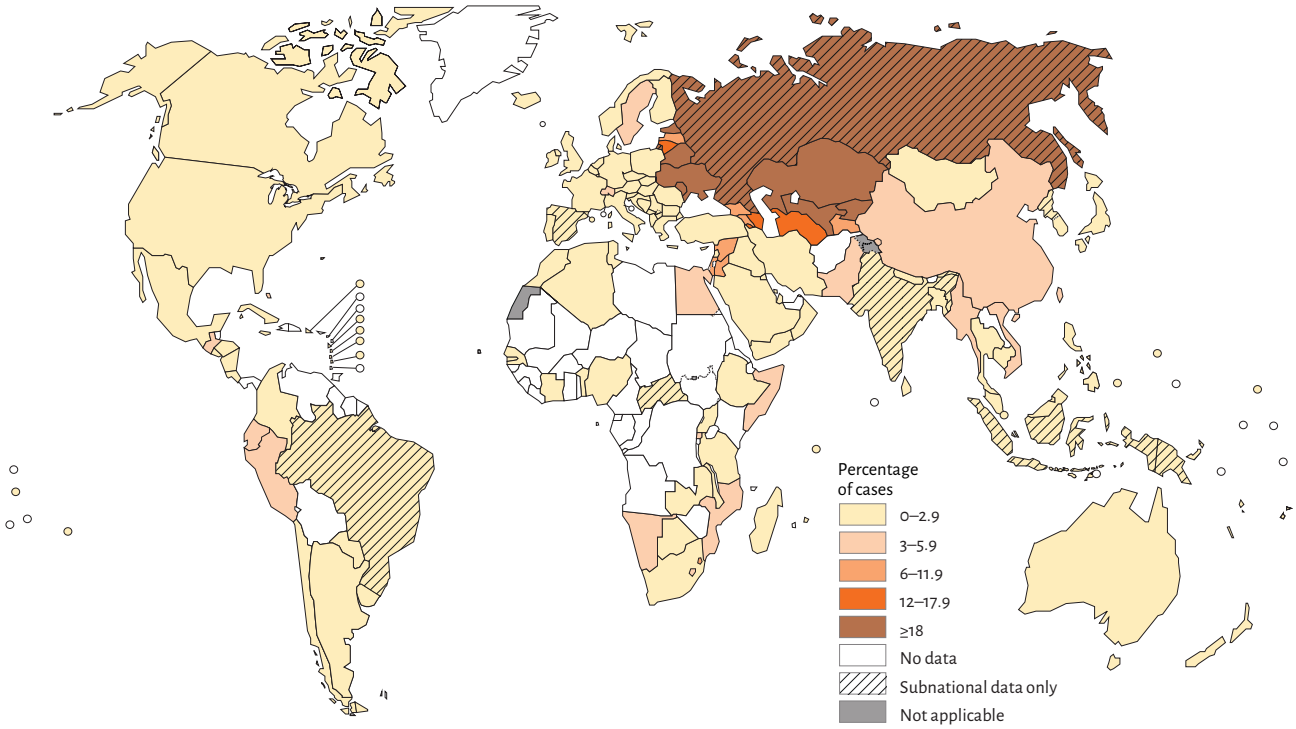
Levels of drug resistance among new cases remain low (<3%) in many parts of the world, including in almost all countries in the Region of the Americas; most African countries where drug resistance surveys have been conducted; most of the South-East Asia Region; most of western Europe; and several countries in the Western Pacific Region.

4.1.3 Estimated global incidence of MDR-TB and estimated number of MDR-TB cases among notified TB patients in 2014

Data compiled from surveys and continuous surveillance of drug resistance among TB patients can be used to estimate the total number of incident cases of MDR-TB worldwide and the total number of deaths from MDR-TB in 2014. Methods

FIGURE 4.2

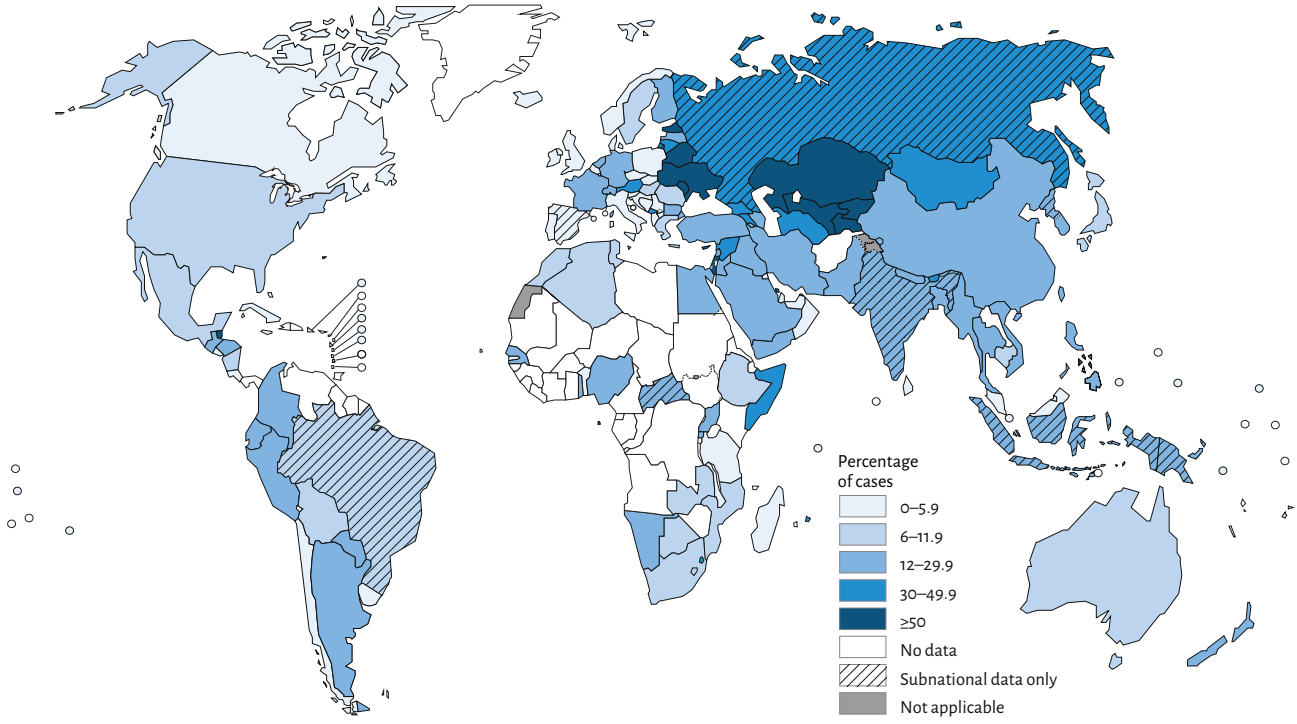
Percentage of new TB cases with MDR-TB[a]



[a] Figures are based on the most recent year for which data have been reported, which varies among countries. Data reported before the year 2000 are not shown.

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. Data reported before the year 2000 are not shown. In six countries or territories, the high percentages of previously treated cases with MDR-TB refer to only a small number (1–8) of notified TB cases. These are: Bahrain; Belize; Bonaire, Saint Eustatius and Saba; Cyprus; Israel; and Sao Tomé and Principe.

used to produce these estimates are described in detail in an online technical appendix (available at www.who.int/tb/data).

The number of incident cases includes cases among notified TB patients, cases among people diagnosed with TB that were not notified to national TB programmes (NTPs) in whom a diagnosis of MDR-TB was missed, and cases among people not diagnosed with TB at all. Globally in 2014, there were an estimated 480 000 (range: 360 000–600 000) incident cases of MDR-TB. This number is essentially unchanged from those published in recent global TB reports, despite an upward revision to global estimates of the burden of TB following results from the 2013/2014 national TB prevalence survey in Indonesia (which indicated that there are about 1 million rather than 0.5 million incident TB cases per year in this country; see **Chapter 2**). The explanation is that the upward revision to the estimated number of incident cases of MDR-TB in Indonesia (equivalent to approximately 12 000 extra cases) has been compensated for by reductions in the reported numbers of previously treated cases in several high MDR-TB burden countries (for example, India); this category of case (especially those not defined as relapse cases) has an important influence on estimates of the total number of incident cases of MDR-TB.[1] There were approximately 190 000 (range: 120 000–260 000) deaths from MDR-TB in 2014, comparable to estimates published in recent global TB reports.

Data compiled from surveys and continuous surveillance of drug resistance among TB patients also allow the production of global as well as country-specific estimates of the number of MDR-TB cases among notified TB patients with pulmonary TB. *These are the MDR-TB cases that could be detected if all notified patients were tested for drug resistance to rifampicin and isoniazid using WHO-recommended diagnostic tests.* Globally, in 2014 there were an estimated 300 000 (range: 220 000–370 000) MDR-TB cases among notified TB patients; this is unchanged from the estimate for 2013.[2] Of the 300 000 cases, 53% were among new cases and 47% were among previously treated cases. Of note, the increased number of TB cases notified in India between 2013 and 2014 (**Chapter 3**) and the higher proportions of MDR-TB detected in Ukraine in the latest survey of drug resistance were counter-balanced by lower numbers of new TB cases notified in China, the Russian Federation and Ukraine and lower numbers of previously treated TB cases notified in India and several Eastern European countries. Country-specific estimates are discussed in **section 4.2**.

Given the increasing use of molecular diagnostics that detect RR-TB (**Chapter 5**), their growing importance in detection of TB patients with RR-TB (**section 4.2**) and the fact that the recommended treatment for people with RR-TB is the same as for those with MDR-TB, monitoring and evaluation of the response to drug-resistant TB requires more attention to and emphasis on the underlying burden of RR-TB. The burden of rifampicin resistance is presented in **Box 4.1** and compared with that of MDR-TB.

4.1.4 Resistance to second-line drugs

XDR-TB, defined as MDR-TB plus resistance to at least one fluoroquinolone and a second-line injectable, had been reported by 105 countries globally by the end of 2014. A total of 83 countries and five territories reported representative data from continuous surveillance or surveys regarding the proportion of MDR-TB cases that had XDR-TB. Combining their data, the average proportion of MDR-TB cases with XDR-TB was 9.7% (95% CI: 7.4–12%), similar to estimates for previous years (9.0% in 2013 and 9.6% in 2012). Fourteen of these countries reported ≥10 XDR-TB cases in the most recent year for which data were available. Among those countries, the proportion of MDR-TB cases with XDR-TB was highest in Belarus (29% in 2014), Georgia (15% in 2014), Latvia (19% in 2014) and Lithuania (25% in 2013). Among the 36 high TB and/or MDR-TB burden countries, 23 have surveillance data on second-line drug resistance but only eight have established a national continuous surveillance system for second-line drug resistance among patients with MDR-TB. Increased efforts should be made to ensure that all patients diagnosed with MDR-TB undergo testing for susceptibility to fluoroquinolones and injectable agents, and that results are recorded and reported.

The proportion of MDR-TB cases with resistance to any fluoroquinolone for which testing was done, including ofloxacin, levofloxacin and moxifloxacin, was 21% (95% CI: 8.3–34%).

4.2 Management of drug-resistant TB

4.2.1 Coverage of drug susceptibility testing (DST)

Targets included in the *Global Plan to Stop TB 2011–2015* call for 20% of all new bacteriologically-confirmed TB cases (i.e. those considered to be at high risk for MDR-TB) as well as all previously treated cases to undergo DST to first-line TB drugs.[3] According to WHO recommendations, all patients with MDR-TB should undergo testing for susceptibility to fluoroquinolones and second-line injectable agents, to determine if they have XDR-TB.

There was major progress in DST coverage between 2013

[1] The number of incident cases of MDR-TB is estimated as the sum of the number of cases in three distinct groups. These are (i) new cases of TB; (ii) relapse cases and (iii) all previously treated cases of TB, excluding those in the relapse category. A review of methods used by WHO to estimate MDR-TB incidence and mortality is scheduled for 2016. In line with retaining current methods for the 2015 targets assessment, methods to estimate the burden of MDR-TB have not been changed this year (see also **Chapter 2**, particularly **Box 2.1** and **Box 2.2**). Further details about the methods used to estimate the burden of MDR-TB are provided in the **online technical appendix**, available at www.who.int/tb/data

[2] WHO. *Global tuberculosis report 2014*. Geneva: World Health Organization; 2014 (WHO/HTM/TB/2014.08).

[3] *The Global Plan to Stop TB 2011–2015: transforming the fight towards elimination of tuberculosis*. Geneva: World Health Organization; 2010 (WHO/HTM/STB/2010.2).

Box 4.1 Monitoring and evaluation of progress in the response to drug-resistant TB: the increasing importance of rifampicin-resistant TB (RR-TB)

Following the rollout of molecular tests for the detection of *M. tuberculosis* and rifampicin resistance (line probe assays and Xpert MTB/RIF) (**Chapter 5**), the Global TB Programme in WHO has collected and reported notifications of drug-resistant TB that combine rifampicin-resistant TB (RR-TB) and MDR-TB since 2013. All RR-TB and/or MDR-TB cases detected by either rapid molecular diagnostics or conventional DST are reported as cases of drug-resistant TB. Furthermore, in accordance with WHO recommendations to enrol all patients diagnosed with RR-TB on an MDR-TB drug regimen,[a] treatment enrolment and treatment outcomes of patients receiving MDR-TB treatment have been reported for all patients diagnosed with RR-TB, including those that did not have MDR-TB.

To date, estimates of the burden of drug-resistant TB at global, regional and country levels have focused on MDR-TB. The number of cases with MDR-TB will be slightly lower than the combined number of cases with MDR-TB or RR-TB (that is not MDR-TB). This means that when the burden of MDR-TB is used as the denominator for estimating detection and treatment coverage, the values for both indicators will be slightly overstated.

For these reasons, it is becoming increasingly important to estimate the combined burden of MDR-TB and RR-TB. In 2014, the global proportion of TB cases with MDR-TB, irrespective of treatment history, was 7.7% (95%CI: 4.6–10.8%), with an estimated number of MDR-TB cases among notified pulmonary TB patients of 300 000. In the same year, the global proportion of TB cases with RR-TB was 8.8% (95%CI: 6.2–11.3%), meaning that there were approximately 40 000 additional cases of RR-TB that were not MDR-TB. In future global TB reports, greater emphasis will be given to estimates of the combined burden of MDR-TB and RR-TB when assessing global, regional and national progress in the detection and treatment of drug-resistant TB.

[a] *Companion Handbook to the WHO Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis*. Geneva: World Health Organization; 2014 (WHO/HTM/TB/2014.11). http://apps.who.int/iris/bitstream/10665/130918/1/9789241548809_eng.pdf.

and 2014 (**Figure 4.4a**, **Figure 4.5**). Globally in 2014, 12% of the 2.7 million new bacteriologically-confirmed TB cases and 58% of the 0.7 million previously treated TB patients were tested for drug resistance in 2014, up from 8.9% and 17% respectively in 2013. This represents proportional increases in DST coverage of 43% and 223% among new and previously treated cases, respectively.[1]

Coverage was highest in the European Region, where 97% of new cases were tested in 2014 (**Table 4.2**). In the South-East Asia and Western Pacific regions combined, two-thirds of previously treated cases underwent testing, reflecting relatively better access to DST in these regions. Levels of testing remained below 5% among new cases in the South-East Asia and Eastern Mediterranean regions, while there was a substantial increase in testing coverage among new bacteriologically confirmed cases in the African Region (from 0.9% in 2013 to 6.4% in 2014). Testing coverage among previously treated cases also improved considerably in most regions, notably from 5.8% to 67% in the South-East Asia Region (driven largely by improved reporting from India) and from 9.6% to 33% in the African Region.

Among the 27 high MDR-TB burden countries – which account for >85% of estimated MDR-TB cases in the world – the proportion of TB patients who were tested for drug susceptibility in 2014 varied markedly (**Table 4.2**). In nine of the 12 European countries that reported data, testing was done for ≥95% of new cases; three of these countries reported universal coverage among previously treated cases. Among

[1] These figures are based on data reported by 160 (73%) countries and territories for new TB cases and by 157 (72%) countries and territories for previously treated cases.

FIGURE 4.4

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** circles show the actual situation in 2009–2014.

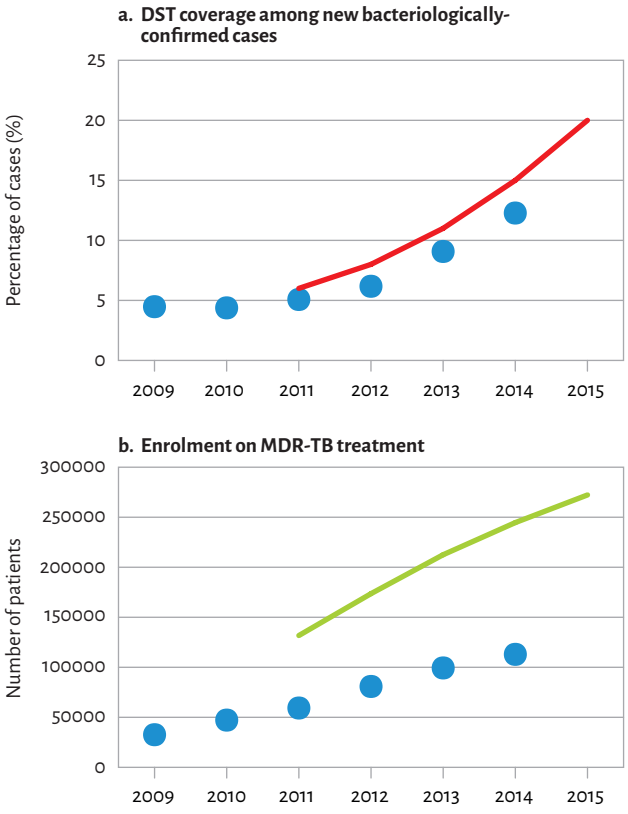
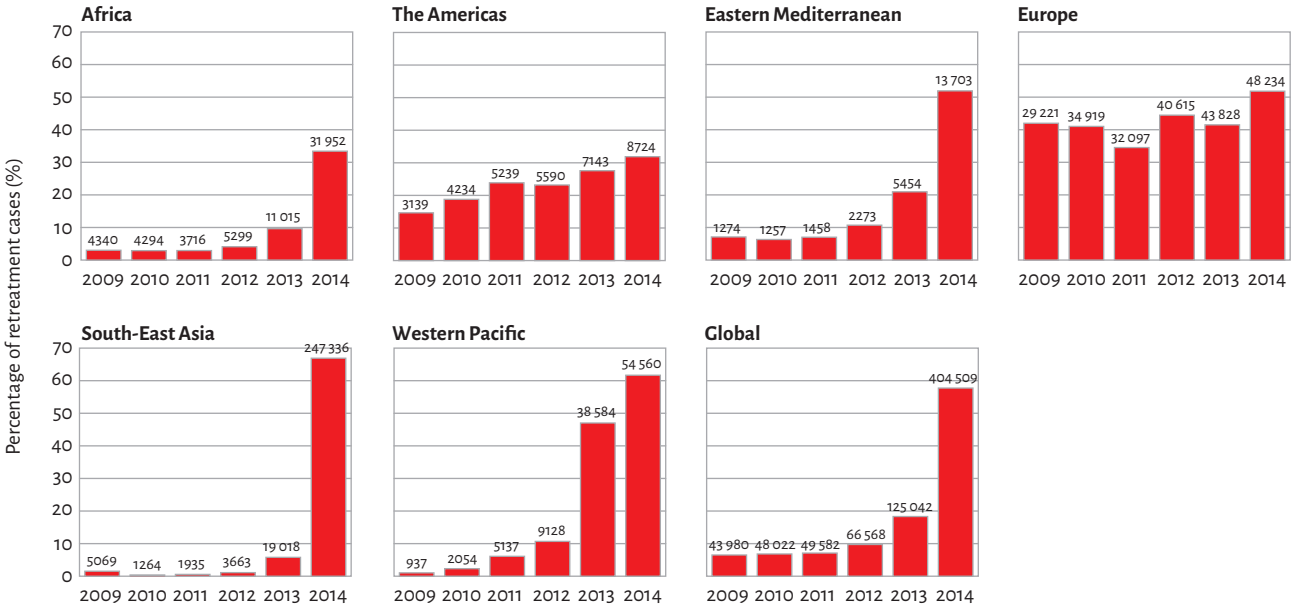


FIGURE 4.5

DST coverage in previously treated TB cases, globally and for WHO regions, 2009–2014.[a] Numbers of cases tested are shown for each bar.



[a] DST is for rifampicin only or for both rifampicin and isoniazid.

the high MDR-TB burden countries outside Europe, testing among new cases was highest in Myanmar (24%) and China (19%). Among previously treated cases, testing coverage was higher overall, and reached 96% in Viet Nam, 88% in Indonesia and 75% in the Democratic Republic of the Congo. In South Africa, the equivalent of 69% of all notified TB cases were tested, although DST data were not available separately for new and previously treated cases.

Among MDR-TB patients notified in 2014, only 24% had DST performed for both fluoroquinolones and second-line injectable drugs. Coverage was lowest in the European Region, likely as a result of incomplete reporting of DST results from laboratories.

Evidence of progress in DST coverage notwithstanding, diagnostic DST must be further expanded, especially given the call for universal DST in the post-2015 End TB Strategy (**Chapter 1**). This requires continued strengthening of laboratory capacity and wider uptake of new rapid diagnostics (see **Chapter 5**), as well as increased deployment of information and communication technologies (ICT) to improve the completeness of reporting from laboratory and treatment centres.

4.2.2 Notification of RR-TB and MDR-TB cases

Globally, 123 000 cases of MDR-TB or RR-TB, who are eligible for treatment with MDR-TB regimens, were notified to WHO in 2014. India, the Russian Federation and South Africa accounted for almost half of the total (**Table 4.3**). These 123 000 cases represented 41% of the estimated 300 000 (range, 220 000–370 000) MDR-TB cases among pulmonary TB patients that were notified in 2014 (**Figure 4.6**),[1] and 26% of the estimated 480 000 (range: 360 000–600 000) incident MDR-TB cases in the world in 2014.

The number of MDR/RR-TB cases reported for 2014 was nearly identical to the latest figure for 2013. In this context, it should be highlighted that the data available at the time of preparation of this report show that the number of MDR/RR-TB cases detected globally in 2013 was lower than previously published,[2] following a downward correction to numbers originally reported for India. Increases in the number of detected cases did however occur between 2013 and 2014 in India (23 162 to 25 748), China (4 183 to 5 807), the Russian Federation (13 521 to 15 585), and Myanmar (1 984 to 3 495). There were reductions between 2013 and 2014 in the Philippines, South Africa, Ukraine, Uzbekistan and several other countries (**Figure 4.7**). The reasons for the apparent stagnation in detection, given increasing DST coverage, are not clear and should be investigated as a matter of priority. A comparison of the number of Xpert MTB/RIF cartridges procured and the number of MDR/RR-TB cases detected in eight countries is provided in **Box 4.2**.

The number of notified MDR/RR-TB cases as a proportion of the estimated number of MDR-TB cases among pulmonary TB patients ranged from 19% in the Western Pacific Region to 80% in the African Region. In Kazakhstan, South

[1] When compared with the estimate of all MDR/RR-TB cases (not just the MDR-TB cases), this value would decrease to 36% (see also **Box 4.1**).

[2] The number published in the 2014 global TB report was 136 000 in 2013.

TABLE 4.2

DST coverage among TB and MDR-TB cases, globally and for 27 high MDR-TB burden countries and WHO regions, 2014

	NEW BACTERIOLOGICALLY CONFIRMED CASES		RETREATMENT CASES		CONFIRMED MDR–TB CASES	
	NUMBER WITH DST[a] RESULTS	% OF CASES WITH DST RESULT	NUMBER WITH DST[a] RESULTS	% OF CASES WITH DST RESULT	NUMBER WITH DST[b] RESULTS	% OF CASES WITH DST RESULT
Armenia	343	96	50	17	100	100
Azerbaijan	2 059	>100	3 901	>100	840	100
Bangladesh	12 573	12	4 959	51	182	19
Belarus	1 990	97	877	84	1 251	100
Bulgaria	639	80	101	45	36	97
China	45 664	19	17 210	54		–
DR Congo	545	0.7	6 135	75	41	19
Estonia	175	>100	29	71	47	96
Ethiopia	2 405	6	7 682	–	25	15
Georgia	1 700	95	634	61	357	93
India	12 795	1.7	214 209	69	3 572	25
Indonesia	1 058	0.5	8 445	88	229	35
Kazakhstan	9 597	>100	6 377	>100		–
Kyrgyzstan		–		–		–
Latvia	483	99	107	86	70	100
Lithuania	968	>100	294	100	232	86
Myanmar	10 295	24	15 166	>100		–
Nigeria		–		–		–
Pakistan	361	0	11 685	72	2 380	98
Philippines	4 415	4.7	20 196	67	868	80
Republic of Moldova	1 764	99	831	61	277	31
Russian Federation	31 250	84	13 925	28		–
South Africa		–		–	3 416	42
Tajikistan	2 432	100	800	64	371	100
Ukraine	13 833	97	9 707	69		–
Uzbekistan	11 956	>100	5 888	77	927	29
Viet Nam	2 756	5.5	8 511	96	246	78
High MDR–TB burden countries	**172 056**	**8.6**	**357 719**	**64**	**15 467**	**22**
AFR	40 940	6.4	31 952	33	3 898	35
AMR	30 531	24	8 724	32	606	20
EMR	8 404	4.6	13 703	52	2 465	78
EUR	108 569	97	48 234	52	5 294	14
SEAR	45 056	3.8	247 336	67	4 610	27
WPR	92 801	21	54 560	62	2 251	30
Global	**326 301**	**12**	**404 509**	**58**	**19 124**	**24**

Blank cells indicate data not reported.
– indicates values that cannot be calculated.
The percentages may exceed 100% as a result of the inclusion of extrapulmonary patients among cases tested or inadequate linkages between laboratory and clinical registers.
[a] DST is for rifampicin only or for both rifampicin and isoniazid.
[b] DST for a fluoroquinolone and a second-line injectable drug.

TABLE 4.3

Estimated MDR-TB cases in 2014, notified cases of rifampicin-resistant TB and MDR-TB and enrolments on MDR-TB treatment in 2014, and treatment outcome reporting for 2012 cohort, globally and for 27 high MDR-TB burden countries and WHO regions

	ESTIMATED MDR-TB AMONG NOTIFIED PULMONARY TB CASES, 2014		NOTIFIED MDR/RR-TB CASES, 2014		CASES ENROLLED ON MDR-TB TREATMENT, 2014		MDR-TB CASES REPORTED WITH TREATMENT OUTCOME DATA, 2012 COHORT	
	BEST ESTIMATE	UNCERTAINTY INTERVAL	NUMBER	NOTIFIED/ ESTIMATED MDR-TB (%)[a]	NUMBER	ENROLLED/ NOTIFIED MDR/RR–TB (%)	NUMBER	%[b]
Armenia	160	140–190	111	69	120	>100	115	>100
Azerbaijan	1 300	1 100–1 500	1 007	77	814	81	373	63
Bangladesh	4 800	3 400–6 200	994	21	945	95	505	98
Belarus	1 700	1 600–1 800	1 282	75	1 903	>100	2 502	>100
Bulgaria	72	53–91	44	61	29	66	44	90
China	52 000	42 000–61 000	5 807	11	2 846	49	1 906	63
DR Congo	2 800	980–4 500	442	16	436	99	134	>100
Estonia	62	48–75	50	81	48	96	50	81
Ethiopia	1 300	700–2 300	503	39	557	>100	271	95
Georgia	640	590–700	441	69	501	>100	623	>100
India	71 000	57 000–85 000	25 748	36	24 073	93	9 874	80
Indonesia	6 800	5 200–8 400	1 812	27	1 284	71	432	>100
Kazakhstan	4 900	4 800–5 000	5 877	>100	7 315	>100	7 213	95
Kyrgyzstan	2 000	1 800–2 100	1 267	63	1 157	91	775	81
Latvia	84	66–100	71	85	70	99	90	82
Lithuania	300	270–340	279	93	271	97	219	81
Myanmar	9 000	6 500–12 000	3 495	39	1 537	44	443	57
Nigeria	3 300	2 500–4 200	798	24	423	53	154	>100
Pakistan	12 000	8 800–15 000	3 243	27	2 662	82	858	54
Philippines	11 000	8 600–13 000	3 000	27	2 680	89	1 798	>100
Republic of Moldova	1 500	1 400–1 600	925	62	930	>100	856	96
Russian Federation	39 000	33 000–45 000	15 585	40	21 904	>100	16 021	>100
South Africa	6 200	5 100–7 300	18 734	>100	11 538	62	8 084	52
Tajikistan	880	810–950	902	>100	804	89	535	77
Ukraine	13 000	12 000–14 000	7 735	60	8 201	>100	5 556	80
Uzbekistan	7 000	6 100–7 900	4 955	71	3 665	74	1 491	86
Viet Nam	5 100	3 900–6 300	2 198	43	1 532	70	713	>100
High MDR-TB burden countries	**260 000**	**180 000–330 000**	**107 305**	**41**	**98 245**	**92**	**61 635**	**87**
AFR	32 000	15 000–49 000	25 531	80	17 352	68	10 246	56
AMR	7 000	4 700–9 300	3 745	54	3 568	95	2 866	97
EMR	15 000	12 000–19 000	4 348	29	3 423	79	1 271	57
EUR	72 000	62 000–81 000	42 293	59	49 074	>100	37 638	>100
SEAR	99 000	90 000–110 000	33 264	34	28 536	86	11 566	77
WPR	71 000	47 000–94 000	13 437	19	8 850	66	6 176	>100
Global	**300 000**	**220 000–370 000**	**122 618**	**41**	**110 803**	**90**	**69 763**	**86**

[a] Notified cases of MDR/RR-TB in 2014 as a percentage of the best estimate of MDR-TB cases among all cases of pulmonary TB in the same year. The percentage may exceed 100% if estimates of the number of MDR-TB are too conservative and if linkage between the clinical and laboratory registers is inadequate. Percentages shown are slightly higher than what would be expected if an estimate for all RR-TB cases (rather than MDR-TB) was used as a denominator (see also **Box 4.1**).

[b] The percentage of MDR-TB cases originally notified in 2012 with outcomes reported. The percentage may exceed 100% as a result of updated information about MDR-TB cases in 2012, inadequate linkages between notification systems for TB and MDR-TB, the inclusion of RR-TB cases in the numerator who were not confirmed MDR-TB, and the inclusion in the treatment cohort of cases of MDR-TB from a year prior to 2012.

Box 4.2 The roll-out of rapid TB diagnostics compared with changes in the number of cases of MDR/RR-TB notified by national TB programmes

Global progress in the detection of drug-resistant TB should be related to the roll-out of molecular diagnostics such as Xpert MTB/RIF and line probe assays (LPAs).[a] However, as use of these technologies expands, the number of tests required to detect one case may increase. This is because initial use of the test is likely to focus on groups with a higher risk of having MDR/RR-TB (such as previously treated TB patients), in line with policy recommendations,[b] and then broaden to cover people at lower risk for drug-resistance (such as patients being evaluated for TB). Variation among countries is also expected given differences in the prevalence of MDR/RR-TB (for example, the prevalence of MDR-TB is much higher in Ukraine compared with Bangladesh).

The relationship between annual procurements of Xpert MTB/RIF cartridges and notifications of MDR/RR-TB cases for 8 high MDR-TB burden countries is shown in **Figure B4.2.1**. These countries are among the major users of Xpert globally (each having procured 42 000–82 000 cartridges in 2014) and Xpert is often the leading diagnostic test for drug resistance that is in use. Although there was substantial variation in the number of MDR/RR-TB cases reported for every 100 Xpert cartridges procured, the ratio tended to decrease over time in all countries.

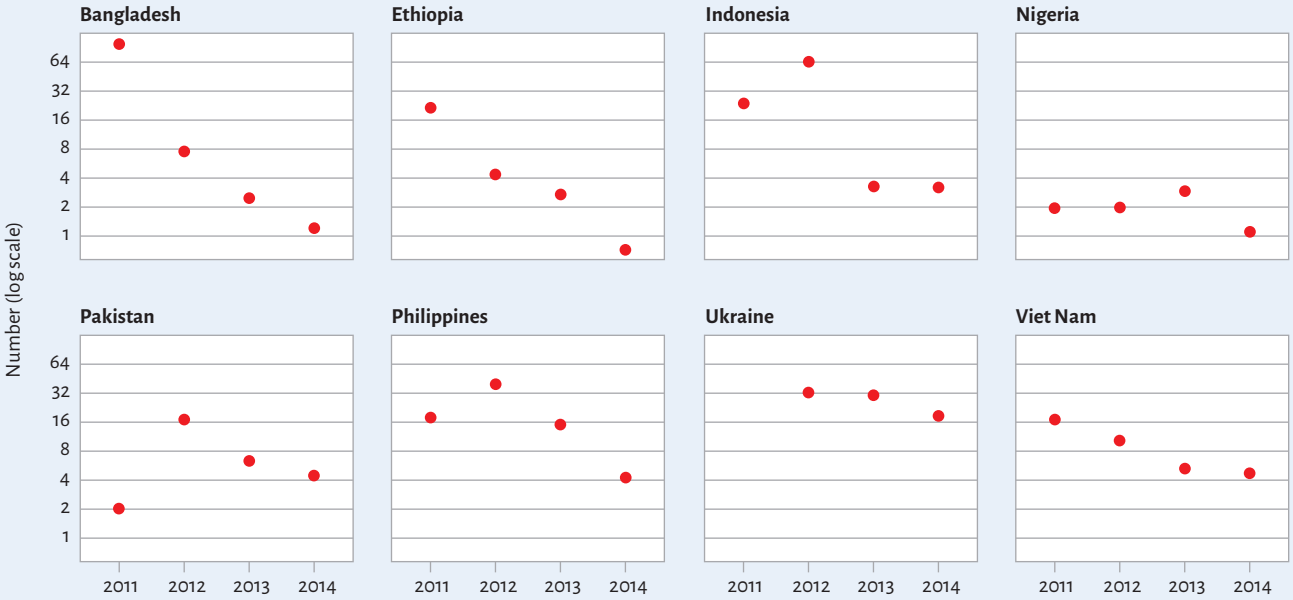
It was striking that sharp falls in the number of MDR/RR-TB cases detected for every 100 Xpert cartridges procured in Ethiopia and the Philippines between 2013 and 2014 occurred alongside an absolute reduction in the total number of reported MDR/RR-TB cases. The reasons for this are not well understood. Possible explanations include issues with reporting of cases, as opposed to actual levels of testing or laboratory results, and lag times between orders and actual use of tests.

[a] For further details about these technologies, see **Chapter 5**.

[b] *Xpert MTB/RIF implementation manual: technical and operational "how-to"; practical considerations*. Geneva: World Health Organization; 2014 (WHO/HTM/TB/2014.1). http://apps.who.int/iris/bitstream/10665/112469/1/9789241506700_eng.pdf.

FIGURE B4.2.1

The number of MDR/RR-TB cases reported for every 100 Xpert cartridges procured in selected high MDR-TB burden countries, 2011–2014



Africa, and Tajikistan the figure was above 100% (**Table 4.3**), indicating either repeated reporting of cases when information systems are based on laboratory results without linkage to patient registers, and/or that estimates of MDR-TB are too conservative (for example, because drug resistance surveillance data have become outdated).

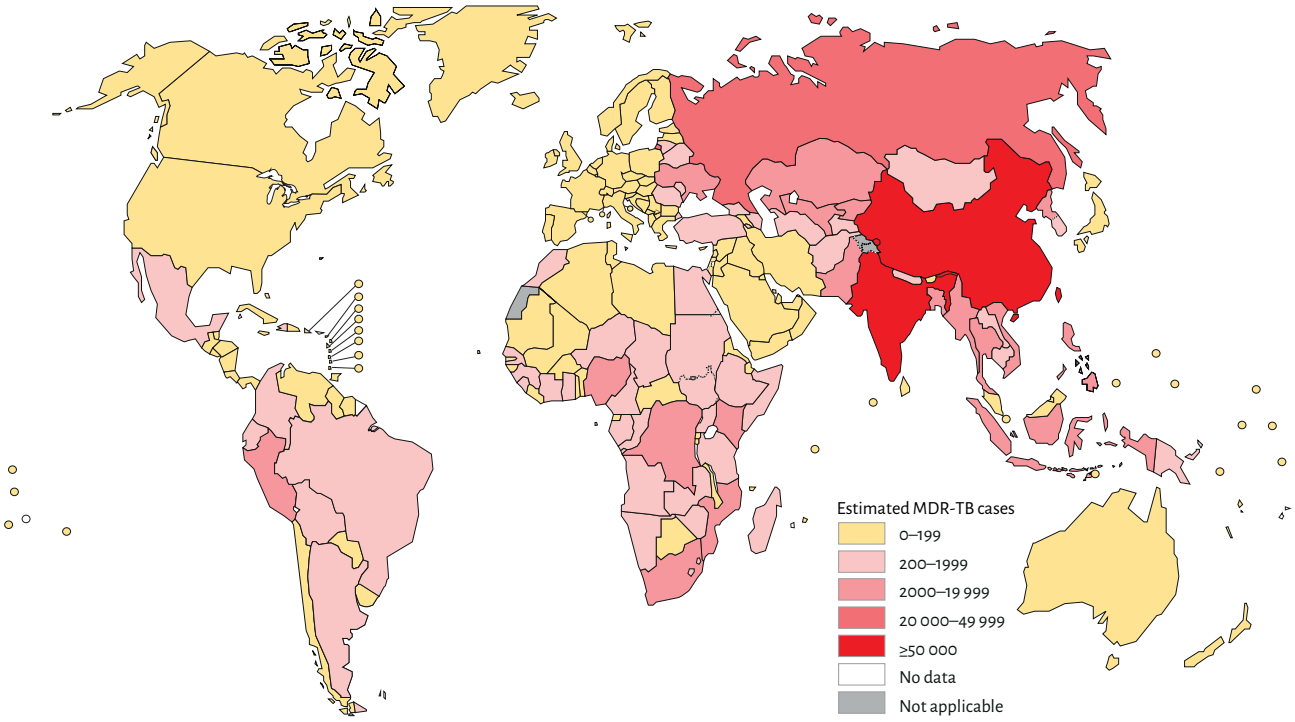
4.2.3 Enrolment of notified RR-TB and MDR-TB cases on treatment

The number of patients enrolled globally on MDR-TB treatment was 111 000 in 2014, up from 97 000 in 2013. There was a 13% increase in enrolments between 2013 and 2014 in the 27 high MDR-TB burden countries, with increments exceeding 1000 patients in India, Pakistan, the Russian Federation and Uzbekistan.

Globally, the number of patients starting second-line

FIGURE 4.6

Number of MDR–TB cases estimated to occur among notified pulmonary TB cases, 2014



MDR-TB treatment was 90% of those notified with MDR/RR-TB in 2014 (**Table 4.3**). The ratio was over 90% in 15 high MDR-TB burden countries, the European Region and the Region of Americas. The ratio was lowest in the Western Pacific (66%) and African (68%) regions.

In eight high MDR-TB burden countries, enrolments outstripped notifications of MDR/RR-TB (**Figure 4.7**). This may be caused by empirical treatment of TB patients considered at risk of having MDR-TB but for whom a laboratory-confirmed diagnosis was missing, incomplete reporting of laboratory data, or enrolment of "waiting lists" of people with MDR-TB who were detected before 2014. In contrast, the ratio of enrolled to diagnosed cases was under 60% in 3 high MDR-TB burden countries in 2014, and below 50% in China (49%) and Myanmar (44%). These low ratios show that progress in detection is far outstripping capacity to provide treatment but may also reflect weaknesses in data collection systems.

Overall, while the number of patients being enrolled on treatment for MDR-TB continues to increase, progress falls far short of Global Plan targets (**Figure 4.4b**, **Table 4.3**). Getting closer to the Global Plan targets requires intensification of efforts in many countries, but particularly China and the Russian Federation. These two countries rank second and third globally in terms of estimated numbers of cases, while levels of detection and treatment coverage remain relatively low. Continued support to NTPs through updated guidance, as well as direct technical assistance provided through the mechanisms of the Regional Green Light Committees and the Global Drug-resistant TB Initiative (www.stoptb.org/wg/mdrtb/), is expected to improve global detection and treatment of drug-resistant TB.

In 2014, 49 countries and territories reported treating people with XDR–TB (**Figure 4.8**). Globally, 4 044 patients with XDR-TB were enrolled on treatment (higher than the level of 3 284 in 2013). Most of the cases in 2014 were notified from India (1 262, up from 392 in 2013), Ukraine (657), South Africa (562), Belarus (431), and Kazakhstan (318).

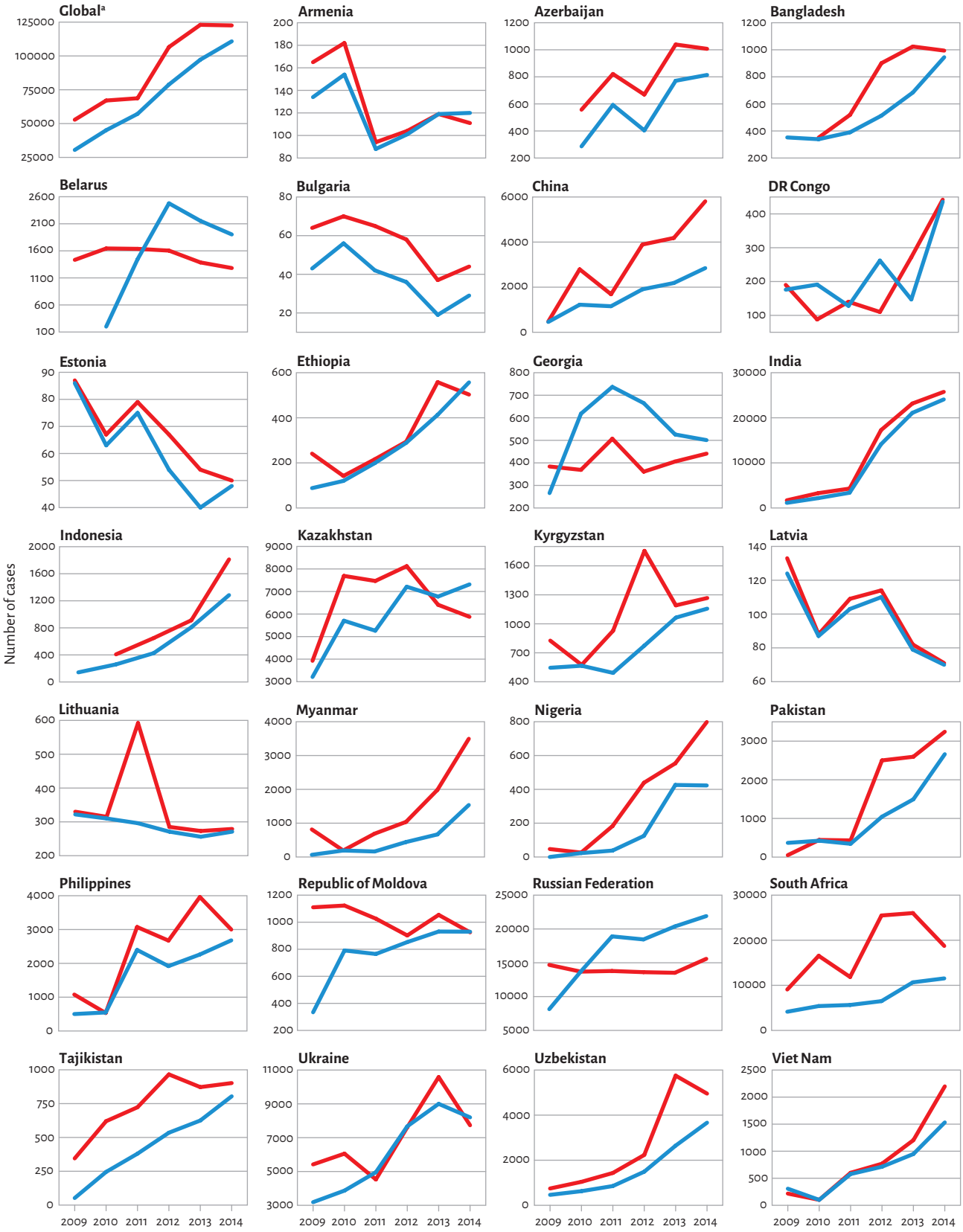
4.2.4 Accelerating the scale-up of detection and enrolment on treatment for people with drug-resistant TB: the role of models of care and non-NTP providers

In many countries, one of the reasons for inadequate access to diagnosis and treatment of drug-resistant TB is that the network for the programmatic management of drug-resistant TB (PMDT) is too centralized. Hospital-based models of care, which are still dominant in many countries, are a barrier to the expansion of PMDT because they depend on hospitals or referral centres. Greater use of ambulatory care as part of decentralized PMDT services is necessary to expand access. However, national policies and practices vary and hospitalization is still the predominant model of care in many countries.

Among the 27 high MDR-TB burden countries, the Democratic Republic of the Congo reported the lowest level of

FIGURE 4.7

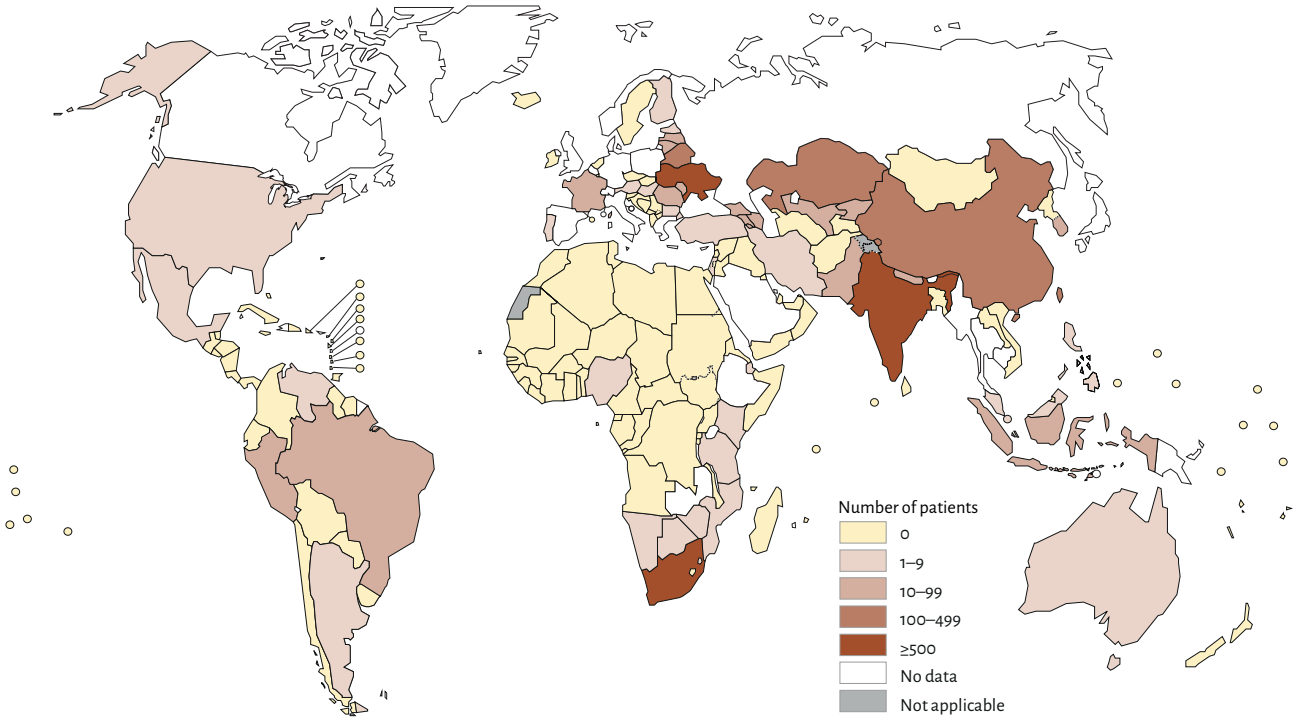
MDR–TB cases and additional rifampicin–resistant TB cases detected (red) compared with TB cases enrolled on MDR–TB treatment (blue), global trend and trend in 27 high MDR–TB burden countries, 2009–2014



[a] The global total of MDR/RR-TB cases detected in 2013 (123 001) is lower than previously published in the 2014 *Global TB Report* (136 412) following revisions to data reported by India.

FIGURE 4.8

Number of patients with laboratory–confirmed XDR–TB started on treatment in 2014



hospitalization (5% of MDR-TB patients), followed by Myanmar (10%). In contrast, hospitalization for 100% of MDR-TB patients in 2014 (at least for part of their treatment) was reported by 10 high MDR-TB countries, including two of the top three MDR-TB burden countries: China and the Russian Federation. In a further six high MDR-TB burden countries, at least 90% of MDR-TB patients were hospitalized. When MDR-TB patients are hospitalized the duration of stay was relatively short in Indonesia, at five days, and ranged from 30–60 days in five other countries (Bangladesh, China, Estonia, Ethiopia, Myanmar). In the other 15 countries that reported data, the average length of stay was 160 days.

The number of visits to a health facility after diagnosis of MDR-TB also varied markedly, from less than 30 (Bangladesh, Estonia, Myanmar, and South Africa) to over 700 (Armenia, Georgia, Indonesia, Russian Federation and Ukraine). The involvement of all relevant non-NTP health care providers is important to scale up PMDT and improve access to services. Unfortunately, reliable data on these activities are often not collected by NTPs. In 2014, only nine high MDR-TB burden countries provided information on the numbers of patients started on MDR-TB treatment by non-NTP health care providers. The Philippines, Latvia and Kyrgyzstan reported that 22%, 14% and 11% respectively of MDR-TB cases were treated by non-NTP providers, while figures of 1–5% were reported to be treated in the private sector in Myanmar, Viet Nam and four Eastern European countries: Armenia, Republic of Moldova, Ukraine and Uzbekistan.

In 2014, only 39 countries (including 13 of the 27 high MDR-TB burden countries) reported that palliative and end-of-life care were provided within the scope of their NTPs. This finding attests to the huge unmet need for such services, which should be delivered alongside proper infection control measures (since most of these patients remain a source of infection).

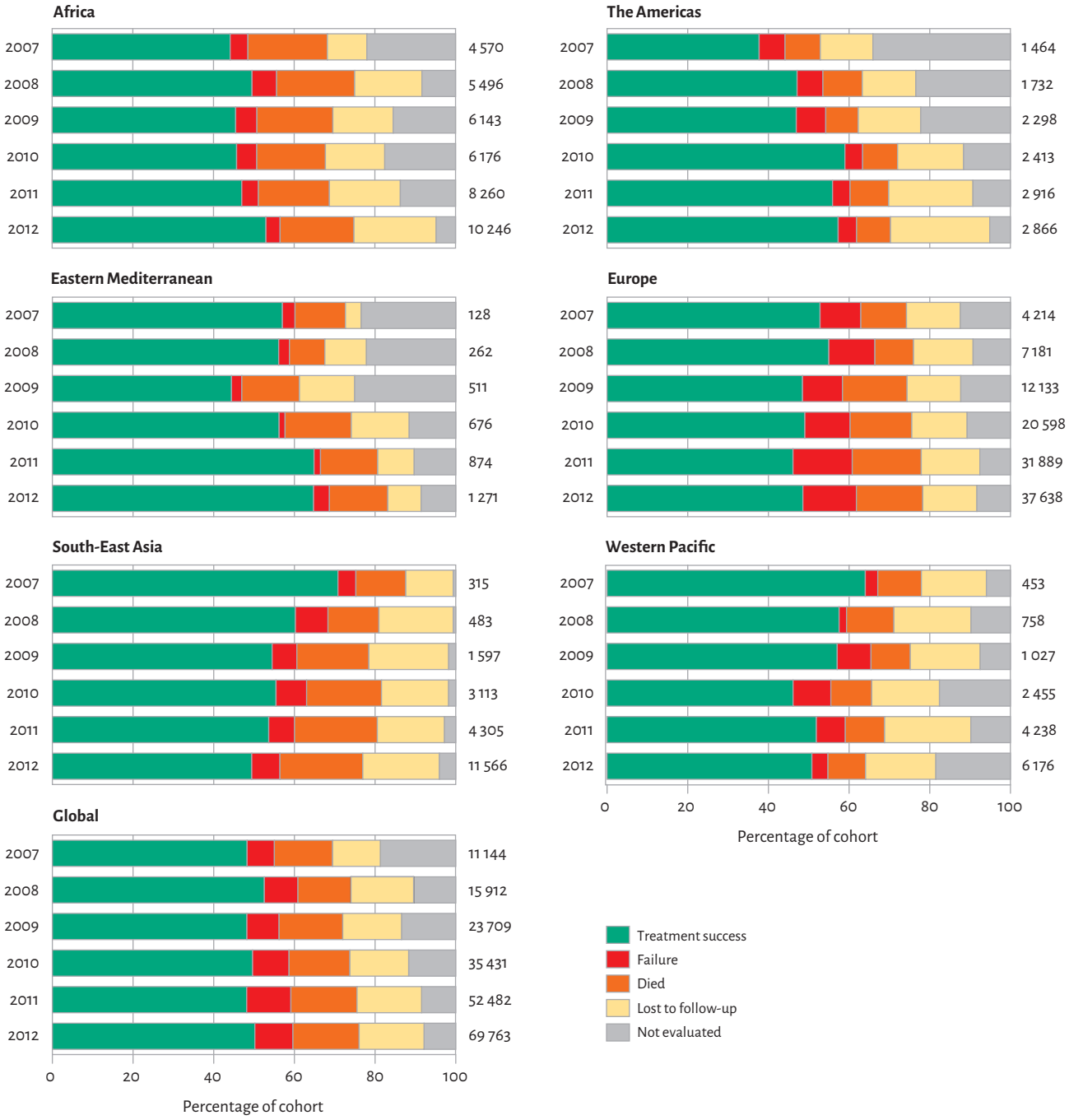
4.2.5 Treatment outcomes for patients with MDR-TB and XDR-TB

The Global Plan included a target that all countries should report outcomes for all notified MDR-TB cases by 2015. A total of 127 countries and territories reported treatment outcomes for cases started on MDR-TB treatment in 2012. The country cohort size ranged from 1 to 16 000 cases. The number of cases reported in annual cohorts has steadily increased in all six WHO regions over time (with the exception of a small decrease in the Region of the Americas between the 2011 and the 2012 cohorts). The total reached 70 000 cases globally in 2012, 33% more than in 2011 (**Table 4.3 and Figure 4.9**).

The use of electronic systems to manage MDR-TB patient data could help to improve the completeness of reporting on treatment outcomes. One of the Global Plan targets is for all 27 high MDR-TB countries to manage their data on treatment of MDR-TB patients electronically by 2015. By 2014, 15 of these countries reported that national electronic databases were in place for TB patients and another six had systems for MDR-TB patients only.

FIGURE 4.9

Treatment outcomes for patients diagnosed with MDR–TB by WHO Region, 2007–2012 cohorts. The total number of cases with outcome data is shown beside each bar

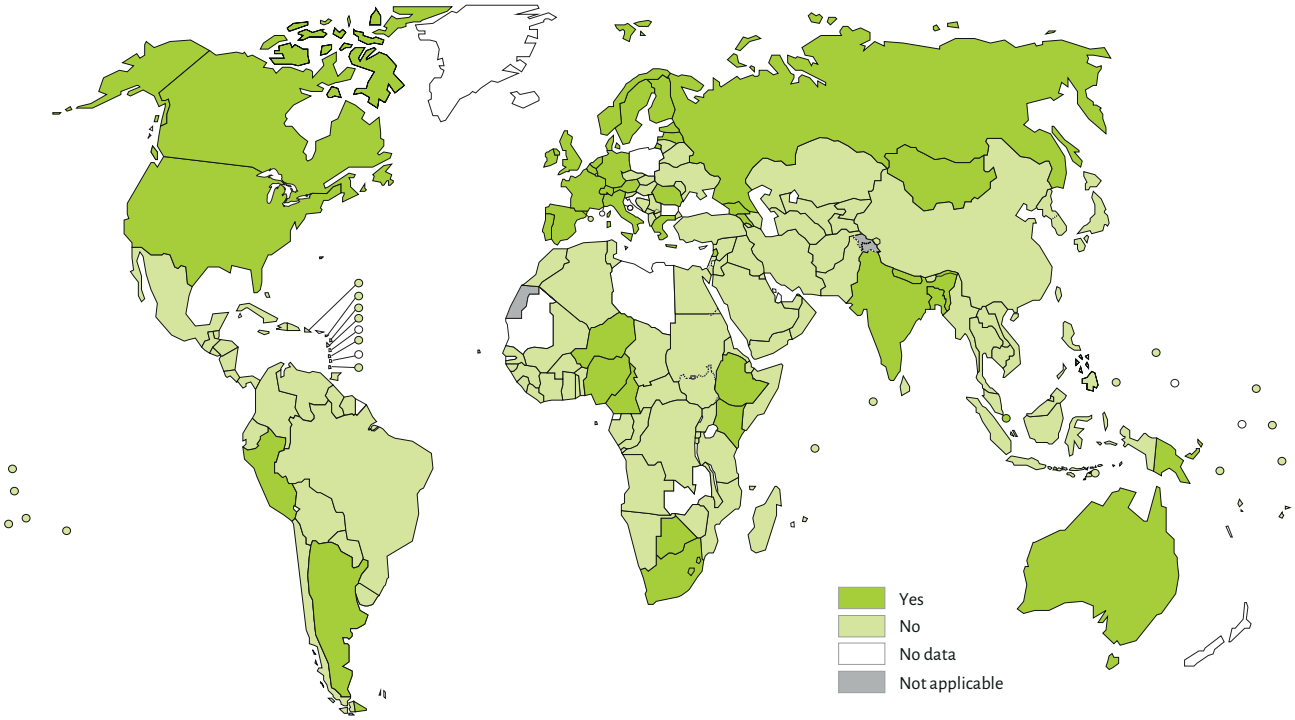


Overall, the proportion of MDR-TB patients in the 2012 cohort who successfully completed treatment (i.e. cured or treatment completed) was 50%; 16% died, 16% were lost to follow-up, treatment failed for 10% and 8% had no outcome information (**Figure 4.9**). The treatment success rate was highest in the Eastern Mediterranean Region (65%), and lowest in the European and South-East Asia regions (49%). In the 2012 cohort, treatment failure was highest in the European Region (13%), and the death rate was highest in the South-East Asia Region (21%).

The Global Plan target of achieving a treatment success rate of ≥75% by 2015 had already been reached in 40 of the 122 countries that reported outcome data for the 2012 cohort, including three of the 27 high MDR-TB burden countries (Estonia, Ethiopia, and Myanmar). Between 2007 and 2012, more than 100 000 people who started MDR-TB treat-

FIGURE 4.10

Countries that had used bedaquiline for the treatment of M/XDR-TB as part of expanded access, compassionate use or under normal programmatic conditions by the end of 2014



ment were reported to have had a successful outcome and numbers have increased over time (data not shown).

Among 2 685 XDR-TB patients in the 2012 cohorts of 41 countries for whom outcomes were reported, 682 (26%) completed treatment successfully; 809 (30%) died; treatment failed for 510 (19%); and 684 (25%) were lost to follow-up or their treatment outcome was not evaluated. The Russian Federation accounted for 51% of the XDR-TB patients for whom outcomes were reported in 2012. The high mortality of XDR-TB patients in South Africa (47%) is likely to be associated with a high level of HIV co-infection in TB patients (see **Chapter 6**).

The introduction of new drugs and novel regimens could potentially improve the treatment outcomes of patients with MDR- and XDR-TB. By the end of 2014, at least 43 countries reported having used bedaquiline to treat patients as part of efforts to expand access to treatment for MDR-TB, either for compassionate use or under normal programmatic conditions in the public or private sectors (**Figure 4.10**). Most (75%) of these patients were from two countries: the Russian Federation and South Africa. In addition, at least 16 countries in Africa and Asia have introduced shorter regimens as part of trials or observational studies under operational research conditions, and several have started to include repurposed drugs in treatment regimens, to try to improve the treatment outcomes of MDR-TB and XDR-TB patients.

Since the start of global monitoring, treatment success rates among patients with MDR-TB and XDR-TB have remained consistently and unacceptably low. Major efforts are required to address this situation, using measures that are part of the End TB Strategy. These include adequate resources for detection and treatment and building capacity among health care workers to provide high quality care. Research and development is also crucial. Without new TB drugs and regimens, it will be very difficult to improve treatment outcomes in the near future.

CHAPTER 5

Diagnostics and laboratory strengthening

Key facts and messages

The End TB Strategy calls for the early diagnosis of TB and universal drug susceptibility testing (DST), highlighting the critical role of laboratories in the post-2015 era for rapidly and accurately detecting TB and drug resistance.

Laboratory confirmation of TB and drug resistance is essential to ensure that individuals with TB are correctly diagnosed and have access to the appropriate treatment as soon as possible. Of the 5.2 million incident (new and relapse) pulmonary TB patients notified globally in 2014, 3.0 million (58%) were bacteriologically confirmed, i.e., were smear- or culture-positive or positive according to a WHO-recommended rapid diagnostic such as Xpert® MTB/RIF. Among new (previously untreated) cases of bacteriologically confirmed TB, 12% had access to DST; among previously treated cases, 58% had access to DST.

A new *WHO Policy framework for implementing tuberculosis diagnostics* was published in April 2015. This provides an overview of all current WHO policy recommendations on TB diagnostics and the role of each test within effective diagnostic algorithms across a laboratory network. The document also describes the managerial, technical and operational processes required for developing and implementing a comprehensive national strategy for TB laboratories.

WHO has recently issued policy recommendations on the use of the urine lateral flow lipoarabinomannan (LF-LAM) assay (Alere Determine™ TB LAM Ag test). The test is not recommended for TB screening or diagnosis of TB in most population groups. However, it is recommended to help with the diagnosis of TB in two population groups: HIV-positive people who are inpatients with signs or symptoms of TB and who have a CD4 cell count less than or equal to 100 cells/μL, and HIV-positive people who are "seriously ill" (both inpatients and outpatients) with danger signs, regardless of CD4 count or if the CD4 count is unknown.

The use of the rapid molecular test Xpert MTB/RIF continues to expand in line with WHO recommendations for its use since December 2010. By the end of 2014, 69% of countries reported that national policy by the end of 2014 indicated the use of Xpert MTB/RIF as the initial diagnostic test for people at risk of drug-resistant TB, and 60% reported that national policy indicated its use as the initial diagnostic test for people living with HIV. In 116 of the 145 countries eligible for concessional pricing that have purchased the technology, a total of 3 763 GeneXpert machines had been procured for use in the public sector by the end of 2014. In 2014 alone, 4.8 million Xpert MTB/RIF test cartridges were procured, up from 550 000 in 2011.

Ensuring the quality of microscopy networks is critical, given that smear microscopy remains the most widely used tool for TB diagnosis in low- and middle-income countries. Among the 22 HBCs, only four reported an external quality assessment scheme that encompassed all microscopy centres in 2014, and five more reported a programme that included at least 90% of centres.

Several sources of guidance and training platforms have been developed to assist TB reference laboratories to implement a quality management system that meets international accreditation standards. In 2014, 123 of 173 responding countries and territories (71%) indicated that a formal quality management system towards achieving laboratory accreditation had at least been started at the national reference laboratory (NRL).

In 2015, the WHO TB Supranational Reference Laboratory Network expanded to include three newly designated National Centres of Excellence in the Russian Federation. The three laboratories are of particular value for establishing and maintaining high-quality laboratory services within the country for the programmatic management of drug-resistant TB, including through the coordination of technical assistance, provision of monitoring and supervision, and organization of training for laboratory staff involved in diagnostic testing for drug resistance and monitoring of treatment for patients with drug-resistant TB.

The microbiological detection of TB and drug susceptibility using rapid WHO-recommended diagnostics, together with an efficient system for transfer of specimens and results, allows patients to be correctly diagnosed and started on the most effective treatment regimen as early as possible. One of the core components of the first pillar of the post-2015 End TB Strategy (**Chapter 1**) is the early diagnosis of TB, including universal drug susceptibility testing (DST). Operational guidance on the implementation of the strategy calls for all patients to receive DST at least for rifampicin, with further tests for drug susceptibility to first and second-line drugs for any TB patients found to have rifampicin resistance. A well-equipped and staffed, quality-assured laboratory network with an efficient referral system is therefore an essential requirement for any national TB programme (NTP) in the post-2015 era.

For decades, resource-constrained countries have relied on sputum smear microscopy as the primary method for detect-

ing TB. While inexpensive and requiring minimal biosafety standards, microscopy is not a sensitive test (particularly for people living with HIV and children) and it provides no information on the resistance profile of the bacilli. Furthermore, microscopy is not able to distinguish between *Mycobacterium tuberculosis* complex and non-tuberculosis mycobacteria. Bacteriological culture is considered the reference standard for detecting TB, but suffers from the disadvantages that results take weeks to obtain and that testing requires a well-equipped laboratory, highly trained staff, and an efficient transport system to ensure the viability of specimens. Phenotypic DST on cultured specimens is the conventional method used to detect resistance to first- and second-line TB drugs, and faster commercial liquid culture systems are now available. Building adequate culture capacity in many countries with a high burden of TB has been slow, given the cost and infrastructure requirements.

In recent years, a limited but growing number of rapid and more sensitive tests for TB and drug-resistant TB based on molecular methods, including Xpert® MTB/RIF (Cepheid, USA) and line probe assays (LPAs), have become available to replace or complement existing conventional tests. Despite the advantages of molecular tests, conventional microscopy and culture remain necessary for monitoring patients' response to treatment. Furthermore culture-based DST methods are currently the only methods available for accurate testing of susceptibility to second-line drugs.

Of the 5.2 million incident pulmonary TB patients notified globally in 2014, only 3.0 million (58%) were bacteriologically confirmed, i.e., were smear- or culture-positive or positive according to a WHO-recommended rapid diagnostic such as Xpert MTB/RIF (**Chapter 3**). The remaining 42% of patients who were not bacteriologically confirmed were diagnosed clinically, i.e. based on symptoms, chest X-ray abnormalities or suggestive histology. The common symptoms of TB combined with the poor specificity of X-ray screening may result in false diagnoses and people without TB being enrolled on TB treatment when it is not needed. Furthermore, a low rate of laboratory confirmation reflects under-diagnosis of true TB cases and contributes in part to the continuing global gap between notified and estimated incident TB cases: 6 million and 9.6 million in 2014, respectively (**Chapter 3**). The proportion of new and previously treated cases receiving DST has steadily increased but much remains to be done. Globally, 12% of new bacteriologically-confirmed TB cases and 58% of those previously treated for TB were tested for drug resistance in 2014 (**Chapter 4**).

Laboratory strengthening and new diagnostics are crucial to improve the proportion of notified TB cases with a definitive (bacteriologically confirmed) diagnosis of TB, and to close detection and treatment gaps for TB and drug-resistant TB. This chapter summarizes the status of progress in 2014. **Section 5.1** highlights key developments in WHO guidance on TB diagnostics and laboratory strengthening during 2014–2015. **Section 5.2** presents the status of laboratory capacity globally, regionally and nationally in 2014, based on data reported to WHO by countries in 2015. Here, the focus is on the 36 countries in the combined list of 22 high burden countries (HBCs) and 27 high MDR-TB burden countries. **Section 5.3** describes recent activities to strengthen TB laboratories, including quality management systems, external quality assessment and the WHO TB Supranational Reference Laboratory (SRL) Network.

5.1 Developments in WHO policy guidance on TB diagnostics and laboratory strengthening, 2014–2015

The WHO Global TB Programme follows a systematic process for development of policy recommendations on TB diagnostics, involving synthesis of the available evidence on performance and cost effectiveness through systematic reviews, meta-analyses and modelling as appropriate, assessment of the evidence by an external Guideline Development Group using the GRADE approach,[1] and development of policy guidance[2] for dissemination to Member States and other stakeholders. Policy documents are reviewed periodically, and revised as necessary when new evidence becomes available.

In June 2015, WHO convened a Guideline Development Group to review the evidence on the use of the urine lateral flow lipoarabinomannan (LF-LAM) assay (Alere Determine™ TB LAM Ag test, Alere Inc, USA) for detection of TB in people living with HIV. A lipoarabinomannan (LAM) antigen is a lipopolysaccharide present in mycobacterial cell walls, which is released from metabolically active or degenerating bacterial cells and appears to be present only in people with active TB disease. Tests based on the detection of LAM in urine have the potential to be point-of-care tests for TB. Further advantages over sputum-based testing are that urine is easy to collect and store, and lacks the infection control risks associated with sputum collection.

The urinary LAM assays currently available are unsuitable as general diagnostic or screening tests for TB, due to suboptimal sensitivity. However, unlike traditional diagnostic methods for TB, they demonstrate improved sensitivity among people living with HIV, which further increases as CD4 counts fall. Following the Guideline Development Group's evaluation of the LF-LAM assay, the resulting 2015 WHO policy recommendations on its use are summarized in **Box 5.1**.

In the coming year, evaluations and updated reviews are planned for several other technologies. These include LPAs for detection of resistance to first- and second-line drugs (Hain LifeScience, Germany; and Nipro Corp., Japan); the use of sequencing for detection of resistance-conferring mutations; and the Xpert® Ultra assay and GeneXpert® Omni (Cepheid, USA). Further potential technologies on the evalu-

[1] www.gradeworkinggroup.org

[2] *WHO handbook for guideline development, 2nd ed.* Geneva, World Health Organization; 2014. Available at: http://www.who.int/kms/handbook_2nd_ed.pdf.

Box 5.1 WHO recommendations on urine lateral flow lipoarabinomannan (LF-LAM) assay (Alere Determine™ TB LAM Ag test, Alere Inc, USA)

The 2015 WHO recommendations on LF-LAM assay are:

1. LF-LAM **should not** be used for the diagnosis of TB, *except as specifically described below for persons with HIV with low CD4 counts or who are seriously ill*[a] (strong recommendation; low quality of evidence).
2. LF-LAM **may be used to assist** in the diagnosis of TB in HIV-positive adult *inpatients* with signs or symptoms of TB (pulmonary and/or extrapulmonary) who have a CD4 cell count less than or equal to 100 cells/μL, or HIV-positive patients who are seriously ill[a] regardless of CD4 count or with unknown CD4 count (conditional recommendation; low quality of evidence).

Remarks

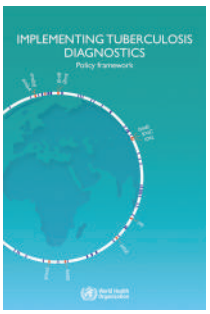
- This recommendation also applies to HIV-positive adult *outpatients* with signs and symptoms of TB (pulmonary and/or extrapulmonary) who have a CD4 cell count less than or equal to 100 cells/μL, or HIV-positive patients who are seriously ill[a] regardless of CD4 count or with unknown CD4 count, based on the generalisation of data from inpatients.
- This recommendation also applies to children, based on the generalisation of data from adults while acknowledging very limited data and concern regarding the low specificity of the LF-LAM assay in children.

3. LF-LAM **should not be used** as a screening test for TB (strong recommendation; low quality of evidence).

[a] "seriously ill" is defined based on four danger signs: respiratory rate > 30/min, temperature >39 °C, heart rate >120/min and unable to walk unaided.

ation horizon include several rapid and sensitive diagnostic tests that are expected to be available for use at reference laboratory level as well as closer to – or at – the point of patient care (**Chapter 8**).

In April 2015, a new *WHO Policy framework for implementing tuberculosis diagnostics* was published.[1] This document provides comprehensive guidance on the managerial, technical and operational processes required for developing and implementing a comprehensive national strategy for TB laboratories, which encompass early diagnosis of TB and universal access to DST as well as systematic screening of contacts of people with TB and high-risk groups. The positioning of WHO-recommended diagnostics at different levels of a laboratory network is described, and templates of diagnostic algorithms are presented. This generic policy framework can be adapted and customized at country level to account for the wide variation in country resources and needs, as well as differences in the epidemiology of TB, HIV-associated TB and drug-resistant TB.



A comprehensive list of existing WHO policy documents, including on the use of microscopy, culture, DST and non-commercial and molecular diagnostic methods, is available at: www.who.int/tb/laboratory/policy_statements.

5.2 Status of laboratory capacity globally, regionally and nationally

Smear microscopy continues to be the most widely used tool for TB diagnosis in low- and middle-income countries, despite its shortcomings. A microscopy network with adequate population coverage and high quality performance (see **Section 5.3**) is therefore critical. The *Global Plan to Stop TB 2011–2015* includes the target that countries maintain at least one smear microscopy centre per 100 000 population.[2] Globally, the target has been met (1.1 centres per 100 000 population in 2014), but significant disparities remain at regional and country levels (**Table 5.1**). For example, the Western Pacific and Eastern Mediterranean regions had less than one centre per 100 000 population in 2014. The target now requires country-specific adaptation given the increased use of Xpert MTB/RIF as an initial diagnostic test, especially in settings with high burdens of HIV and MDR-TB. In addition, it is important to emphasize that geographic variations in the TB epidemic within a country as well as differences in access between urban and rural settings require that the number and placement of microscopy centres are strategically considered within countries.

Fluorescent light-emitting diode (LED) microscopy is more sensitive than conventional Ziehl–Neelsen (ZN) light microscopy and has further qualitative, operational and cost advantages. In 2009, WHO recommended that LED microscopy be phased in as an alternative for ZN microscopy. Globally, the switch to LED microscopes has been gradual: the technology was reported to have been present in only 7% of microscopy centres in 2014, up from 2% in 2012. Nonetheless, major progress is evident in certain countries. Among HBCs, major adopters of LED microscopy include South Africa (100% of microscopy sites in 2014), China (38%), Myanmar (31%), Bangladesh (22%), Kenya (21%) and Mozambique (21%). Adoption of LED microscopy remains particularly low in Indonesia (0%), Afghanistan (<1%), Brazil (<1%), Philippines (<1%), the Democratic Republic of the Congo (1%), India (2%), and Viet Nam (2%).

The current target in the *Global Plan to Stop TB 2011–2015* for both culture and DST (to at least rifampicin and isoniazid)

[1] WHO Policy framework for implementing tuberculosis diagnostics. Geneva, World Health Organization; 2015. Available at: http://www.who.int/tb/publications/implementing_TB_diagnostics/en/

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

TABLE 5.1

Laboratory capacity, 2014[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	■	□	720	2.3	<1	3	0.5	0	0	0	0	1
Armenia	□	■	26	0.9	4	1	1.7	1	1.7	1	1.7	2
Azerbaijan	□	■	72	0.7	4	7	3.6	3	1.6	2	1	7
Bangladesh	■	■	1 104	0.7	22	3	<0.1	3	<0.1	1	<0.1	38
Belarus	□	■	154	1.6	2	29	15	8	4.2	8	4.2	15
Brazil	■	□	3 382	1.6	<1	324	7.9	26	0.6	1	<0.1	48
Bulgaria	□	■	34	0.5	38	30	21	9	6.2	4	2.8	0
Cambodia	■	□	215	1.4	13	4	1.3	3	1	0	0	17
China	■	■	2 952	0.2	38	1 825	6.7	399	1.5	157	0.6	654
DR Congo	■	■	1 604	2.1	1	4	0.3	3	0.2	1	<0.1	39
Estonia	□	■	6	0.5	33	2	7.6	2	7.6	2	7.6	4
Ethiopia	■	■	2 972	3.1	9	8	0.4	8	0.4	8	0.4	28
Georgia	□	■	11	0.3	9	2	2.5	1	1.2	2	2.5	11
India	■	■	13 583	1	2	67	0.3	62	0.2	50	0.2	121
Indonesia	■	■	5 689	2.2	0	20	0.4	15	0.3	2	<0.1	41
Kazakhstan	□	■	466	2.7	0	85	24	22	6.3	12	3.5	23
Kenya	■	□	1 920	4.3	21	3	0.3	3	0.3	5	0.6	70
Kyrgyzstan	□	■	131	2.2	8	7	6	2	1.7	2	1.7	8
Latvia	□	■	12	0.6	0	5	13	1	2.5	1	2.5	2
Lithuania	□	■	13	0.4	15	6	10	6	10	2	3.4	4
Mozambique	■	□	336	1.2	21	3	0.6	2	0.4	1	0.2	24
Myanmar	■	■	492	0.9	31	3	0.3	2	0.2	2	0.2	38
Nigeria	■	■	1 765	1	15	8	0.2	8	0.2	6	0.2	96
Pakistan	■	■	1 483	0.8	3	12	0.3	5	0.1	4	0.1	42
Philippines	■	■	2 561	2.6	<1	22	1.1	4	0.2	1	<0.1	84
Republic of Moldova	□	■	59	1.4	0	4	4.9	4	4.9	4	4.9	28
Russian Federation	■	■	5 347	3.7	6	405	14	299	10	6	0.2	96
South Africa	■	■	207	0.4	100	12	1.1	12	1.1	12	1.1	207
Tajikistan	□	■	84	1	6	5	3	1	0.6	3	1.8	14
Thailand	■	□	908	1.3	3	53	3.9	20	1.5	12	0.9	14
Uganda	■	□	1 365	3.6	18	5	0.7	5	0.7	3	0.4	74
Ukraine	□	■	676	1.5	0	65	7.2	24	2.7	3	0.3	25
UR Tanzania	■	□	945	1.8	14	4	0.4	1	<0.1	3	0.3	59
Uzbekistan	□	■	325	1.1	<1	7	1.2	2	0.3	3	0.5	24
Viet Nam	■	■	989	1.1	2	23	1.2	2	0.1	2	0.1	30
Zimbabwe	■	□	220	1.4	10	2	0.7	2	0.7	1	0.3	62
High-burden countries			–	**1.1**	**8**	–	**3.1**	–	**1**	–	**0.3**	–
High MDR-TB burden countries			–	**1**	**7**	–	**3.2**	–	**1.1**	–	**0.4**	–
AFR			–	1.6	14	–	1	–	1.2	–	0.3	–
AMR			–	2	2	–	15	–	0.7	–	0.3	–
EMR			–	0.7	5	–	2.2	–	0.3	–	0.2	–
EUR			–	1.2	5	–	11	–	5.5	–	1.6	–
SEAR			–	1.2	3	–	0.4	–	0.3	–	0.2	–
WPR			–	0.5	16	–	6	–	1.3	–	0.5	–
Global			–	**1.1**	**7**	–	**4.7**	–	**1.3**	–	**0.5**	–

– 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.

capacity is one laboratory per 5 million population. In 2014, 12 of the 27 high MDR-TB burden countries did not reach the target (**Table 5.1**), and several countries with large TB caseloads continue to completely lack in-country capacity for phenotypic DST (**Figure 5.1**). In 2014, 12 countries reported more than 1000 notified TB cases but no capacity to perform phenotypic DST: Afghanistan, Burkina Faso, Chad, Congo, Equatorial Guinea, Gabon, Guinea-Bissau, Papua New Guinea, Sierra Leone, Somalia, South Sudan and Timor Leste. Among these, Equatorial Guinea and Sierra Leone also reported lacking any capacity for Xpert MTB/RIF testing, which would at least allow for detection of rifampicin resistance.

Patients with MDR-TB require DST for second-line drugs to refine and optimize their treatment regimen. Some countries with small caseloads of MDR-TB patients have reasonably opted to rely on partner laboratories (including WHO Supranational Reference Laboratories) for such testing, instead of building in-country capacity. However, 28 countries with reported RR/MDR-TB cases indicated that they had neither in-country capacity nor a linkage with a partner laboratory for second-line DST: Albania, Cambodia, Central African Republic, Chad, Congo, Djibouti, Eritrea, Gabon, Ghana, Guinea, Guinea-Bissau, Guyana, Jordan, Kenya, Kuwait, Malawi, Mali, Mauritania, Mauritius, Morocco, Panama, Paraguay, Sao Tome and Principe, Saudi Arabia, Syrian Arab Republic, Togo, Turkmenistan and Yemen. Countries with sizeable TB and MDR-TB caseloads should aim as a priority to build sustainable in-country capacity to undertake DST to at least rifampicin, to allow the timely diagnosis of drug-resistant strains.

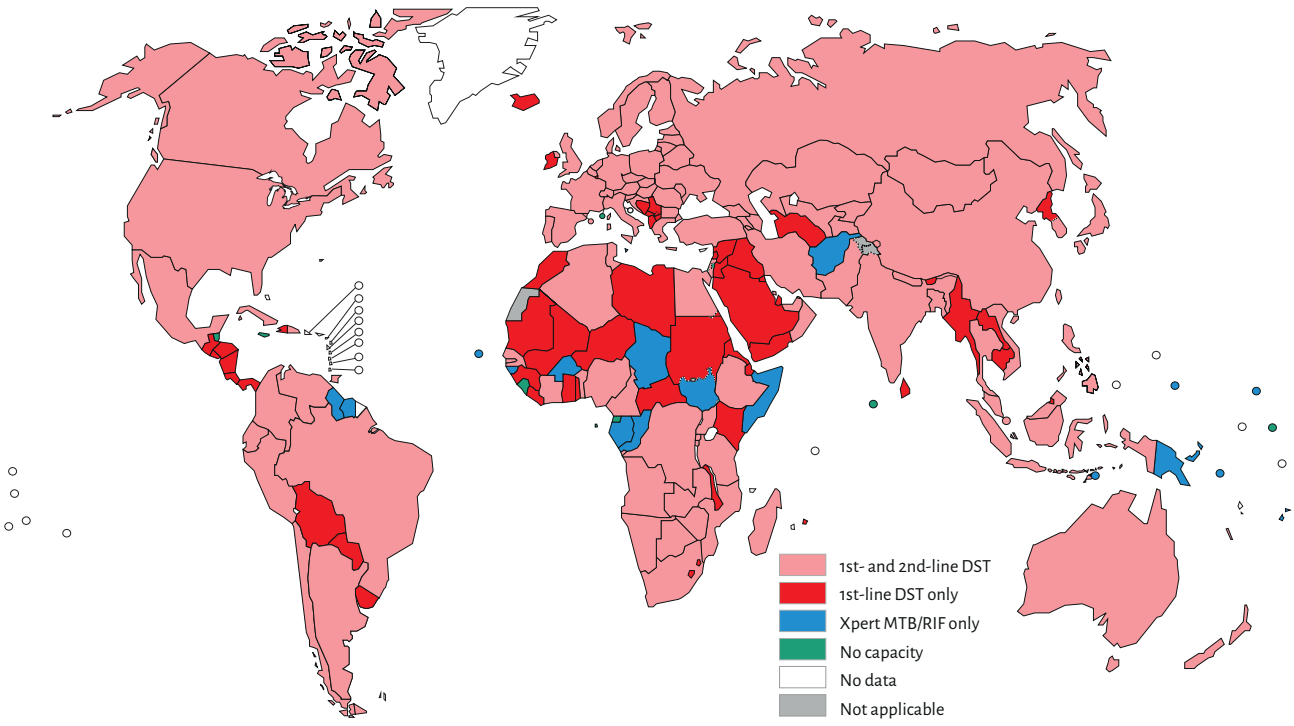
As a high-throughput molecular tool for use at central and regional levels, LPAs have been adopted by many countries for rapid first-line DST (to rifampicin and isoniazid) on smear-positive specimens or cultures. In 2014, 92 countries and territories reported at least one facility with capacity to perform LPA tests. Of the 27 high MDR-TB burden countries, 13 reported LPA capacity in more than one laboratory per 5 million population.

Following initial WHO recommendations issued in December 2010, Xpert MTB/RIF has been quickly adopted by countries as an effective tool for the rapid detection of TB and rifampicin resistance at lower levels of the health system. By the end of December 2014, a total of 3 763 GeneXpert instruments comprising 17 883 modules had been procured in the public sector in 116 of the 145 countries eligible for concessional pricing. In 2014, 4.8 million test cartridges were procured by eligible countries (**Figure 5.2**), up from 550 000 in 2011. Of these, 51% (2.4 million) went to South Africa.

The original WHO policy guidance on Xpert MTB/RIF issued in 2010 recommends its use as the initial diagnostic test in individuals suspected of having MDR-TB or HIV-associated TB (strong recommendations). A policy update in 2013 expanded its recommended uses, including for the diagnosis of TB in children, on selected specimens for the diagnosis

FIGURE 5.1

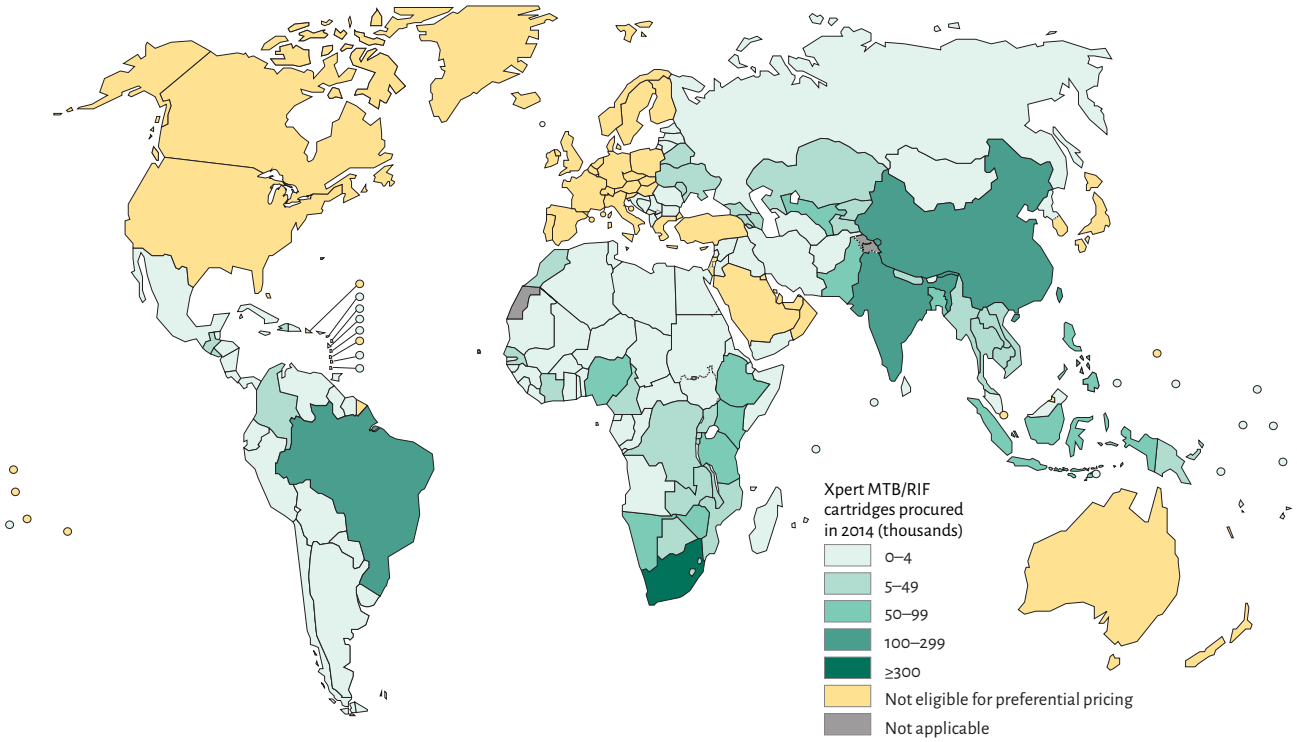
Global capacity for drug-susceptibility testing (DST), 2014[a]



[a] Data for 2013 were used if data for 2014 were not reported (n=6).

FIGURE 5.2

Xpert MTB/RIF cartridge procurements in 2014 at concessional prices



of extrapulmonary TB, and for all individuals suspected of having pulmonary TB (conditional recommendations). High-burden countries have largely adopted the strong recommendations on its use as the initial diagnostic test for individuals suspected of having MDR-TB or HIV-associated TB (**Table 5.2**). While 19 of the 22 high TB burden countries have indicated policies on the use of Xpert MTB/RIF for individuals suspected of having HIV-associated TB, not all of the 41 TB/HIV priority countries reported having such a policy: by the end of 2014, Central African Republic, Chad, China, Cote d'Ivoire, Malawi, Myanmar, Namibia, Sierra Leone and Sudan indicated that Xpert MTB/RIF was not yet the initial diagnostic test for people suspected of having HIV-associated TB (see also **Box 6.2** in **Chapter 6**).

Increasingly, countries are also updating their policies to include the use of Xpert MTB/RIF for children and for detection of extrapulmonary TB (50% and 41% of all reporting countries, respectively). A small number of countries with sufficient resources, including South Africa, Swaziland and Moldova, are also placing Xpert MTB/RIF as the initial diagnostic test for all people suspected of having TB. Some countries that cannot afford the use of Xpert MTB/RIF as the initial diagnostic test for all people with suspected TB have introduced diagnostic algorithms in which chest X-ray is used as an initial screening tool, with those with X-ray abnormalities then eligible for testing using Xpert MTB/RIF. As countries continue to scale-up coverage of Xpert MTB/RIF testing, algorithms should be widened to increase patient access to the test as a sensitive and rapid tool both for detection of rifampicin resistance and for TB case-finding.

The growing number of drug-resistant cases being detected by Xpert MTB/RIF and LPAs requires adjustment of country culture and phenotypic DST capacities. The introduction of Xpert MTB/RIF and LPAs reduces the need for culture as the initial diagnostic test, but at the same time the growing detection of drug-resistant TB cases requires culture capacity for monitoring of treatment and DST of other anti-TB drugs to guide treatment adjustments. It is also imperative that the increasing capacity of countries to diagnose drug-resistant TB is matched by increased capacity to provide appropriate treatment to all diagnosed cases (see also **Chapter 4**).

One of the main reasons for low TB and drug-resistant TB case detection rates in many parts of the world (**Chapter 3**) is the existence of a significant private sector, in which care providers frequently diagnose people with TB and drug-resistant TB but fail to notify these to national authorities. The quality of diagnostic services in the private sector is highly variable or unknown. Furthermore, in some settings, laboratories in the public sector that are not under the auspices of the NTP also diagnose TB and drug-resistant TB without necessarily following recommended guidelines and quality assurance procedures. Collaboration between NTPs and all laboratories offering TB and drug-resistant TB diagnosis is critical to ensure that national guidelines are followed, that appropriate diagnostic tests are used, and that patients diagnosed

TABLE 5.2

Incorporation of WHO policy guidance on Xpert MTB/RIF, 2014[a]

YES ■ NO □	HIGH TB BURDEN	HIGH MDR-TB BURDEN	XPERT MTB/RIF AS THE INITIAL DIAGNOSTIC TEST			
			PEOPLE LIVING WITH HIV	PEOPLE AT RISK OF DRUG-RESISTANT TB	CHILDREN SUSPECTED OF HAVING TB	EXTRAPULMONARY TB USING SELECTED SPECIMENS
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			**86%**	**100%**	**77%**	**64%**
High MDR-TB burden countries			**85%**	**93%**	**81%**	**70%**
AFR			72%	84%	67%	40%
AMR			52%	48%	35%	30%
EMR			56%	62%	38%	44%
EUR			50%	57%	45%	44%
SEAR			55%	82%	36%	45%
WPR			72%	83%	56%	50%
Global			**60%**	**69%**	**50%**	**41%**

[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.

with TB and drug-resistant TB are notified to the NTP and receive proper care. In 2014, 17 of 36 high TB and MDR-TB burden countries reported some level of collaboration with laboratories in the private sector, and 23 reported collaboration with non-NTP laboratories in the public sector.

5.3 Strengthening TB laboratories globally, regionally and nationally

Strengthening TB laboratories involves not only equipping them with modern diagnostics suitable to the various levels of the network (**Section 5.2**), but also ensuring the quality of every step in the diagnostic process, from the collection and testing of samples, to the recording and reporting of results. Implementing a system of quality management should be a priority across all TB laboratories in a network. A comprehensive quality management system allows for the necessary activities to be carried out at the right time and by the appropriately trained people, for the necessary equipment and consumables to be in stock, and for all manuals, guidelines, forms and standard operating procedures to be in place so that processes are carried out correctly.

Several sources of guidance and training platforms have been developed to assist TB reference laboratories to implement a quality management system that meets international accreditation standards. The *GLI stepwise process towards TB laboratory accreditation* is an online interactive guide[1] divided into four phases, developed by the Royal Tropical Institute (KIT), the Union, the United States Centers for Disease Control and Prevention, the United States Agency for International Development (USAID) and WHO. The framework known as the *WHO guide for the stepwise laboratory improvement process toward accreditation in the African Region* (SLIPTA) is based on 12 quality-system essentials, and it is applicable to all laboratory settings and disciplines. The United States Centers for Disease Control and Prevention has developed a task-based mentoring programme known as *Strengthening laboratory management towards accreditation* (SLMTA). The Foundation for Innovative New Diagnostics (FIND) has modified both the SLMTA programme and the SLIPTA framework to include TB-specific guidance, to form TB-SLMTA and TB-SLIPTA. In 2014, 123 of 173 responding countries and territories (71%) indicated that a formal quality management system towards achieving laboratory accreditation had at least been started at the national reference laboratory (NRL).

Quality assurance of microscopy remains a critical activity of all laboratory networks, and a comprehensive external quality assessment (EQA) programme should be implemented that includes on-site evaluation, random blinded rechecking, and panel testing. Of the 140 countries and territories that reported data on the number of smear microscopy centres undergoing EQA in 2013, only 34% indicated the existence of a scheme that covered all centres in the country, with a further 16% covering at least 90% of centres. Among the 22 HBCs, only four reported a scheme that encompassed all centres in 2014 (Bangladesh, India, Uganda and Zimbabwe) and five more reported a programme that included at least 90% of centres (Cambodia, China, Pakistan, South Africa and Viet Nam).

Quality-assured DST is critical to ensure accurate detection of drug resistance to inform treatment decisions and to avoid false diagnoses. Of the high TB and MDR-TB burden countries that reported on EQA coverage of DST laboratories in 2014 (34 of 36), 24 (71%) reported having a scheme that encompassed all DST laboratories. Of the 116 reporting countries globally, 78 (67%) indicated a scheme that encompassed all laboratories. Ensuring quality needs to be a priority for all levels of a laboratory network.

As a key partner in strengthening the capacity and quality of TB laboratories globally, the WHO TB Supranational Reference Laboratory (SRL) Network comprises 36 laboratories that provide long-term technical assistance to low- and middle-income countries under the framework of collaborative agreements. The network was formed in 1994 to ensure the quality of drug resistance surveys, but today SRLs provide a wide range of technical assistance services, including training, on-site supervisory missions, guidance to the development of national laboratory strategic plans, and proficiency testing. 156 countries and territories reported having a formal link with a partner SRL in 2014.

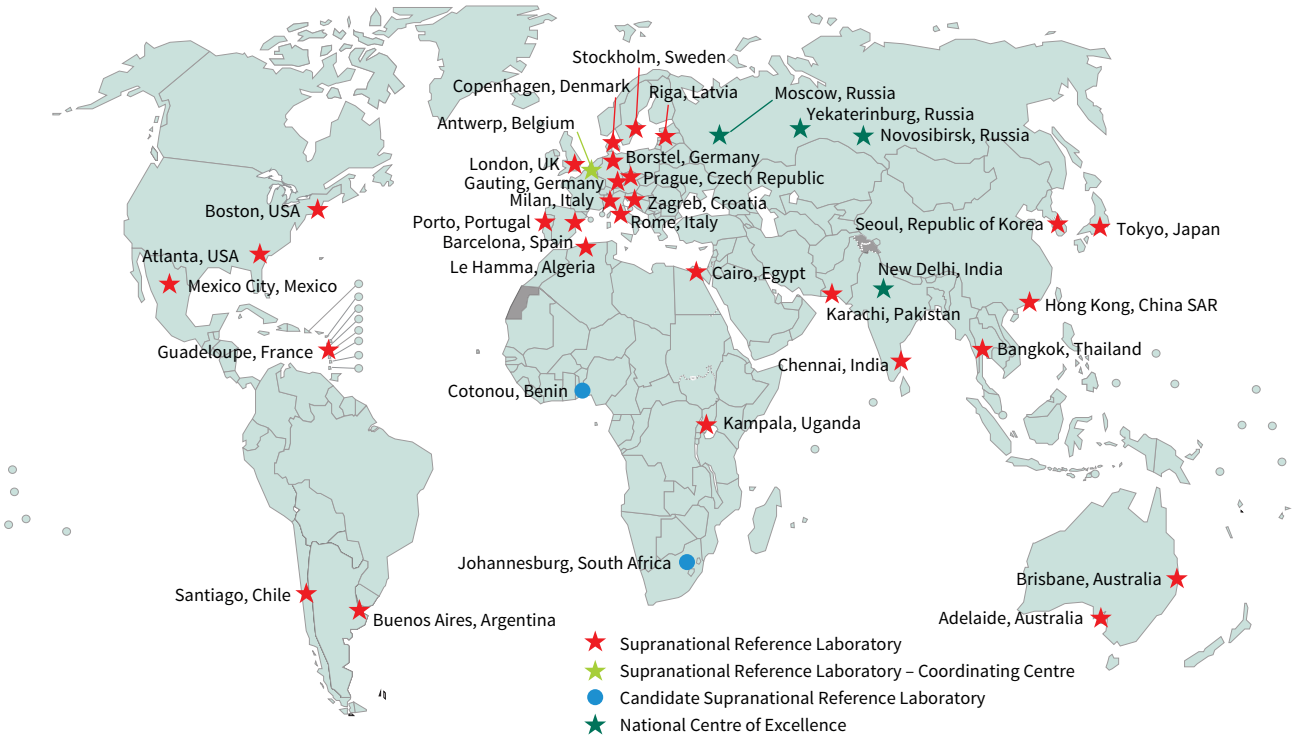
The SRL Network also includes 'National Centres of Excellence' (SRL-CEs), which are well-performing national and regional TB reference laboratories in large, middle-income countries. These SRL-CEs have similar terms of reference (and national status) to that of an SRL but with an in-country focus for its laboratory strengthening activities. To meet its objectives, a SRL-CE commits to provide minimum service requirements including establishing formal links with at least two intermediate level laboratories within the country and undertaking at least one annual technical assistance visit to each laboratory. A SRL-CE needs to be nominated by its NTP to the WHO country office, establish a collaborative agreement with an existing SRL, undergo a laboratory assessment by WHO, and actively implement a quality management system towards accreditation.

In 2014, the Ministry of Health of the Russian Federation nominated TB laboratories of three Federal Institutes to undergo evaluations to assess their suitability for designation as SRL-CEs: Central Tuberculosis Research Institute, Moscow; Novosibirsk Tuberculosis Research Institute, Novosibirsk; and Ural Research Institute for Phthisiopulmonology, Yekaterinburg. Following assessment missions, all three of the laboratories were recognized as performing well, with high-quality infrastructure and a high calibre of suitably-qualified technical staff. They were all subsequently designated as SRL-CEs in April 2015. These laboratories have a particular value for establishing and maintaining high-quality laboratory services within the country for the

[1] http://gliquality.org

FIGURE 5.3

The WHO TB Supranational Reference Laboratory Network



programmatic management of drug-resistant TB, including through the coordination of technical assistance, provision of monitoring and supervision, and organization of trainings to laboratory staff involved in diagnostic testing for drug resistance and monitoring of treatment for patients with drug-resistant TB.

The SRL network as of July 2015 is shown in **Figure 5.3**.

CHAPTER 6

Addressing the co-epidemics of TB and HIV

Key facts and messages

In 2014, an estimated 1.2 million (12%) of the 9.6 million people who developed TB worldwide were HIV-positive. The African Region accounted for 74% of the estimated number of HIV-positive incident TB cases.

The number of people dying from HIV-associated TB peaked at 570 000 in 2004 and has since fallen to 390 000 in 2014 (a reduction of 32%). In 2014, HIV-associated TB deaths accounted for 25% of all TB deaths (among HIV-negative and HIV-positive people) and one third of the estimated 1.2 million deaths from HIV/AIDS.

In 2004, WHO recommended the implementation of 12 collaborative TB/HIV activities. Between 2005 and 2014, an estimated 5.8 million lives were saved by TB/HIV interventions.

Globally, 51% of notified TB patients had a documented HIV test result in 2014, a small increase from 49% in 2013. The figure was highest in the African Region, at 79%, and ≥90% in 18 of the 41 high TB/HIV burden countries.

The prevalence of HIV co-infection among TB patients is highest in the African Region. Of the 1.1 million TB patients with known HIV status in 44 countries, 39% were HIV-positive in 2014, a slight decline compared with 41% in 2013. The proportion of TB patients who were known to be HIV-positive in the African Region ranged from 6% in Eritrea to 73% in Swaziland.

In 2014, coverage of antiretroviral therapy (ART) for notified TB patients who were known to be co-infected with HIV reached 77% globally. Further efforts are needed to reach the target of 100%. This is especially the case given that the number of HIV-positive TB patients on ART in 2014 represented only 33% of the estimated number of people living with HIV who developed TB in 2014.

Coverage of co-trimoxazole preventive therapy (CPT) among HIV-positive TB patients remains high, and increased slightly to 87% globally and 89% in the African Region in 2014.

The number of people living with HIV who were treated with isoniazid preventive therapy (IPT) reached 933 000 in 2014, an increase of about 60% compared with 2013. However, provision of IPT was reported by just 23% of countries globally, including only 13 of the 41 high TB/HIV burden countries. As in previous years, a large proportion of the people living with HIV who were initiated on IPT were in South Africa (59%), although in most countries that reported data in 2013 and 2014, coverage levels grew.

Preventing TB deaths among HIV-positive people requires intensified scale-up of TB prevention, diagnosis and treatment interventions, including earlier initiation of ART among people living with HIV and those with HIV-associated TB. Increased efforts in joint TB and HIV programming could facilitate further scale-up and consolidation of collaborative TB/HIV activities.

Globally, people living with HIV are 26 times more likely to develop TB disease than those who are HIV-negative.[1] Beginning in the 1980s, the HIV epidemic led to a major upsurge in TB cases and TB mortality in many countries, especially in southern and eastern Africa (**Chapter 2**).

In 2014, 1.2 million (12%) of the 9.6 million people who developed TB worldwide were HIV-positive (**Chapter 2**, **Table 2.1**); 74% of these HIV-positive TB cases were in the African Region. The number of people dying from HIV-associated TB peaked at 570 000 in 2004 and has since fallen to 390 000 in 2014 (a reduction of 32%).[2] However, this still represents an enormous burden of preventable deaths and ill-health. In 2014, TB deaths among HIV-positive people accounted for 25% of all TB deaths (among HIV-negative and HIV-positive people) and one third of the estimated 1.2 million deaths from HIV/AIDS.[3] Current trends indicate that the target set by WHO, UNAIDS and the Stop TB Partnership to halve the number of HIV-associated TB deaths by 2015 (compared with 2004) will not be met globally (**Chapter 2**).[4]

WHO recommendations on the interventions needed to

[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 mean estimated global IRR (all ages) in 2014 was 26 (range 24–28). However, there is considerable variation among countries: in 2014, the median IRR was 23 (interquartile range 14-36). Further details are provided in the **online technical appendix**.

[2] Estimates of the total burden of TB disease and of the number of TB cases and deaths among HIV-positive people are updated annually by WHO. For further details, see **Chapter 2** and the online technical appendix (www.who.who.int/data).

[3] http://www.unaids.org/en/resources/documents/2015/HIV_estimates_with_uncertainty_bounds_1990-2014

[4] Of the 41 countries with the highest burden of HIV associated TB, 17 are estimated to have met the target by the end of 2014.

prevent TB in HIV-positive people and to reduce the impact of HIV among TB patients were first issued in 2004, and are collectively known as collaborative TB/HIV activities.[1] They include: establishing and strengthening coordination mechanisms for delivering integrated TB and HIV services; HIV testing for all TB patients as well as people with TB signs or symptoms; providing antiretroviral therapy (ART) and cotrimoxazole preventive therapy (CPT) to all HIV-positive TB patients; 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 preventing the transmission of TB infection in health care and congregate settings. The latter three activities are referred to as the *Three 'Is' for HIV/TB* and, together with earlier ART, are the principal interventions for preventing TB among people living with HIV. Between 2005 and 2014, TB/HIV interventions saved an estimated 5.8 million lives.[2]

In addition, use of the rapid molecular test, Xpert MTB/RIF and early ART among HIV positive TB patients are increasingly considered critical components of collaborative TB/HIV activities. WHO recommends the use of Xpert MTB/RIF as the primary diagnostic test for TB among people living with HIV who have TB signs and symptoms, and ART for all HIV-positive TB patients within the first eight weeks of starting TB treatment (irrespective of their CD4 cell count). Early initiation of ART (within two weeks of starting TB treatment) is also important, particularly for TB patients with profound immunosuppression (e.g. CD4 cell count less than 50) among whom it has been shown to significantly improve survival.

WHO began monitoring the implementation of collaborative TB/HIV activities in 2004. This chapter presents the latest status of progress, using data for each year from 2004 through 2014.

6.1 HIV testing and documentation of HIV status among TB patients

WHO recommends that routine HIV testing should be offered to all TB patients, to all those with TB signs and symptoms, and to partners of known HIV-positive TB patients.[3] In the WHO online data collection system, data are reported for TB patients only.

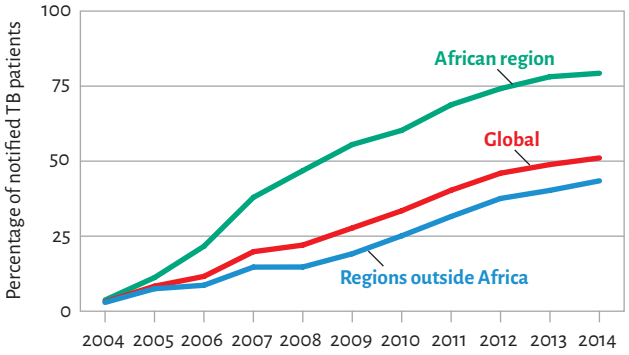
In 2014, 3.2 million notified TB patients had a documented HIV test result, equivalent to 51% of notified TB cases (**Table 6.1**, **Figure 6.1**). This represented an increase from 3 million and 49% respectively in 2013, and more than 17 times the coverage reported in 2004 (Figure 6.1). There were 89 countries in which ≥75% of TB patients had a documented HIV test result in 2014 (**Figure 6.2**); this was unchanged from 2013.

Overall, among the 41 countries identified as priorities for the global TB/HIV response (listed in **Table 6.1**), 60% of notified TB patients had a documented HIV test result in 2014, up from 58% in 2013. There has been a steady increase in these 41 countries since 2007. However, levels of coverage vary significantly, ranging from 5% in Indonesia to 99% in Rwanda in 2014.[4] Eighteen of the 41 countries reported that ≥90% of TB patients knew their HIV status in 2014, of which five (Botswana, Kenya, Mozambique, Rwanda and Swaziland) have managed to maintain this level since 2011. A further 14 countries (Burkina Faso, Cambodia, Cameroon, Côte d'Ivoire, Lesotho, Malawi, Namibia, Nigeria, South Africa, Togo, Uganda, Tanzania, Zambia and Zimbabwe) have reported that ≥80% TB patients know their HIV status since 2011. In seven high TB/HIV burden countries, the percentage of TB patients who know their HIV status has remained persistently low, at under 50% since 2011: China, Congo, the Democratic Republic of the Congo, Indonesia, Mali, Myanmar and Sudan.[5]

The percentage of TB patients with known HIV status remains highest in the African Region, where it continues to increase and reached 79% in 2014, up from 78% in 2013 (**Table 6.1**, **Figure 6.1**). Of the 47 African countries, 30 countries reported ≥75% of TB patients had a documented HIV test result in 2014, and 23 achieved levels of ≥90% (**Figure 6.2**).

FIGURE 6.1

Percentage of notified TB patients with known HIV status, 2004–2014



[1] An update was issued in 2012. See *WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders*. Geneva, World Health Organization, 2012 (WHO/ HTM/TB/2012.1). Available at http://whqlibdoc.who.int/publications/2012/9789241503006_eng.pdf

[2] Estimates of lives saved by TB and HIV interventions are covered in more detail in **Chapter 2**.

[3] *WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders*. Geneva: World Health Organization; 2012 (WHO/ HTM/TB/2012.1). Available at http://whqlibdoc.who.int/publications/2012/9789241503006_eng.pdf

[4] In India, the national figure fell slightly between 2013 and 2014, from 63% to 61%. This reflects a large increase in notifications (see **Chapter 3**, **Box 3.2**) from the private sector (included in the denominator), without a corresponding increase in reporting related to HIV testing. When analysis is restricted to units that reported data in both 2013 and 2014, the percentage of TB patients who knew their HIV status rose from 63% to 72%.

[5] The reported figure is also relatively low for the Russian Federation. However, this is because the denominator available for calculations is the total number of new and relapse cases that were notified while the numerator available for calculations includes only new TB patients in the civilian sector. In practice, testing coverage is estimated to be close to 100% in the Russian Federation.

TABLE 6.1

HIV testing for TB patients, treatment for HIV-positive TB patients and prevention of TB among people living with HIV, 41 high TB/HIV burden countries and WHO regions, 2014. Numbers in thousands except where indicated.

	ESTIMATED HIV-POSTIVE INCIDENT TB CASES[a]		NUMBER OF NOTIFIED TB PATIENTS WITH KNOWN HIV STATUS	% OF NOTIFIED TB PATIENTS WITH KNOWN HIV STATUS	% OF TB PATIENTS WITH AN HIV TEST RESULT WHO WERE HIV-POSITIVE	% OF NOTIFIED HIV-POSITIVE TB PATIENTS STARTED ON ART	NUMBER OF HIV-POSTIVE TB PATIENTS ON ART AS % OF ESTIMATED HIV-POSITIVE INCIDENT TB CASES[b]	NUMBER OF HIV-POSITIVE PEOPLE PROVIDED WITH IPT	% OF PEOPLE NEWLY ENROLLED IN HIV CARE WHO WERE NOTIFIED AS A TB CASE THE SAME YEAR
Angola	23	14–34	28	50	10	–	–		–
Botswana	4.5	4.1–5.0	5.5	91	60	78	57		–
Brazil	16	14–17	57	70	17	–	–		–
Burkina Faso	1.2	1.0–1.3	5.6	96	12	86	47		9.8
Burundi	1.9	1.6–2.1	6.7	91	14	68	32		–
Cambodia	1.8	1.6–2.0	36	81	2.7	98	52	0.9	19
Cameroon	20	17–23	23	87	37	70	30		–
Central African Republic	7.6	5.9–9.4	5.2	51	34	–	–		–
Chad	6.0	4.7–7.4	6.6	54	19	56	12		–
China	13	11–16	344	42	1.5	69	28		2.9
Congo	5.5	4.3–6.9	1.3	13	29	24	1.7		–
Côte d'Ivoire	8.5	7.5–9.6	22	93	24	21	13		3.2
Djibouti	0.54	0.44–0.65	1.9	84	8.5	68	20		–
DR Congo	34	27–42	53	46	14	67	14		4.4
Ethiopia[c]	19	15–23	89	75	9.7	39	18	10	22
Ghana	11	5.2–19	12	77	24	39	10		–
Haiti	3.7	3.2–4.3	14	88	19	54	38	22	–
India	110	96–120	1 035	61	4.3	90	36		3.1
Indonesia	63	41–90	15	4.6	16	26	1.0		–
Kenya	40	38–42	84	95	36	87	65		–
Lesotho	12	8.5–16	9.1	93	72	74	41		–
Malawi	19	10–31	16	93	54	92	43	135	1.5
Mali	0.71	0.64–0.78	2.6	43	14	100	52		–
Mozambique	85	65–110	56	96	52	81	28	94	–
Myanmar	19	15–24	56	40	11	90	30	3.0	8.5
Namibia	5.6	4.8–6.5	9.1	92	44	84	60		–
Nigeria	100	59–160	84	92	19	75	12	26	–
Russian Federation	5.5	4.5–6.6	67[d]	–	–	–	–		38
Rwanda	1.8	1.5–2.1	5.9	99	25	87	72		–
Sierra Leone	2.3	1.7–3.0	11	87	12	68	39	1.3	8.8
South Africa	270	240–310	295	93	61	79	53	552	10
Sudan	1.2	0.65–2.0	5.5	27	6.0	45	12		18
Swaziland	5.9	4.2–7.9	5.4	97	73	79	53	1.2	–
Thailand	15	7.8–24	51	71	13	69	31		–
Togo	0.83	0.67–1.0	2.5	97	21	76	48		–
Uganda	28	24–32	44	95	45	81	57		–
Ukraine	8.1	7.0–9.3	39	97	20	56	53	16	–
UR Tanzania	62	29–110	58	91	35	83	27	23	12
Viet Nam	7.0	5.7–8.5	74	73	5.2	73	40		–
Zambia	38	25–52	40	93	61	73	46		–
Zimbabwe	25	17–35	29	89	68	86	66	30	15
High TB/HIV burden countries	**1 100**	**1 000–1 200**	**2 804**	**60**	**18**	**78**	**34**	**916**	**9.0**
AFR	870	790–950	1 064	79	39	77	37	876	9.1
AMR	36	34–38	169	74	13	63	20	29	8.4
EMR	12	10–15	68	15	2.4	63	7.9	0.5	20
EUR	20	18–21	200	62	8.2	58	31	21	32
SEAR	210	180–240	1 171	45	5.1	85	24	3.0	3.7
WPR	31	28–35	552	40	2.3	68	27	3.7	3.9
Global	**1 200**	**1 100–1 300**	**3 224**	**51**	**16**	**77**	**33**	**933**	**8.9**

Blank cells indicate data not reported.

– indicates values that cannot be calculated.

[a] Best estimates are followed by the lower and upper bounds of the 95% uncertainty interval.

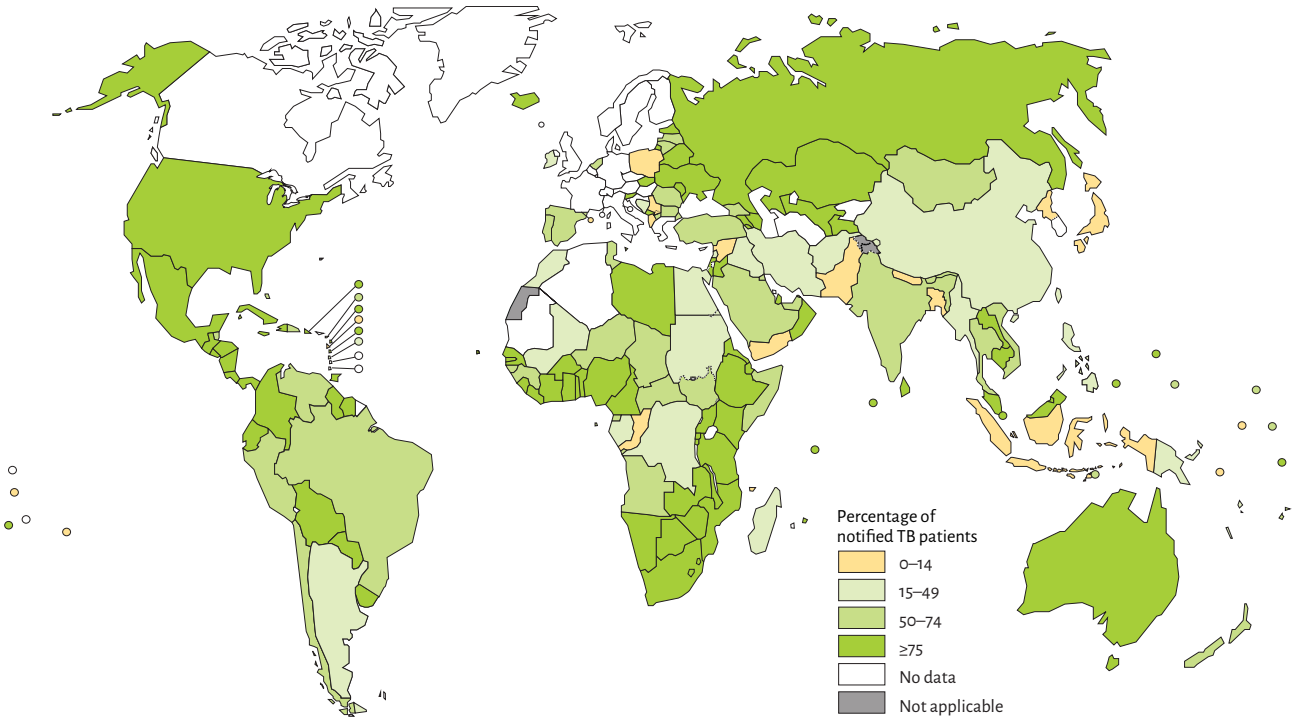
[b] The numerator (i.e. all notified HIV-positive TB cases on ART) includes all notified new, relapse and non-relapse retreatment cases. The denominator (i.e. estimated HIV-positive incident TB cases) includes new and relapse cases only.

[c] In 2014, ART and IPT data were missing for 3 of Ethiopia's 11 regions, which in previous years had accounted for about one third of the national totals. In the 8 regions that reported data, 65% of HIV-positive TB patients were on ART.

[d] Data for the Russian Federation are for new TB patients in the civilian sector only.

FIGURE 6.2

Percentage of notified TB patients with known HIV status by country, 2014[a]



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

In the Region of the Americas and the European Region, there were small improvements between 2013 and 2014: from 72% to 74% and from 59% to 62% respectively.[1] Larger increases were evident in some countries in the Americas, notably Bolivia (70% to 77%), Chile (35% to 50%), Colombia (74% to 80%), Guatemala (80% to 86%), Mexico (77% to 85%), Nicaragua (69% to 77%) and Peru (66% to 74%).

In the other three WHO regions in which concentrated HIV epidemics are the norm, the percentage of TB patients with known HIV status has remained low (15%–45%). Impressive gains were made in three countries, however: Myanmar (from 12% to 40%), Sri Lanka (from 49% to 78%) and the Philippines (from 2% to 20%). In Cambodia, 81% of TB patients knew their HIV status in 2014, similar to the level achieved in 2013. It should also be noted that in China, 91% of TB patients knew their HIV status in the counties defined as having a high TB/HIV burden, much higher than the national average of 42%.

In some countries with concentrated epidemics, the programmatic feasibility and value of testing all TB patients for HIV has been questioned, especially in settings where both access to HIV treatment and funding are limited. At the same time, HIV testing for TB patients is a basic standard of care and provides a pathway to HIV treatment and prevention services. National programmes should aim to ensure that the benefits of HIV testing are available to TB patients, their partners, families and the community at large, in the context of their specific programmatic settings.[2]

6.2 Levels of HIV infection among TB patients with HIV test results

Globally, 16% of TB patients with an HIV test result were HIV-positive (Table 6.1). The figure was 18% among the 41 high TB/HIV burden countries that accounted for more than 94% of estimated HIV-positive incident TB cases in 2014. Overall, the percentage of TB patients testing HIV-positive has been falling globally since 2008 (**Figure 6.3**).

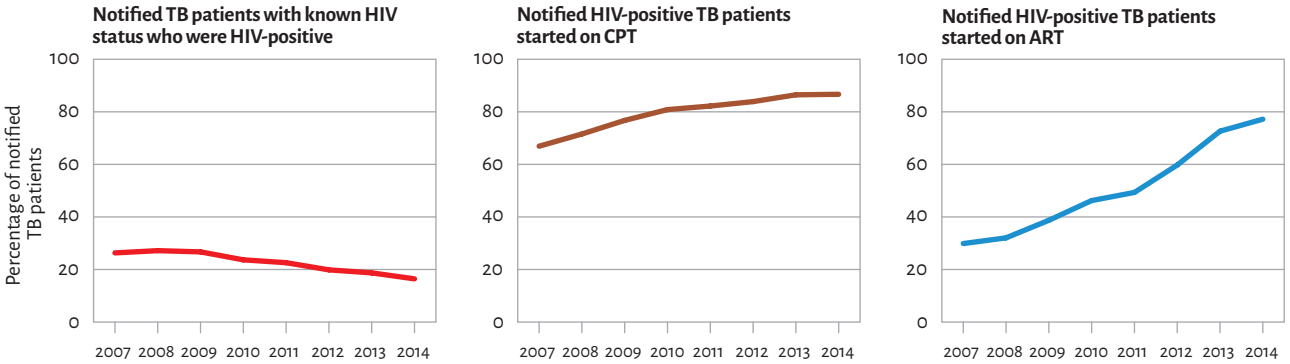
The highest rates of HIV co-infection were reported for TB patients in the African Region (Table 6.1), where 39% of those with an HIV test result were HIV-positive (compared with 41% in 2013). The percentage of TB patients found to be HIV-positive in the 28 African countries in the list of 41 high TB/HIV burden countries ranged from about 10% in Angola and Ethiopia to more than 70% in Lesotho and Swaziland. In all other regions, the percentage of TB patients with a documented HIV test result who were HIV-positive was much lower.

[1] Figures for the European Region are an underestimate, due to under-estimation of testing coverage for the Russian Federation.

[2] *WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders*. Geneva: World Health Organization; 2012 (WHO/ HTM/TB/2012.1). Available at http://whqlibdoc.who.int/publications/2012/9789241503006_eng.pdf

FIGURE 6.3

Percentage of notified TB patients with known HIV status who were HIV-positive, and percentage of notified HIV-positive TB patients enrolled on co-trimoxazole preventive therapy (CPT) and antiretroviral therapy (ART), 2007–2014



Globally, a total of 528 000 HIV-positive TB patients were reported by NTPs in 2014. This represented less than 50% of the 1.2 million HIV-positive people estimated to have developed TB in the same year (**Figure 6.4**), although there was considerable variation among regions. The proportion was highest in the European Region (81%), followed by the Region of the Americas (60%) and the African Region (50%), and much lower in the Eastern Mediterranean, South-East Asia and Western Pacific Regions (13%, 29% and 39%, respectively).

6.3 Antiretroviral therapy and co-trimoxazole preventive therapy for HIV-positive TB patients

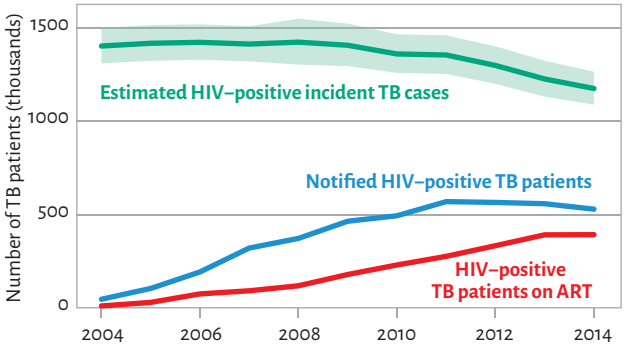
6.3.1 Antiretroviral therapy

ART is an intervention that can have an important impact on TB morbidity and mortality among HIV-positive TB patients. The number of notified HIV-positive TB patients on ART has grown from a very low level in 2004 (**Figure 6.4**) to reach 392 000 in 2014. Among HIV-positive TB patients notified by NTPs in 2014,[1] 77% were on ART globally (**Table 6.1**, **Figure 6.3**), a further improvement compared with 73% in 2013.

In the African Region in 2014, 77% of HIV-positive TB patients reported by NTPs were started on ART (up from 72% in 2013). ART coverage increased in 28 of the 41 high TB/HIV burden countries between 2013 and 2014 (data not shown). Among the top-ten high TB/HIV burden countries, the biggest increases between 2013 and 2014 were in the Democratic Republic of the Congo (48% to 67%), Mozambique (72% to 81%), the United Republic of Tanzania (73% to 83%), Nigeria (67% to 75%) and South Africa (72% to 79%). Five other countries reported increments of more than 10%: Cambodia, Djibouti, Mali, Myanmar and Viet Nam. Six of the 41 high TB/HIV burden countries have not yet reached levels of 50%: Sudan, Ethiopia, Ghana, Indonesia, Congo and Côte d'Ivoire. In these countries, concerted efforts are needed to improve coverage.

FIGURE 6.4

ART enrolment among HIV-positive TB patients compared with the reported number of HIV-positive TB patients and the estimated number of HIV-positive people who developed TB,[a] 2004–2014



[a] Notified HIV-positive TB patients on ART includes new and relapse TB cases plus prevalent TB cases re-registered for treatment change (e.g. after treatment failure). Estimated HIV-positive incident TB cases includes only new and relapse TB cases.

Early initiation of ART is important to reduce mortality. WHO recommends that ART should be initiated as soon as possible after TB treatment is started, and within the first two to eight weeks of treatment. WHO also encourages programmes to establish mechanisms to monitor the timeliness of ART through national data collection systems, and has provided guidance about how to do this.[2] A recent example from India is highlighted in **Box 6.1**.

Despite overall progress in ART coverage, there is a sub-

[1] 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".

[2] World Health Organization. *WHO guide to monitoring and evaluation of collaborative TB/HIV activities*. Geneva: World Health Organization; 2015. Available at http://www.who.int/tb/publications/monitoring-evaluation-collaborative-tb-hiv/en/

Box 6.1 Monitoring when ART is initiated for HIV-positive TB patients: an example from India

In October–November 2014, data from 70 facilities in India where ART is provided were extracted from a system designed to capture early warning indicators related to the development of drug resistance and the quality of care. This was done by the National AIDS Control Organization and WHO India. Of the 9468 people living with HIV who had been enrolled in HIV care, 1871 (19%) developed TB within two years (**Table B6.1.1**). Data on the timing of initiation on ART were analysed for these individuals.

TABLE B6.1.1

Initiation on ART for HIV-positive TB patients in 62 facilities in India, October–November 2014

STUDY COHORT (ADULTS, N=9468)	NUMBER
Patients diagnosed with TB	1871
Patients already on ART at the time of TB diagnosis	362
Time between start of TB treatment and ART initiation, for the 1429 HIV-positive TB patients who were not already on ART	
<2 weeks	200 (14%, 95% CI: 12–16%)
2–8 weeks	933 (65%, 95% CI: 63–68%)
>8 weeks	296 (21%, 95% CI: 19–23%)
Median	23 days

The median time between the start of TB treatment and ART was 23 days. About 80% of HIV-positive TB patients were started on ART within eight weeks of TB diagnosis, in line with WHO recommendations.

stantial gap between the number of HIV-positive TB patients started on ART, and the estimated total number of HIV-positive people with TB who are in need of both TB treatment and ART. The global number of HIV-positive TB patients reported to be started on ART by NTPs in 2014 represented only 33% of the estimated 1.2 million HIV-positive people who developed TB in the same year (**Table 6.1**, **Figure 6.4**). The ratio of patients started on ART in 2014 to the estimated number of HIV-positive people who developed TB in 2014 was above 50% in only 14 of the 41 high TB/HIV burden countries: Botswana, Burkina Faso, Cambodia, Kenya, Malawi, Mali, Namibia, Rwanda, South Africa, Swaziland, Uganda, Ukraine, the United Republic of Tanzania and Zambia (**Figure 6.5**). While this is an improvement from only eight countries in 2013, much remains to be done to improve the detection of TB among HIV-positive people, the coverage of HIV testing among TB patients, and enrolment of HIV-positive TB patients on ART.

These statistics about ART coverage among all estimated HIV-positive TB cases can also be compared with the level of ART coverage among all people living with HIV. Globally, over 15 million people were on ART as of 31 March 2015.[1] By the end of 2014, 40% (uncertainty interval, 37%–45%) of the estimated number of people living with HIV were receiving ART. This is more than the estimated level of 35% for HIV-positive people who have TB, but also far from universal coverage. Major efforts are urgently required to improve access and narrow these gaps. The UNAIDS 90-90-90 fast track treatment targets (by 2020, 90% of people living with HIV know their status, 90% of those who know their status are on ART, and 90% of those on ART have a suppressed viral load) provide a platform for doing this.[2]

6.3.2 Co-trimoxazole preventive therapy

Globally, 427 000 HIV-positive TB patients were enrolled on CPT in 2014, representing 87% of all notified HIV-positive TB patients, similar to levels achieved in 2013 (**Table 6.1**, **Figure 6.3**). The African and South-East Asia regions maintained their particularly high levels of enrolment on CPT from 2013, at 89% and 85% respectively (**Table 6.1**). Of the 34 high TB/HIV burden countries (out of a total of 41) that reported data, only four reported that less than 50% of HIV-positive TB patients were enrolled on CPT in 2014: Côte d'Ivoire (24%), Congo (27%), Indonesia (41%) and Ukraine (44%).

6.4 Intensified TB case-finding and initiation of isoniazid preventive therapy among people living with HIV

The high proportion of people with undiagnosed TB found in autopsy studies of HIV-positive people[3,4,5] shows that substantial efforts are needed to ensure effective TB screening among people living with HIV, so that TB is promptly diagnosed and treated and so that those without active TB disease are provided with IPT as well as ART. ART reduces the individual risk of TB disease among people living with HIV by 65%,[6] irrespective of CD4 cell count. Its impact is further enhanced when IPT is also provided. Recently, IPT for six

1 *How AIDS changed everything – MDG 6. 15 years, 15 lessons of hope from the AIDS response*. Geneva: UNAIDS; 2015. Available at: http://www.unaids.org/en/resources/documents/2015/MDG6_15years-15lessonsfromtheAIDSresponse

2 *Understanding Fast-Track*. Geneva: UNAIDS; 2015. Available at http://www.unaids.org/sites/default/files/media_asset/201506_JC2743_Understanding_FastTrack_en.pdf)

3 Cox JA et.al. An autopsy study describing causes of death and comparing clinico-pathological findings among hospitalized patients in Kampala, Uganda; *Plos One*, 2012;7(3):e33685. doi: 10.1371/journal.pone.0033685. Epub 2012 Mar 14.

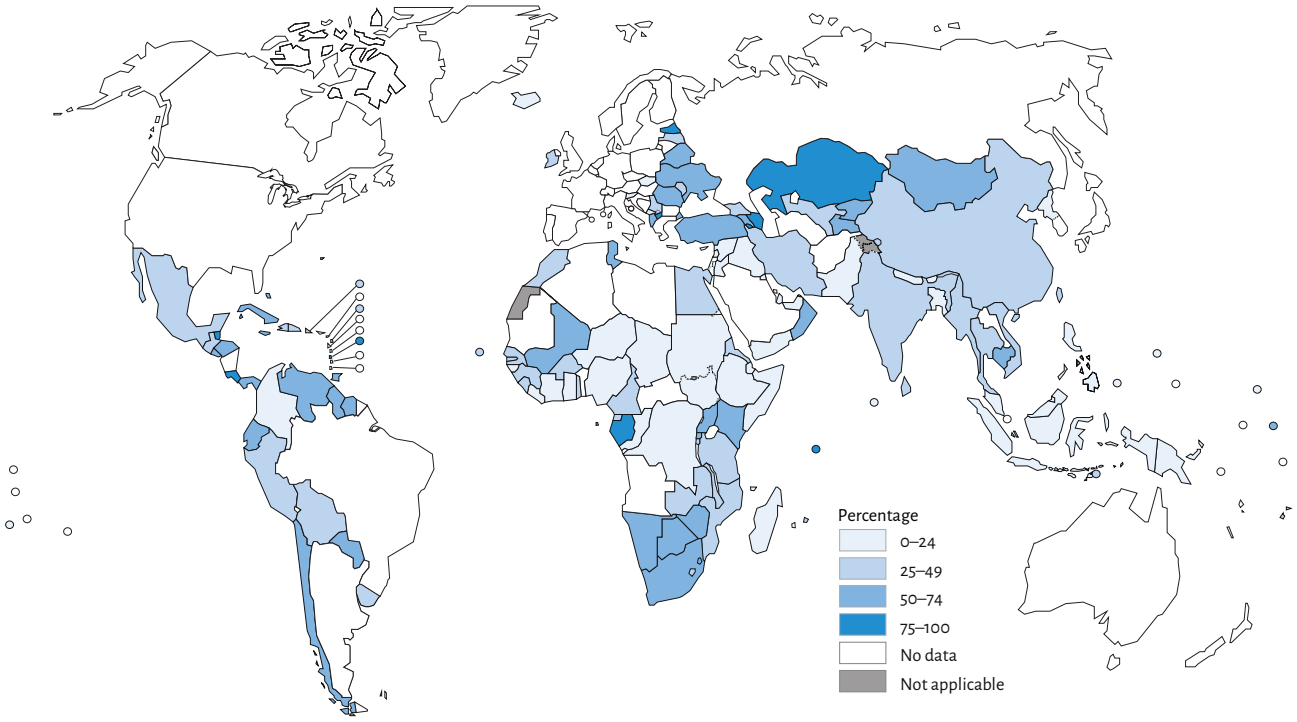
4 Wong EB et.al. Causes of death on antiretroviral therapy: a post-mortem study from South Africa; *Plos One* 2012;7(10):e47542. doi: 10.1371/journal.pone.0047542. Epub 2012 Oct 16.

5 Kilale AM et.al. High prevalence of tuberculosis diagnosed during autopsy examination at Muhimbili National Hospital in Dar es Salaam, Tanzania; *Tanzania Journal of Health Research* 2013; 15.

6 Suthar AB et al. Antiretroviral therapy for prevention of tuberculosis in adults with HIV: a systematic review and meta-analysis. *PLoS Med* 2012, 9(7): e1001270. doi:10.1371/journal.pmed.1001270).

FIGURE 6.5

Number of HIV-positive TB patients on ART as a percentage of estimated HIV-positive incident TB cases, 2014[a]



[a] The numerator (i.e. all notified HIV-positive TB cases on ART) includes all notified new, relapse and non-relapse retreatment cases. The denominator (i.e. estimated HIV-positive incident TB cases) includes new and relapse cases only.

months combined with ART for people with CD4 counts of >500 cells/mm³ was found to reduce the risk of severe HIV-related illness by 44% and the risk of death from any cause by 35%.[1]

6.4.1 Intensified case-finding

Systematic screening for TB among people living with HIV is recommended by WHO as an essential component of the HIV package of care, along with ART, IPT and infection control. It is the first essential step before both IPT initiation and TB diagnosis. In 2014, 78 countries reported about seven million people enrolled in HIV care who were screened for TB, up from 5.5 million in 64 countries in 2013.

Being screened for TB does not necessarily guarantee completion of the TB diagnostic pathway. As part of efforts to improve the utility of TB screening, WHO encourages monitoring of the full cascade of intensified TB case finding, including: 1) identification of TB in those who screened positive for TB symptoms; and 2) documentation of what TB investigations were done to diagnose or rule out TB disease.

In December 2010, the rapid molecular test Xpert MTB/RIF was endorsed by WHO with a strong recommendation for its use as the initial diagnostic test for TB in two groups: people living with HIV with TB signs and symptoms, and people at high risk of having MDR-TB (**Chapter 5**). This was reiterated in the 2013 update to WHO policy recommendations on the use of Xpert MTB/RIF,[2] and in the 2014 Xpert MTB/RIF implementation manual in which it is recommended that people living with HIV should be prioritized for testing with Xpert MTB/RIF when resources are limited.[3]

Discussions at a Global Forum of Xpert MTB/RIF implementers held in 2014 indicated that a major motivation for the roll-out of Xpert MTB/RIF was often the national response to multidrug-resistant TB (MDR-TB),[4] rather than diagnosis of TB among people living with HIV. To maximize the detection of TB cases among HIV-positive people, Xpert MTB/RIF needs to be widely implemented in settings where HIV care is provided, using all available funding sources. Early detection of TB in HIV care settings can in turn help to

[1] The TEMPRANO ANRS 12136 Study Group; A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *The New England Journal of Medicine* 2015; DOI:10. 1056/NEJMoa1507198.

[2] *Policy update: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children*. Geneva: World Health Organization; 2013 (WHO/HTM/TB/2013.16). Available at: http://who.int/tb/laboratory/xpert_policyupdate/en/

[3] *Xpert MTB/RIF implementation manual: technical and operational 'how-to'; practical considerations*. Geneva: World Health Organization; 2014 (WHO/HTM/TB/2014.1). Available at: http://who.int/tb/publications/xpert_implem_manual/en/

[4] *Meeting Report of the Xpert MTB/RIF Implementers Global Forum, 1–2 May 2014*. Geneva: World Health Organization; 2014. Available at: http://www.stoptb.org/wg/gli/assets/documents/Xpert%20Implementers%20Global%20Forum%20meeting%20report.pdf.

Box 6.2 The use of Xpert MTB/RIF in diagnosis of TB among people living with HIV

Data on national policies for using Xpert MTB/RIF as the initial diagnostic test for TB among people living with HIV were collected as part of the 2015 round of global TB data collection. Additional data were requested from 15 countries with the highest TB/HIV burden, of which nine responded: Ethiopia, India, Indonesia, Lesotho, Myanmar, South Africa, Uganda, the United Republic of Tanzania and Zimbabwe.

Of the 41 high TB/HIV burden countries, 33 (80%) had a national policy on the use of Xpert MTB/RIF by the end of 2014. The eight countries that did not report having such a policy in place were Central African Republic, Chad, China, Côte d'Ivoire, Myanmar, Namibia, Sierra Leone and Sudan.

Of the nine countries that responded to the more detailed survey, all except Myanmar reported a policy that recommended Xpert MTB/RIF as the initial diagnostic test for TB among people living with HIV. A nationally standardized TB diagnostic algorithm for people living with HIV that included Xpert MTB/RIF was also reported in these eight countries. Typically, Xpert MTB/RIF testing was restricted to secondary and tertiary level health care facilities. Exceptions were Ethiopia and South Africa, which reported availability at all levels including at primary health care facilities.

In general, routine documentation and reporting of Xpert MTB/RIF test results among people living with HIV was stated to be a major challenge, reflecting the fact that national registers and reporting systems do not capture such data.

To improve testing for TB among people living with HIV and ensure that progress can be monitored, wider adoption of the WHO recommendation to use Xpert/MTB RIF as the initial diagnostic test and updating of national monitoring and evaluation systems that will allow systematic recording and reporting are required.[a] The use of Xpert MTB/RIF by HIV service providers, including in peripheral facilities, also needs to be promoted.

[a] A guide to monitoring and evaluation for collaborative TB/HIV activities. Geneva: World Health Organization; 2015 (WHO/HTM/TB/2015.02). Available at: http://www.who.int/tb/publications/m_and_e_document_page/en/

ensure prompt initiation of ART. Recent analysis suggests that there has been progress in adopting the WHO recommendation to use Xpert MTB/RIF as the initial diagnostic test for TB among people living with HIV, but that more remains to be done (**Box 6.2**).

In 2014, 76 countries reported data about the number of notified TB cases among those newly enrolled in HIV care to UNAIDS (up from 59 countries in 2013). Unfortunately, there were data quality problems for eight of these countries. Among the remaining 68 countries, 9% (211 000/2 304 000) of those newly enrolled in HIV care in 2014 were also notified with TB in the same year. Among the 41 high TB/HIV burden countries, the proportion ranged from 2–3% in China, Côte d'Ivoire, India and Malawi to 38% in the Russian Federation (**Table 6.1**). Ensuring good quality data and monitoring trends in this indicator are important to track the impact of HIV care, especially ART, on the burden of TB in people living with HIV.

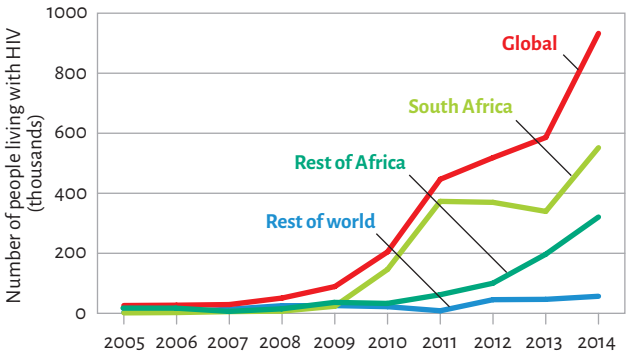
6.4.2 Initiation on isoniazid preventive therapy

A total of 49 countries (representing more than 60% of the estimated global burden of HIV-associated TB) reported initiating people living with HIV on IPT. The total number was 933 000 people in 2014, an increase from just over 600 000 people in 2013 (**Figure 6.6**). Thirteen of the 41 high TB/HIV burden countries reported provision of IPT in 2014, and coverage among people living with HIV who were newly enrolled in care was 41%. Coverage ranged from 5% in Swaziland to 97% in Haiti.

As in previous years, South Africa accounted for a high proportion (59%) of the global total in 2014: 552 000 HIV-

FIGURE 6.6

Provision of isoniazid preventive therapy (IPT) to people living with HIV, 2005–2014



positive people were started on IPT, out of 1 034 000 (53%) people living with HIV who were newly enrolled in care. There was evidence of IPT scale-up in the past four years in other countries in the African Region. Countries reporting higher numbers in 2014 compared with previous years included Malawi (135 000), Mozambique (94 000), Zimbabwe (30 000) Nigeria (26 000), the United Republic of Tanzania (23 000) and Haiti (22 000). Nonetheless, 77% of countries did not report provision of IPT as part of HIV care in 2014, including 68% (28/41) of the high TB/HIV burden countries. As with TB screening, it is clear that countries continue to find it challenging to provide IPT and to record and report data on its provision or treatment completion. A good example is Namibia, where reporting on provision of IPT was not feasible in 2014 following the withdrawal of donor funding that had previously supported the staff required to record and report data. In 2013, more than 15 000 people newly enrolled in HIV care were reported to have been provided with IPT in Namibia. Global coverage of IPT is thus understated.

6.5 Improving data quality

Each year, efforts are made to improve the quality of data related to collaborative TB/HIV activities that are reported as part of global monitoring efforts by WHO and UNAIDS. Two challenges in particular have been evident: discrepancies between the number of HIV-positive TB patients on ART reported by TB and HIV programmes, and inconsistencies in the number of people reported to be newly enrolled in HIV care for the same country within the same data collection form (this number is requested twice in the WHO Universal Access Health Sector TB indicators reported through the UNAIDS global reporting system for HIV for two separate indicators: enrollment on IPT, and TB notifications among those newly enrolled in HIV care). Encouragingly, the number of countries reporting discrepant data fell in 2014 compared with 2013, and in almost all instances these discrepancies were resolved following communications with national TB and HIV programmes. There were two countries for which discrepant data on provision of ART reported by national HIV and TB programmes could not be reconciled (Botswana and Côte d'Ivoire) and four countries for which discrepancies in data about the number of people newly enrolled in HIV care could not be resolved (Guinea-Bissau, Mongolia, Saint Vincent and the Grenadines and Uzbekistan).

In 2015, WHO published *A guide to monitoring and evaluation for collaborative TB/HIV activities*[1] and the *Consolidated strategic information guide for the health sector.*[2] Both documents have harmonized TB/HIV indicators using the same indicator definitions, to help ensure reporting of the same data through global reporting systems for HIV and TB. These guidelines also provide a consolidated set of indicators for monitoring progress in the implementation of collaborative TB/HIV activities. Countries are being encouraged to adopt, monitor and routinely report on these indicators. UNAIDS is currently undertaking a review of the Global AIDS Response Progress Reporting (GARPR) indicators, in the context of these two guidance documents.

[1] World Health Organization. *A guide to monitoring and evaluation of collaborative TB/HIV activities: 2015 revision.* Geneva: World Health Organization; 2015. Available at: http://www.who.int/tb/publications/monitoring-evaluation-collaborative-tb-hiv/en/

[2] World Health Organization. *Consolidated strategic information guidelines for HIV in the health sector.* Geneva: World Health Organization; 2015. Available at: http://who.int/hiv/pub/guidelines/strategic-information-guidelines/en/

CHAPTER 7

Financing

Key facts and messages

The funding required for a full response to the global TB epidemic in low- and middle-income countries is estimated at about US$ 8 billion per year in 2015 (excluding research and development for new TB diagnostics, drugs and vaccines).

Of the US$ 8 billion required in 2015, about two thirds (US$ 5.3 billion) is for the detection and treatment of drug-susceptible TB; 20% (US$ 1.6 billion) for treatment of MDR-TB; 8% (US$ 0.6 billion) for rapid diagnostic tests and associated laboratory strengthening, much of which is to improve detection of drug-resistant TB; and 6% (US$ 0.5 billion) for collaborative TB/HIV activities. Projections made in 2013 suggested that in 2015, about US$ 6 billion could be mobilized from domestic sources and that US$ 2 billion would be needed from international donors.

The 123 countries that reported financial data to WHO in 2015 account for 95% of reported TB cases globally. Based on this self-reporting by countries, funding for TB prevention, diagnosis and treatment reached US$ 6.6 billion in 2015, up from US$ 6.2 billion in 2014 and more than double the level of 2006 (US$ 3.2 billion). Compared with the estimated global resource requirement of US$ 8 billion in 2015 for a full response to the TB epidemic in low and middle-income countries, this leaves a gap of around US$ 1.4 billion. Countries themselves reported smaller gaps, amounting to US$ 0.8 billion in 2015; this reflects the fact that national plans for scaling up TB prevention, diagnosis and treatment are less ambitious than the targets set in the Global Plan to Stop TB, 2011–2015 in many countries.

Overall, 87% (US$ 5.8 billion) of the US$ 6.6 billion available in 2015 is from domestic sources. International donor funding has increased since 2006, reaching US$ 0.8 billion in 2015. However, the global average for the share of funding provided from domestic sources conceals enormous variation among individual countries as well as country groups.

Domestic funding dominates (93–94% of the total funding available in 2015) in three (not mutually exclusive) groups: Brazil, the Russian Federation, India, China and South Africa (BRICS); upper middle-income countries; and regions outside Africa and Asia. In addition to BRICS, only one HBC (Thailand) has consistently reported levels of domestic funding that exceed contributions from international donor funding in recent years.

International donor funding dominates in the group of 17 HBCs outside BRICS (72% of the total funding available in 2015) and in low-income countries (81% of the total funding available in 2015). At the individual country level, international donor funding remains absolutely critical in most of the 22 HBCs. In four HBCs (Afghanistan, Bangladesh, the Democratic Republic of the Congo and Mozambique), ≥90% of available funding in 2015 is from international donor sources.

The cost per patient treated for drug-susceptible TB in 2014 fell into the range of US$ 100–US$ 500 in most countries with a high burden of TB. The cost per patient treated for MDR-TB was most often in the range US$ 5000–10 000, but the average varied from US$ 6 826 in low-income countries to US$ 21 265 in upper middle-income countries.

Health financing data from national health accounts provide insights into the current status of progress towards universal health coverage (UHC). Two suggested benchmarks required to achieve UHC are that health spending reaches at least 6% of gross domestic product (GDP) and that out-of-pocket expenditures account for less than 15% of total health spending. Most countries, including all of the 22 HBCs and all low-income countries, have not yet reached these benchmarks. Among HBCs, Brazil, Thailand and South Africa are closest to doing so.

Progress in TB prevention, diagnosis and treatment requires adequate funding sustained over many years. WHO began annual monitoring of funding for TB in 2002, with findings published in global TB reports and peer-reviewed publications.[1] Particular attention has always been given to the 22 high-burden countries (HBCs) that account for about 80% of estimated incident cases (**Chapter 2**) and about 80% of TB cases reported by national TB programmes (NTPs) to WHO (**Chapter 3**).

This chapter covers five main topics. It starts with a summary of the most up-to-date estimates of financial resources required for a full response to the TB epidemic in 2015. This is followed by presentation and discussion of trends in funding for TB prevention, diagnosis and treatment by category of expenditure and source of funding for the period 2006 (when the *Stop TB Strategy* and *Global Plan to Stop TB 2006–2015* were

[1] The most recent publication is: Floyd K, Fitzpatrick C, Pantoja A and Raviglione M. Domestic and donor financing for tuberculosis care and control in low-income and middle-income countries: an analysis of trends, 2002–11, and requirements to meet 2015 targets. *The Lancet Global Health*, 2013; 1: e105–15.

both launched)[1,2] to 2015, for 123 countries (accounting for 95% of reported TB cases in 2013) for which data were available. The third part of the chapter analyses funding gaps reported by NTPs to WHO, with breakdowns by category of expenditure and country group. The fourth part of the chapter includes the latest estimates of the unit costs of treatment for drug-susceptible and multidrug-resistant TB (MDR-TB).

The new End TB Strategy includes 2025 milestones for a 75% reduction in TB deaths and a 50% reduction in the TB incidence rate, compared with a baseline of 2015 (**Chapter 1**). Achievement of these milestones requires that universal health coverage (UHC), defined as access for all to essential preventive and treatment health care interventions, with financial protection, is in place by 2025.[3,4] In this context, the fifth and final part of the chapter introduces a new topic to the global TB report: an analysis of health financing data and what insights these can offer about the current status of progress towards UHC.

Further country-specific data can be found in finance profiles that are available online.[5]

7.1 Estimates of funding required in 2015 for a full response to the global TB epidemic

An updated version of the *Global Plan to Stop TB 2006–2015*, covering the last five years of the plan, was issued in 2010.[6] This set out the actions and estimated funding requirements for a full response to the TB epidemic for the five-year period 2011–2015 in low and middle-income countries, based on the *Stop TB Strategy*, with the overall goal of achieving the 2015 global targets for reductions in cases of and deaths from TB i.e. that incidence should be falling and that prevalence and mortality rates should be halved compared with their levels in 1990 (**Chapter 1**, **Chapter 2**). Key components of the plan included increasing the number of patients detected and treated according to WHO's recommended strategy from 5.8 million in 2011 to 6.9 million by 2015 (equivalent to more than 80% of the forecast number of incident cases in 2015 at the time the projections were done); ensuring testing for drug susceptibility for all previously treated patients and all new patients with known risk factors for MDR-TB by 2015; enrolment of all reported TB patients with MDR-TB (projected at approximately 300 000) in 2015 on second-line treatment; HIV testing of all patients with TB; and prompt initiation of ART in all HIV-positive TB patients.

From January to March 2013, the Global Plan datasets were used in combination with new country-specific planning and budgeting work with nine high TB or high MDR-TB burden countries to produce updated estimates of funding needs for TB prevention, diagnosis and treatment in low and middle-income countries.[7] The nine countries were Ethiopia, India, Indonesia, Kazakhstan, Kenya, Nigeria, Pakistan, South Africa and Ukraine. Analyses were conducted in the context of estimates of funding needs and funding gaps required for the Global Fund's replenishment efforts in 2013.[8] WHO subsequently extended these analyses to cover all low- and middle-income countries, including those not eligible to apply to the fund.[9] Notable countries (in terms of TB burden and funding requirements) that are not eligible to apply to the Global Fund include Brazil, China and the Russian Federation.

During the course of the work done for the first pre-replenishment meeting held in April 2013, it should be highlighted that the Global Fund, WHO, UNAIDS, and other partners agreed that funding needs for ART for HIV-positive TB patients should be included in estimates of HIV resource needs to avoid double counting. For this reason, the estimates of resource requirements for TB/HIV interventions included in the updated estimates of resource needs for TB are lower than those shown in the Global Plan.

The total funding required in all low and middle-income countries was estimated at about US$ 8 billion in 2015. Of this total, about two-thirds (US$ 5.3 billion) was for the detection and treatment of drug-susceptible TB; 20% (US$ 1.6 billion) for treatment of MDR-TB; 8% (US$ 0.6 billion) for rapid diagnostic tests and associated laboratory strengthening, especially for the detection of MDR-TB; and 6% (US$ 0.5 billion) for collaborative TB/HIV activities (excluding ART). It was also estimated that of the total required in 2015, about US$ 6 billion could be mobilized from domestic sources and around US$ 2 billion would be needed from international donor sources. The capacities of Brazil, the Russian Federation, India, China and South Africa (BRICS, which collectively account for almost 50% of reported TB cases worldwide) to mobilize most of their funding needs from domestic sources, in contrast with other country groups including the 17 other HBCs and low-income countries (mostly in Africa) where large amounts of international funding would be needed, were highlighted.

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1 Raviglione M, Uplekar M. WHO's new Stop TB strategy. *Lancet* 2006; 367: 952–5.

2 *The Global Plan to Stop TB, 2006–2015*. Geneva, World Health Organization; 2006 (WHO/HTM/STB/2006.35).

3 World Health Organisation, World Bank Group. *Monitoring progress towards universal health coverage at country and global levels. Framework, measures and targets*. Geneva: World Health Organization; 2014 (WHO/HIS/HIA/14.1).

4 World Health Organisation. *The World Health Report 2010: Health systems financing: the path to universal coverage*. Geneva, World Health Organization; 2010.

5 www.who.int/tb/data

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

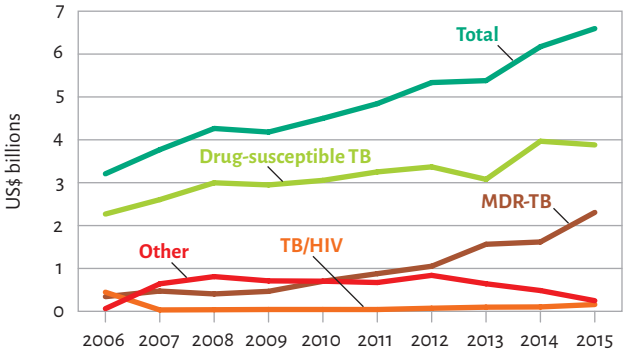
7 Funding required for research and development for new TB diagnostics, drugs and vaccines was not considered. In the Global Plan, it is estimated that about US$ 2 billion per year is needed for research and development. In 2013, funding for research and development amounted to US$ 0.7 billion (see http://www.treatmentactiongroup.org/tbrd2014).

8 *The Global Fund to Fight AIDS, Tuberculosis and Malaria fourth replenishment (2014–2016): needs assessment*. Geneva, Global Fund to Fight AIDS, Tuberculosis and Malaria; 2013.

9 Floyd K, Fitzpatrick C, Pantoja A and Raviglione M. Domestic and donor financing for tuberculosis care and control in low-income and middle-income countries: an analysis of trends, 2002–11, and requirements to meet 2015 targets. *The Lancet Global Health*, 2013; 1: e105–15.

FIGURE 7.1

Funding for TB prevention, diagnosis and treatment by intervention area, 2006–2015 (constant 2015 US$ billions)



7.2 TB funding, overall and by category of expenditure and source of funding, 2006–2015

Data reported by NTPs to WHO since 2006 allowed analysis of funding trends 2006–2015 in 123 countries (**Table 7.1**). These countries accounted for 95% of the global number of TB cases reported in 2014, and included 120 low and middle-income countries plus three high TB and/or MDR-TB burden countries that have reached high-income status (Estonia, Latvia and the Russian Federation). The methods used to collect, review and analyse financial data are summarized in **Box 7.1**.

FIGURE 7.2

Funding for drug-susceptible TB and MDR-TB, 2006–2015, by country group (constant 2015 US$ millions)

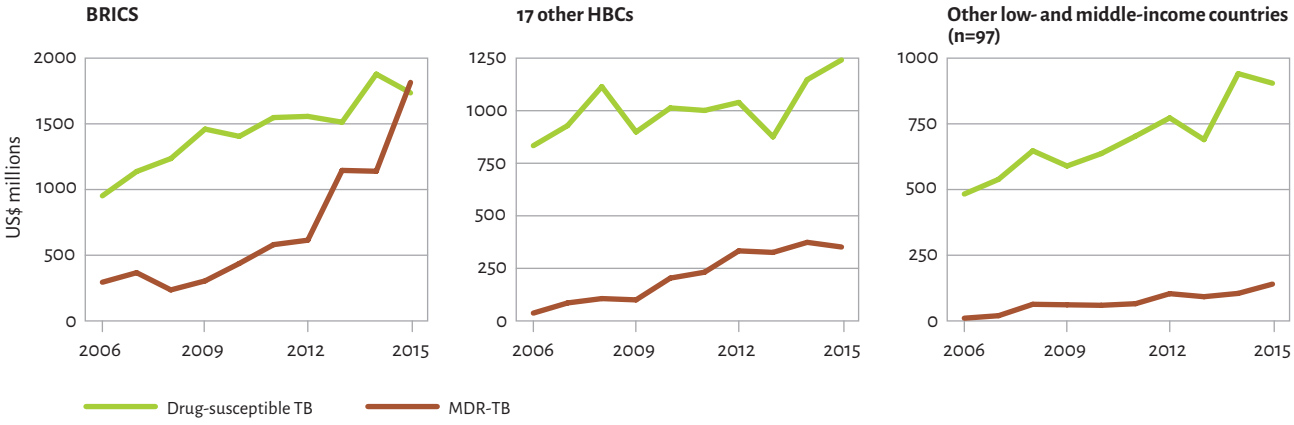
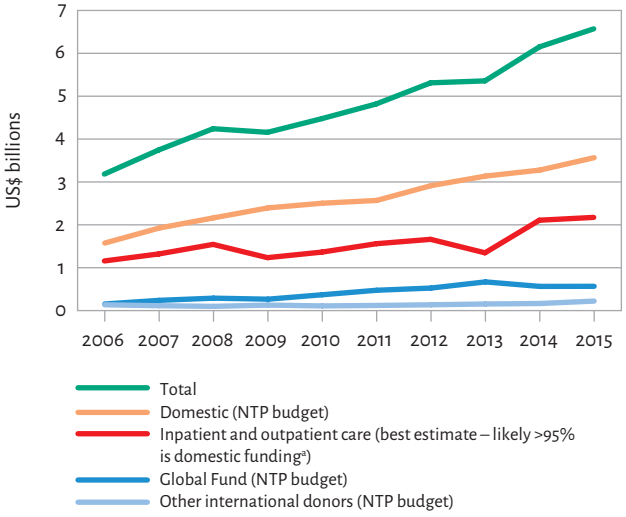


FIGURE 7.3

Funding for TB prevention, diagnosis and treatment by funding source, 2006–2015 (constant 2015 US$ billions)



[a] 96% of funding for inpatient and outpatient care is accounted for by middle and high-income countries; such countries do not typically receive international donor funding for inpatient and outpatient care services. Data is an estimate based on country-reported utilization.

In these 123 countries, funding for TB prevention, diagnosis and treatment reached US$ 6.6 billion in 2015, up from US$ 6.2 billion in 2014 and more than double the US$ 3.2 billion that was available in 2006 (**Figure 7.1**). Of the total of US$ 6.6 billion, most is for the diagnosis and treatment of drug-susceptible TB (US$ 3.9 billion). Funding for MDR-TB has grown, especially since 2009, reaching US$ 2.3 billion in 2015 (**Figure 7.1**, **Figure 7.2**). However, it should be highlighted that more than half of this funding is accounted for by the Russian Federation (**Table 7.2**), reflecting extensive use of hospitalization for patients with MDR-TB. Given the still large detection gaps for MDR-TB as well as gaps between the numbers of cases detected and started on treatment (**Chapter 4**), much more funding is required for MDR-TB globally and in most of the high MDR-TB burden countries.

A detailed breakdown of the funding estimated to be required for drug-susceptible TB, MDR-TB and collaborative TB/HIV activities in 2015, based on NTPs assessments of their needs, is shown for the 36 high TB and MDR-TB burden countries in **Table 7.2**.

Domestic funding for the TB-specific budgets of NTPs accounts for the largest single share of funding, followed by funding for inpatient and outpatient care (**Figure 7.3**). Since

TABLE 7.1

123 low and middle-income countries included in analyses of TB financing, by income group and WHO region, 2015[a]

	LOW-INCOME (13% OF NOTIFIED CASES GLOBALLY IN 2014)	LOWER-MIDDLE-INCOME (57% OF NOTIFIED CASES GLOBALLY IN 2014)	UPPER-MIDDLE-INCOME (25% OF NOTIFIED CASES GLOBALLY IN 2014)	BRICS (48% OF NOTIFIED CASES GLOBALLY IN 2014)	17 HIGH-BURDEN COUNTRIES EXCLUDING BRICS (33% OF NOTIFIED CASES GLOBALLY IN 2014)	14 HIGH MDR-TB BURDEN COUNTRIES (NOT IN THE LIST OF 22 HIGH-BURDEN COUNTRIES) (2% OF NOTIFIED CASES GLOBALLY IN 2014)
Africa	Benin, Burkina Faso, Burundi, Central African Republic, Chad, DR Congo, Eritrea, Ethiopia, Gambia, Guinea, Guinea-Bissau, Liberia, Madagascar, Malawi, Mali, Mozambique, Niger, Rwanda, Sierra Leone, South Sudan, Togo, Uganda, UR Tanzania, Zimbabwe	Cabo Verde, Cameroon, Congo, Côte d'Ivoire, Ghana, Kenya, Lesotho, Mauritania, Nigeria, Sao Tomé and Principe, Senegal, Swaziland, Zambia	Angola, Botswana, Gabon, Namibia, South Africa	South Africa	DR Congo, Ethiopia, Kenya, Mozambique, Nigeria, Uganda, UR Tanzania, Zimbabwe	
Americas	Haiti	Bolivia, El Salvador, Guatemala, Guyana, Honduras, Nicaragua	**Belize**, Brazil, Colombia, Dominican Republic, Ecuador, Jamaica, Mexico, Panama, **Paraguay**, Peru, Suriname	Brazil		
Eastern Mediterranean	Afghanistan, Somalia	Djibouti, Egypt, Morocco, Pakistan, Sudan, Syria, West Bank and Gaza Strip, Yemen	Iran (Islamic Republic of), Iraq, Jordan, Lebanon, Tunisia		Afghanistan, Pakistan	
Europe		Armenia, Georgia, Kyrgyzstan, Republic of Moldova, Tajikistan, Ukraine, Uzbekistan	Bosnia and Herzegovina, Bulgaria, Kazakhstan, Montenegro, Romania, Serbia, The Former Yugoslav Republic of Macedonia, Turkey	Russian Federation		Armenia,Bulgaria, Estonia, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Republic of Moldova, Tajikistan, Ukraine, Uzbekistan
South-East Asia	Democratic People's Republic of Korea, Nepal	Bangladesh, Bhutan, India, Indonesia, Myanmar, Sri Lanka, Timor-Leste	Maldives, Thailand	India	Bangladesh, Indonesia, Myanmar, Thailand	
Western Pacific	Cambodia	Kiribati, Lao People's Democratic Republic, Micronesia (Federal States of), Papua New Guinea, Philippines, **Samoa**, Solomon Islands, Vanuatu, Viet Nam	**American Samoa**, China, Fiji, Malaysia, Marshall Islands, Mongolia, Palau, Tonga, Tuvalu	China	Cambodia, Philippines, Viet Nam	
Not included	Comoros		Albania, Algeria, Azerbaijan, Belarus, Costa Rica, Cuba, Dominica, Grenada, Libya, Palau, Saint Lucia, Saint Vincent and the Grenadines, Turkmenistan			Azerbaijan, Belarus, Lithuania

[a] Analyses focus primarily on low and middle-income countries. Three high-income countries (Estonia, Latvia and the Russian Federation) were included because they are in the list of 22 high-burden countries or the list of 27 high MDR-TB burden countries. Additional countries included in trend analyses of TB financing compared with those included in previous global reports are shown in bold.

TABLE 7.2

TB budget reported by NTP by intervention area, and estimated cost of inpatient and outpatient care for drug-susceptible (DS-TB) and MDR-TB, 36 high TB or MDR-TB burden countries, 2015 (current US$ millions)

	TB BUDGET REPORTED BY NTP				RESOURCES REQUIRED FOR INPATIENT AND OUTPATIENT CARE		RESOURCES REQUIRED FOR TB CARE
	TOTAL	DS-TB	MDR-TB	TB/HIV	DS-TB	MDR-TB	
22 HIGH-BURDEN COUNTRIES							
Afghanistan	15	13	1.3	0.1	6.7	0.2	22
Bangladesh	48	42	5.6	0.1	1.0	0.1	49
Brazil	77	65	9.4	2.3	47	1.9	126
Cambodia	31	28	1.9	0.6	6.4	0	37
China[a]	340	313	27	0	–	–	340
DR Congo	55	48	3.3	3.1	2.7	0	57
Ethiopia	82	57	19	5.6	8.0	0.3	91
India	261	179	78	4.0	456	70	788
Indonesia	133	119	11	2.7	27.6	5.1	165
Kenya	45	39	0.8	5.2	4.4	0.9	50
Mozambique	29	18	6.4	4.3	3.7	0.3	33
Myanmar	36	23	9.5	4.4	3.0	0.5	40
Nigeria	228	156	54	17	8.5	3.8	240
Pakistan	50	33	17	0	3.0	0.2	53
Philippines	106	84	21	0.9	185	5.9	298
Russian Federation[a,b]	1 894	637	1 211	47	–	–	1 894
South Africa	248	129	61	58	99	363	710
Thailand	32	27	5.2	0.1	7.0	0.1	39
Uganda	24	21	2.1	1.1	0.6	0	25
UR Tanzania	67	53	9.6	4.5	2.4	0.3	70
Viet Nam	66	60	5.9	0.8	33	2.7	102
Zimbabwe	28	22	2.2	3.5	0.5	0	29
22 high-burden countries	3 895	2 166	1 563	165	910	455	5 261
REMAINING HIGH MDR-TB BURDEN COUNTRIES							
Armenia	4.2	4.2	0	0	3.7	2.1	10
Azerbaijan	6.3	2.5	3.7	0	19	7.9	33
Belarus	15	1.9	13	<0.1	22	29	66
Bulgaria	15	15	0.2	0	11	0.6	27
Estonia	0.6	0.3	0.3	0	1.3	1.1	3.1
Georgia	17	8.6	8.0	0	5.4	4.6	27
Kazakhstan	195	163	30	1.2	105	81	381
Kyrgyzstan	29	16	13	0	5.1	5.0	39
Latvia	1.6	0.2	1.4	0	11	2.6	15
Lithuania					7.4	11	18
Republic of Moldova	17	13	4.1	0.1	6.8	5.8	30
Tajikistan	25	16	7.7	0.7	5.0	1.9	32
Ukraine	123	59	62	2.2	32	27	182
Uzbekistan	101	88	12	<0.1	35	10	146
27 high MDR-TB burden countries	4 097	2 268	1 681	148	1 101	640	5 838
36 high-TB or high MDR-TB burden countries	4 445	2 555	1 720	170	1 180	644	6 268

Blank cells indicate data not reported.

– indicates values that cannot be calculated.

[a] No amount is shown for China and the Russian Federation because the NTP budgets reported by those countries include all budgets for inpatient and outpatient care.

[b] In the Russian Federation, the staff and infrastructure reported for TB care and control were allocated to DS-TB (23%) and MDR-TB (77%) by WHO based on the proportion of bed-days used by DS-TB and MDR-TB patients.

Box 7.1 Methods used to compile, validate and analyze financial data reported to WHO

WHO began monitoring government and international donor financing for TB in 2002. All data are stored in the WHO global TB database. The standard methods used to compile, review, validate and analyse these data have been described in detail elsewhere.[a,b] This box provides a summary.

Each year, WHO requests all low and middle-income countries (and the Russian Federation, the only HBC that is a high-income country) to report the funding required for TB prevention, diagnosis and treatment in their current fiscal year, by category of expenditure and source of funding; and expenditures for the most recently completed fiscal year, also by category of expenditure and source of funding. In the 2015 round of global TB data collection, the fiscal years were 2015 and 2014, respectively. Categories of expenditure for diagnosis and treatment of drug-susceptible TB were synthesized compared to those used 2006–2014, to simplify reporting. Six categories were used: laboratory infrastructure, equipment and supplies; NTP staff (central unit staff and subnational TB staff); drugs to treat drug-susceptible TB; programme costs; patient support; and operational research including surveys. The main change was that several subcategories of programme costs were condensed into one category (this means that trends can still be assessed back to 2006). Categories of expenditure used for MDR-TB remained the same as those used since 2006: second-line drugs, and programmatic management of MDR-TB. Budgets and expenditures for collaborative TB/HIV activities were requested as one consolidated category of expenditure, as in previous years. Funding available from four major sources was requested, also as in previous years: domestic funding excluding loans; external loans, also considered domestic funding; the Global Fund; and grant financing from sources other than the Global Fund. A simplification compared with previous years was that only an overall breakdown of total funding was requested, as opposed to a breakdown for each category of expenditure. Again, this does not affect ability to report trends in a format consistent with those published in past reports. For high-income countries (except the Russian Federation which is an HBC), only totals for both funding requirements and expenditures were requested, without any breakdown by category of expenditure or source of funding, as in previous years.

As usual in 2015, all countries were asked to report on the utilization of inpatient and outpatient care required for treatment of people with drug-susceptible and MDR-TB, on a per patient basis (i.e. the average number of days spent in hospital, and the average number of outpatient visits to a health facility). These data are used in combination with other information to estimate the financial resources used for TB prevention, diagnosis and treatment that are not reflected in TB-specific reports of funding requirements, available funding and expenditures (further details are provided below).

Core methods used to review and validate data have remained consistent since 2002. They include:

- **Routine checks for plausibility and consistency, including validation checks that are built into the online reporting system**. Examples of validation checks are checks for implausibly large year-to-year changes (for example in total reported funding by source and by category of expenditure), or implausibly high or low values of funding for drugs relative to the number of TB patients (that differ substantially from prices quoted by the Global TB Drug Facility).
- **Discussions with country respondents to resolve queries.**
- **Triangulation with other data sources.** One example is the detailed budgets prepared by NTPs that are peer-reviewed by WHO as part of efforts to strengthen the budgeting of national strategic plans for TB care and control. Comprehensive and robust budgets for national strategic plans are now an essential requirement for funding applications to the Global Fund, as part of this agency's new funding model introduced in 2013. Two tools promoted by WHO (the WHO TB planning and budgeting tool and the OneHealth tool)[c,d] for estimating funding requirements allow mapping of detailed budgets to the line items used in the WHO TB data collection form, and comparisons with data reported online. Triangulation is also undertaken with data available from the Global Fund,[e] USAID,[f] and the Organization for Economic Cooperation and Development's Creditor Reporting System. In 2015, for example, reported data were compared with data submitted to the Global Fund as part of the funding gap analyses required for funding proposals and follow-up and adjustments made as appropriate.

In 2014 and 2015, additional elements of review and validation included facilitation of communications between focal points for National Health Accounts and NTP managers, with the aim of using expenditure data generated from implementation of the System of Health Accounts 2011 (that allows expenditures to be reported by disease) for reporting of TB expenditures wherever available.

In reviewing and validating data, particular attention has always been given to the 22 HBCs. A summary of data validation methods used for HBCs is provided in **Table B7.1**.

TB funding reported by NTPs usually does not include the financial costs associated with the inpatient and outpatient care required during TB treatment (among HBCs, the notable exceptions are China and the Russian Federation, since treatment is provided in TB-specific clinics or hospitals for which earmarked budgets and funding exist). Since many detailed costing studies in a wide range of countries show that these costs account for a large share of the cost of treating someone with TB,[g] analyses of TB financing undertaken by WHO have always included estimates of the funding used for both inpatient and outpatient care.

As in past reports, WHO estimates the funding used for inpatient and outpatient care of TB patients by multiplying the number of outpatient visits and days of inpatient care per patient (reported by NTPs each year) by the cost per bed-day and clinic visits available from the WHO-CHOICE database[h] and then by the reported number of TB patients notified or projected to be notified. This is done separately for drug-susceptible TB and MDR-TB. For a further three countries (Belarus, Burkina Faso and the Democratic Republic of the Congo), data from a recent National Health Account (NHA) were used.[i] It is hoped that in the near future, NHA data will be routinely available for many more countries, including a breakdown by source of funding (domestic vs international) that is currently not available for any country.

[a] Floyd K, Pantoja A, Dye C. Financing tuberculosis monitoring system. *Bulletin of the World Health Organization*; 2007; 85:334–40.

[b] Floyd K, Fitzpatrick C., Pantoja A and Raviglione M. Domestic and donor funding for tuberculosis care and control in low-income and middle-income countries: an analysis of trends 2002–11, and requirements to meet 2015 targets. *The Lancet Global Health*; 1: e105–15.

[c] *Planning and budgeting for TB control activities*. Geneva, World Health Organization; 2015. http://www.who.int/tb/dots/planning_budgeting_tool/en/

TABLE B7.1

Methods used to review and validate financing data reported by NTPs, high TB and MDR-TB burden countries

COUNTRY	ROUTINE REAL-TIME CHECKS FOR PLAUSIBILITY AND INTERNAL CONSISTENCY (TRENDS OVER TIME), REVIEW AND FOLLOW-UP CHECKS BY WHO FINANCE DATA REVIEWERS, UPDATES/ CORRECTIONS ENCOURAGED	REVIEW BY IN-COUNTRY WHO TB MEDICAL OFFICER	NATIONAL TB STRATEGIC PLANNING AND BUDGETING AND ASSOCIATED ASSESSMENT OF SOURCES OF FUNDING USING WHO RECOMMENDED COSTING TOOLS [b]	UNIT COST DATA AVAILABLE FROM INDEPENDENT ECONOMIC EVALUATION
22 HIGH TB BURDEN COUNTRIES				
Afghanistan	yes	yes	yes (2013)	no
Bangladesh	yes	yes	yes (2014)	yes
Brazil	yes	yes	no	yes
Cambodia	yes	yes	yes (2009)	yes
China	yes	yes	no	yes
DR Congo	yes	yes	yes (2014)	no
Ethiopia	yes	sometimes	yes (2014)	yes
India	yes	yes	yes (2013)	yes
Indonesia	yes	yes	yes (2013)	yes
Kenya	yes	yes	yes (2013)	yes
Mozambique	yes	mostly	yes (2013)	no
Myanmar	yes	yes	yes (2011)	no
Nigeria	yes	yes	yes (2013)	yes
Pakistan	yes	yes	yes (2013)	yes
Philippines	yes	yes	yes (2011)	yes
Russian Federation	yes	yes	no	yes
South Africa	yes	yes	yes (2013)	yes
UR Tanzania	yes	yes	no	yes
Thailand	yes	yes	yes (2015)	yes
Uganda	yes	yes	yes (2013)	yes
Viet Nam	yes	yes	no	yes
Zimbabwe	yes	yes	yes (2013)	yes
REMAINING HIGH MDR-TB BURDEN COUNTRIES				
Armenia	yes	Wolfheze working group on financing	yes (2010)	no
Azerbaijan	yes	no	no	no
Belarus	yes	Wolfheze working group on financing	no	no
Bulgaria	yes	no	no	no
Georgia	yes	no	no	no
Kazakhstan	yes	no	yes (2013)	no
Kyrgyzstan	yes	yes	yes (2013)	no
Latvia	yes	no	no	yes
Lithuania[a]	no	no	no	no
Republic of Moldova	yes	no	no	no
Tajikistan	yes	no	no	yes
Ukraine	yes	yes	yes (2013)	yes
Uzbekistan	yes	no	yes (2011)	no

Source: GTB compilation based on data review process and Lawrence Y. et al, 2015.

[a] Data for Lithuania has never been reported to WHO.

[b] The tools recommended by WHO are the OneHealth tool and the WHO TB Planning and Budgeting tool.

[d] *Planning and budgeting for TB control activities as part of sector wide national strategic health plans and policies*. Geneva, Inter-Agency working group; 2015. Available at: http://www.who.int/choice/onehealthtool/en/

[e] For example, data available at http://web-api.theglobalfund.org/odata/ were accessed in May 2015.

[f] FY 2013 Congressional Budget Justification for Foreign Operations. Released March and April 2012, USAID http://www.state.gov/f/releases/iab/fy2013cbj/pdf/

[g] Laurence YV, Griffiths UK, Vassall A. Costs to Health Services and the Patient of Treating Tuberculosis: A Systematic Literature Review. *PharmacoEconomics*. 2015:1–17.

[h] *Choosing interventions that are cost effective (WHO-CHOICE)*. Geneva, World Health Organization; 2008. Available at: http://www.who.int/choice/cost-effectiveness/inputs/health_service/en/

[i] National Health Accounts http://www.who.int/health-accounts/en/

almost all (96%) of the funding estimated to be used for inpatient and outpatient care is accounted for by middle- or high-income countries, it can be assumed that virtually all of this funding is from domestic sources (international donor funding for inpatient and outpatient care is only likely to occur in low-income countries, via general budget support to the health sector). Overall, 87% of the estimated funding of US$ 6.6 billion in 2015 is from domestic sources. International donor funding for the TB-specific budgets of NTPs has increased since 2006, reaching US$ 0.8 billion in 2015.

It is important to highlight that the funding reported by NTPs does not capture all international donor funding for TB; donor funding is also provided to entities other than NTPs, including international and national governmental and nongovernmental organizations. A more comprehensive analysis of international donor funding, based on donor reports to the Organization for Economic Cooperation and Development (OECD), is provided in **Box 7.2**.[1]

It is also important to emphasize that the global average for the share of funding provided from domestic sources conceals enormous variation among individual countries, as well as country groups that can be defined based on TB burden, geography, political/economic profile and income level (**Figure 7.4**, **Table 7.3**).

Domestic funding dominates (93–94% of the total funding available in 2015) in three (not mutually exclusive) groups: BRICS, upper middle-income countries and regions outside Africa and Asia. In addition to BRICS, only one HBC (Thailand) has consistently reported levels of domestic funding that exceed contributions from international donor funding in recent years.

In lower middle-income countries, domestic funding has risen from US$ 0.2 billion in 2006 to over US$ 0.5 billion in 2015, but international donor funding has also assumed greater and greater importance, reaching parity with domestic funding in 2015. Most of the increase in lower middle-income countries has been driven by grants from the Global Fund.

International donor funding dominates in the group of 17 HBCs outside BRICS (73% of the total funding available in 2015) and in low-income countries (80% of the total funding available in 2015). At the individual country level, it remains absolutely critical to funding for TB prevention, diagnosis and treatment in most of the 22 HBCs, and in four HBCs (Afghanistan, Bangladesh, the Democratic Republic of the Congo and Mozambique), ≥90% of available funding in 2015 is from international donor sources.

[1] Out-of-pocket expenditures are also not included in NTP reports. These are analysed in more detail in **section 7.5**.

7.3 Funding gaps reported by national TB programmes, 2006–2015

Despite growth in funding from domestic and international donor sources, many NTPs continue to be unable to mobilize all the funding required for full implementation of their national strategic plans (**Figure 7.5**). Funding gaps (i.e. the difference between assessments by NTPs of funding needs for TB prevention, diagnosis and treatment and the actual amount of funds mobilized) have persisted and in 2015 amounted to a total of US$ 0.8 billion. This is considerably less than the gap of US$ 1.4 billion that exists between the US$ 8 billion estimated to be needed for a full response to the TB epidemic in 2015 (**section 7.1**) and the US$ 6.6 billion available in 2015 (**section 7.2**). The difference can be explained by the fact that national strategic plans for TB remain less ambitious than the targets set in the Global Plan to Stop TB, 2011–2015 (**section 7.1**) in many countries.

Lower middle-income countries account for the largest reported funding gaps (about US$ 0.5 billion in 2015), of which US$ 0.4 billion was in five countries (Nigeria, Indonesia, Ukraine, Viet Nam and the Philippines, in descending order). There may be additional capacity to mobilize more domestic funding in these countries. Funding gaps were relatively small in upper middle-income countries in 2015 (**Figure 7.5**), and have fallen in recent years – mostly explained by large reductions in the funding gaps reported by the Russian Federation and Kazakhstan. These two countries reported no funding gaps in 2014 or 2015. Funding gaps reported by low-income countries fell between 2014 and 2015, reflecting a shift of some countries from the low to middle-income country group between 2014 and 2015.

Geographically, the African Region has by far the largest funding gap: US$ 0.4 billion in 2015, equivalent to half of the global total. The largest gap was reported by Nigeria (US$ 154 million, see **Table 7.3**).

Of the US$ 0.8 billion funding gap reported by NTPs in 2015, US$ 0.64 billion is for drug-susceptible TB and US$ 0.14 billion is for MDR-TB. Relative to total funding needs, the funding gap is larger for drug-susceptible TB. Domestic funding accounts for a larger share of the funding for MDR-TB compared with drug-susceptible TB, which is not surprising given that most of the high MDR-TB burden countries are middle or high-income countries and 14 of 27 are in the European Region.

7.4 Unit costs of treatment for drug-susceptible and MDR-TB, 2014

The cost per patient treated for drug-susceptible and MDR-TB could be estimated for 117 countries and 90 countries, respectively. The analysis of the cost per TB patient with drug-susceptible TB was limited to countries that had notified at least 100 TB cases in 2014. Estimates of the unit cost of MDR-TB treatment were restricted to countries that reported at least 10 patients on second-line treatment for MDR-TB.

TABLE 7.3

TB budget reported by NTP, available funding from domestic and international donor sources, funding gap and share of budget provided by domestic and international donor funding, 36 high TB or MDR-TB burden countries, 2015 (current US$ millions)

	TB BUDGET REPORTED BY NTP	DOMESTIC FUNDING (A)	INTERNATIONAL DONOR FUNDING (B)	SHARE OF AVAILABLE FUNDING (A+B) PROVIDED FROM DOMESTIC SOURCES (%)	SHARE OF AVAILABLE FUNDING (A+B) PROVIDED BY INTERNATIONAL DONORS (%)	FUNDING GAP[a]
22 HIGH-BURDEN COUNTRIES						
Afghanistan	15	0.9	10	8.1%	92%	4.0
Bangladesh	48	0.1	33	0.4%	100%	14
Brazil	77	55	0.6	99%	1.1%	21
Cambodia	31	3.6	14	20%	80%	13
China	340	306	6	98%	2%	28
DR Congo	55	3.0	27	10%	90%	24
Ethiopia	82	9.1	35	21%	79%	38
India	261	121	140	46%	54%	0
Indonesia	133	18	27	39%	61%	88
Kenya	45	12	13	48%	52%	20
Mozambique	29	1.6	19	7.9%	92%	8.1
Myanmar	36	3.9	25	14%	86%	8
Nigeria	228	30	44	41%	59%	154
Pakistan	50	8.4	30	22%	78%	12
Philippines	106	25	42	37%	63%	40
Russian Federation	1 894	1 893	1.0	100%	0%	0
South Africa	248	208	19	91%	8.6%	21
Thailand	32	17	3.6	82%	18%	12
Uganda	24	2.4	17	12%	88%	5.2
UR Tanzania	67	8.5	12	41%	59%	47
Viet Nam	66	6.7	12	37%	63%	48
Zimbabwe	28	2.0	17	11%	89%	10
22 high-burden countries	**3 895**	**2 735**	**546**	**83%**	**17%**	**614**
REMAINING HIGH MDR-TB BURDEN COUNTRIES						
Armenia	4.2	3.0	1.2	71%	29%	0
Azerbaijan	6.3	1.2	5.1	19%	81%	0
Belarus	15	7.1	3.6	66%	34%	4.7
Bulgaria	15	13	1.8	88%	12%	0
Estonia	0.6	0.6	0	100%	<1%	0
Georgia	17	5.5	7.9	41%	59%	3.2
Kazakhstan	195	195	0	100%	0%	0
Kyrgyzstan	29	11	18	37%	63%	0
Latvia	1.6	1.6	0	100%	0%	0
Lithuania				–	–	
Republic of Moldova	17	10	7.1	59%	41%	0
Tajikistan	25	6.9	13	35%	65%	5.1
Ukraine	123	50	23	68%	32%	50
Uzbekistan	101	86	14	86%	14%	0
27 high MDR-TB burden countries	**4 097**	**3 023**	**536**	**85%**	**15%**	**538**
36 high-TB or high MDR-TB burden countries	**4 445**	**3 126**	**641**	**83%**	**17%**	**678**

Blank cells indicate data not reported.
– indicates values that cannot be calculated.
[a] The funding gap reflects the anticipated gap for the year at the time a country reported data in the 2015 round of global TB data collection.

Box 7.2 International donor funding for TB prevention, diagnosis and treatment, based on donor reports to the Organization for Economic Cooperation and Development

International donor funding provided for TB prevention, diagnosis and treatment is channelled to NTPs and other recipients. The financial data reported to WHO by NTPs therefore understates the total amount of international donor funding being provided each year.

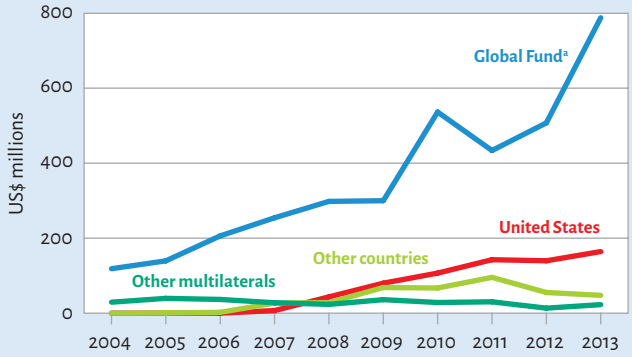
The creditor reporting system (CRS) of the Organization for Economic Cooperation and Development (OECD) is the most comprehensive source of information about international donor funding. Reports are provided by 31 multilateral organizations, the 26 countries that are members of the OECD's Development Assistance Committee and a further two non-committee members (Kuwait and the United Arab Emirates). The OECD compiles data on commitments and disbursements from both governments and multilateral organizations. Disbursement data include both direct transfers to countries as well as the provision of goods and services, such as in-kind transfers or technical assistance.

Data on gross disbursements for TB (as opposed to commitments that may not always be translated into actual funding) were analysed for 2004–2013. All funding coded as for TB (code 12263: tuberculosis control) was included. It should be highlighted that funding for TB that flows between OECD countries is not recorded in the OECD database. It is also important to note that in the OECD database, government contributions to multilateral organizations are *not* attributed to the government of origin but only to the multilateral organization (for example, funding received by countries from Global Fund grants are attributed to the Global Fund, as opposed to the original donor to the Global Fund).

Figure B7.2.1 shows that international donor funding for TB increased from US$ 148 million in 2004 to US$ 1022 million in 2013. Most of the funding that was provided 2004–2013 came from the Global Fund (72%), followed by the government of the United States of America (14%). Remaining funding for TB came from other countries (8%) and other multilateral organizations (6%), among which the largest donors were the governments of Canada (4%) and the United Kingdom (3%). The Global Fund has consistently been the largest provider of international donor funding for TB, including US$ 788 million in 2013.[a] Funding increased steadily from 2004 to 2013 with the exception of a drop from 2010 to 2011. Disbursements from the government of the United States of America steadily increased from 2007 to 2011

FIGURE B7.2.1

International donor funding for TB prevention, diagnosis and treatment by source, 2004–2013



[a] The increase between 2012 and 2013 was mostly accounted for by India, which had a Global Fund disbursement of US$ 11 million in 2012 and US$ 165 million in 2013.

FIGURE B7.2.2

International donor funding for TB prevention, diagnosis and treatment by region, 2004–2013

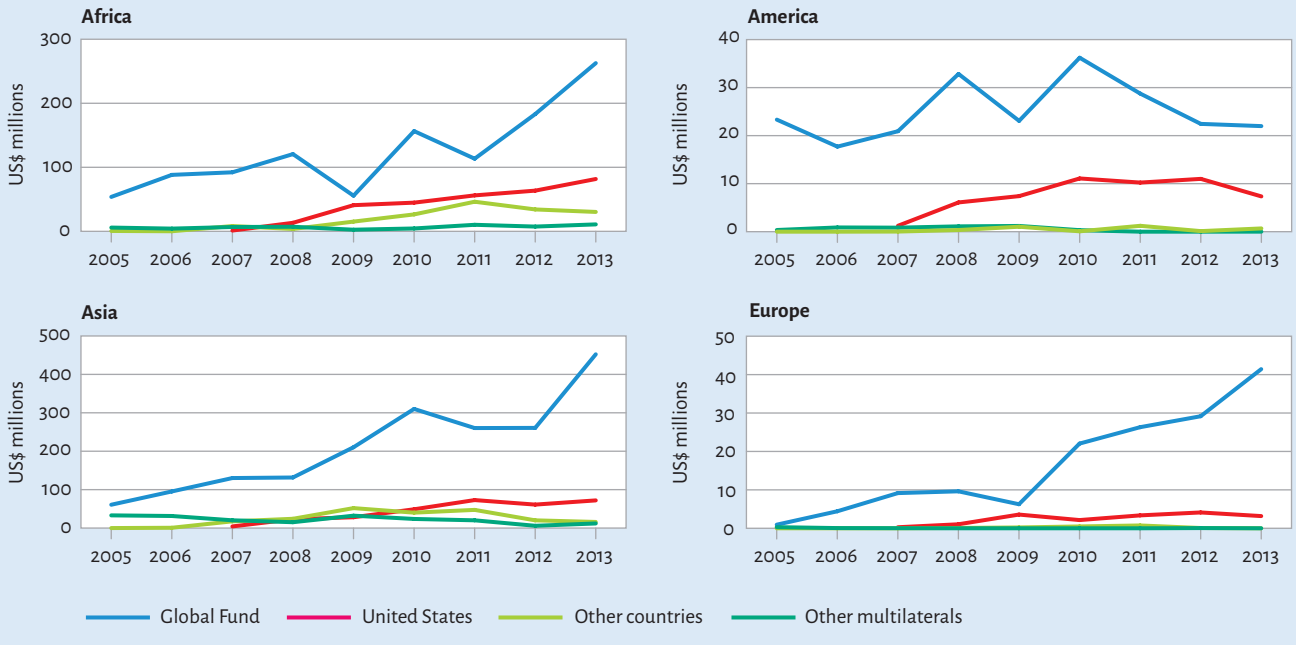
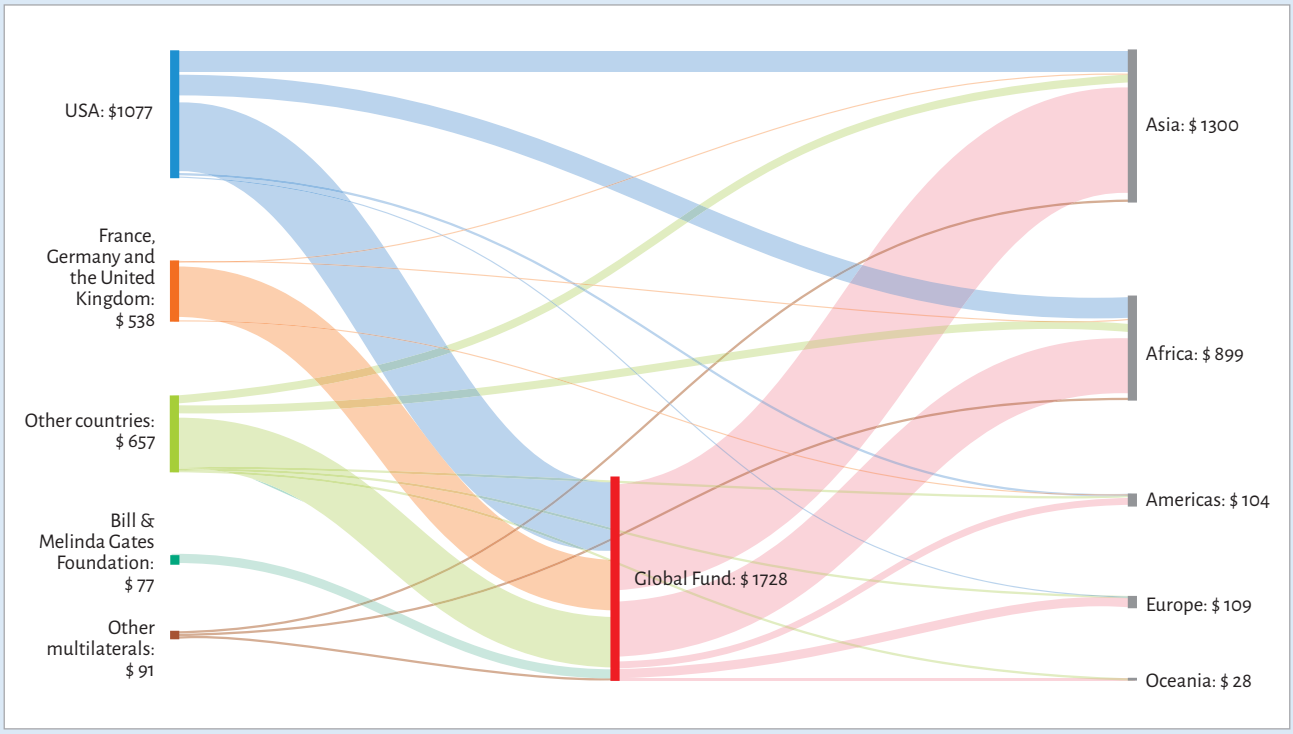


FIGURE B7.2.3

International donor funding for TB prevention, diagnosis and treatment to non-OECD countries, 2011–2013 (constant 2013 US$, million). Donors are listed on the left and recipients of donor funding are listed on the right. The Global Fund through which much donor funding is channelled, is shown in the middle.



and have since levelled off. However, it should also be noted that contributions from the government of the United States of America captured in the OECD database are lower than official allocations. In 2013, the allocation for TB was US$ 232 million and in addition more than US$ 130 million was allocated for TB/HIV via the President's Emergency Plan for AIDS Relief (PEPFAR).

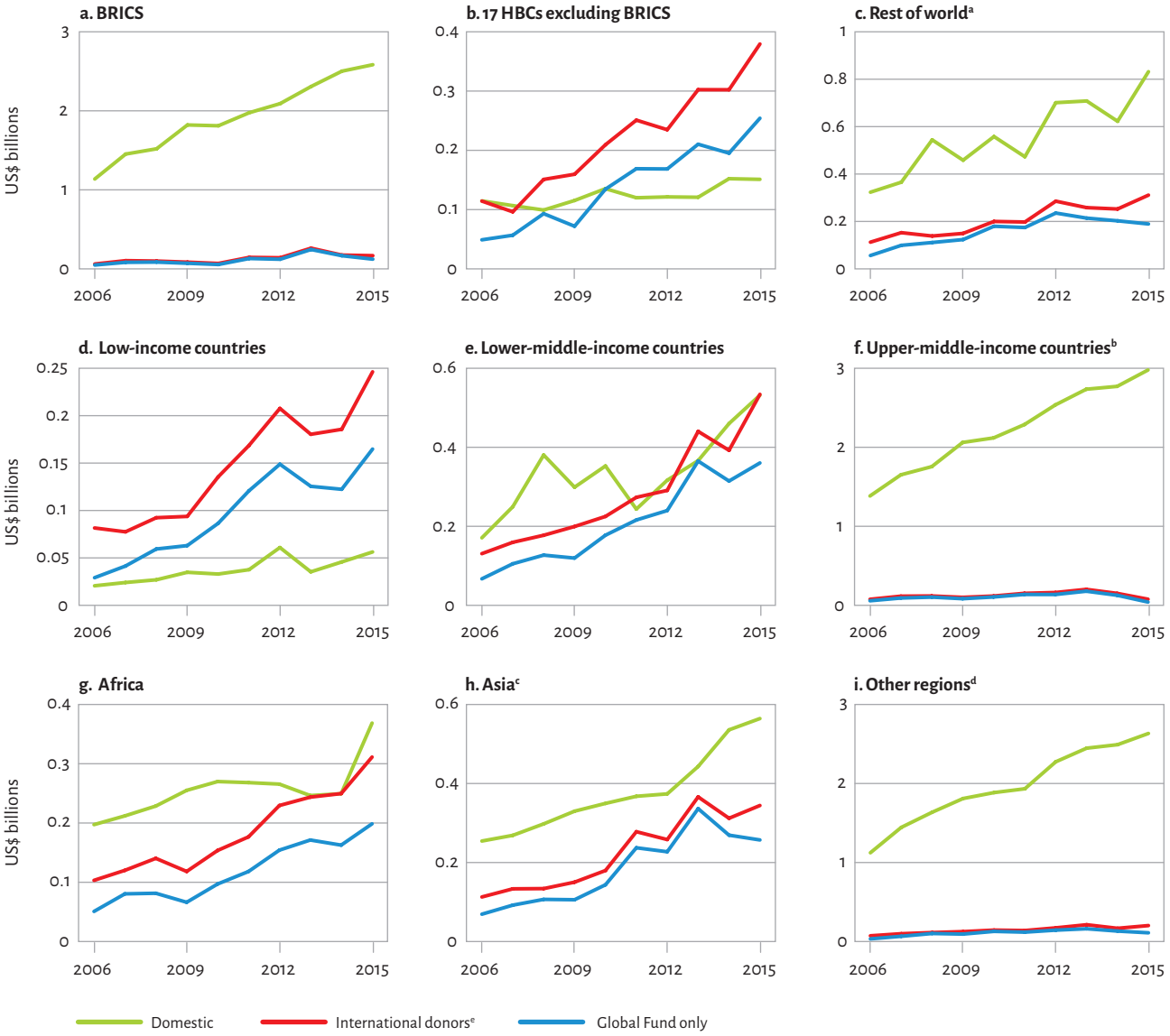
The Global Fund disbursed TB funding (in at least one year between 2004 and 2013) in 105 of the 109 countries that received any TB donor assistance. The top recipients of funding, with total amounts of over US$ 100 million each during the years 2004–2013, were (in descending order of the total funding received): China, India, Indonesia, the Philippines, Bangladesh, Nigeria and Pakistan. Collectively, these countries accounted for over 58% of the TB cases notified in 2014. **Figure B7.2.2** shows that Africa, Asia, and Europe all experienced major increases in disbursements between 2012 and 2013 while amounts disbursed to the Americas remained relatively flat. The main drivers of these changes between 2012 and 2013 were increased financing from the Global Fund for Zambia (US$ 86 million in 2013), India (US$ 165 million in 2013), and Ukraine (US$ 17 million in 2013).

Figure B7.2.3 shows the flow of international donor funding for TB during the period 2011–2013. In this figure, amounts of funding flowing to the Global Fund from countries and other donors were estimated on the assumption that 18% of a donor's total contribution to the Global Fund was for TB, in line with the overall share of Global Fund financing that is used for TB. The Global Fund publishes the amounts received from each donor on its website. The four largest country donors (the United States of America, France, Germany and the UK) are shown separately, as is the largest non-country donor (the Bill and Melinda Gates Foundation). The importance of the United States of America in the global funding of TB is particularly evident in this presentation of data, since it accounted for about one third of contributions to the Global Fund in addition to funding provided via bilateral channels.

[a] For comparison, the total funding reported by countries to WHO amounted to 85% of this total, US$ 669 million.

FIGURE 7.4

Funding for TB prevention, diagnosis and treatment from domestic sources and international donors, 2006–2015, 9 country groups (constant 2015 US$ billions)



[a] Rest of the world includes 101 countries that are not in the list of 22 high TB burden or 27 high MDR-TB burden countries.
[b] The upper-middle-income category includes three high-income countries that are in the list of TB and/or high MDR-TB burden countries: Estonia, Latvia and the Russian Federation.
[c] Asia includes the WHO regions of South-East Asia and the Western Pacific.
[d] "Other regions" consists of three WHO regions: the Eastern Mediterranean Region, the European Region, and the Region of the Americas.
[e] This includes the Global Fund.

Of the 36 countries that are in the list of high TB burden or high MDR-TB countries, 35 could be included in the analysis (the exception was Lithuania). Analytical methods are summarized in **Box 7.3**.

Unit cost estimates for 2014 are shown for drug-susceptible and MDR-TB in **Figure 7.6** and **Figure 7.7**.

7.4.1 Drug-susceptible TB

The cost per patient treated for drug-susceptible TB was generally in the range US$ 100–US$ 1 000. In general, approximately 80% of this cost was accounted for by reported NTP expenditures, with the remainder being inpatient and outpatient care. The cost per patient treated was typically higher, but still quite varied, in countries of the former Soviet Union, ranging from US$ 1 123–US$ 18 836. In these countries, lengthy hospitalizations play a more significant role in the total cost of care, with admissions lasting up to an average of 75 days and accounting for approximately 40–60% of the total cost per patient. However, there are some striking examples of reductions in reliance on hospitalization.

Box 7.3 Methods used to estimate the cost per patient treated for drug-susceptible and MDR-TB

Two main data sources were used. The first was the validated expenditure data reported by NTPs that are stored in the WHO global TB database. The second was country-specific estimates of the unit costs of bed-days and outpatient visits available from WHO's CHOosing Interventions that are Cost-Effective (WHO-CHOICE) model and associated database (managed by the Health Governance and Financing department). In a few instances when no expenditure data could be reported, information about the total funding available was used as a proxy for expenditures. For a few countries, WHO-CHOICE estimates were replaced with estimates of unit costs obtained directly from recent studies or discussions with experts.

Costs were calculated separately for drug-susceptible and MDR-TB. In each case, the numerator was the total estimated cost of treatment, which has two main parts: 1) the national expenditures reported by the NTP; and 2) the costs associated with the utilization of health services by patients with TB and MDR-TB.

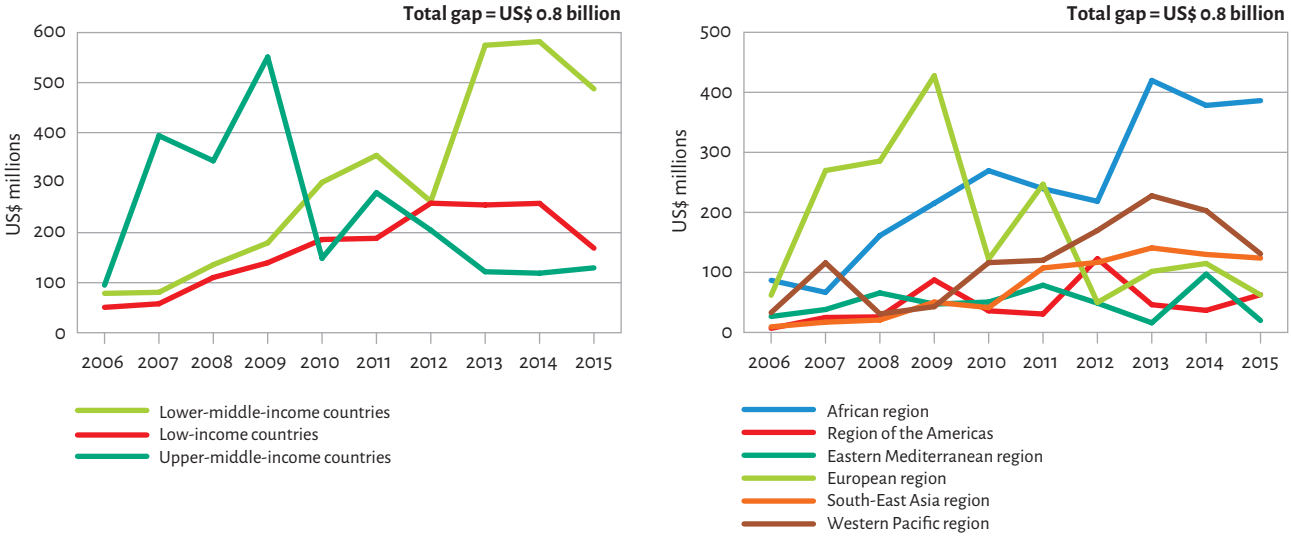
As explained in **Box 7.1**, national NTP expenditures are reported annually to WHO using the online WHO global TB data collection system, and then reviewed and validated. Categories of expenditure considered as costs for MDR-TB were second-line drugs, and all other inputs/activities implemented for the programmatic management of MDR-TB. All other categories (with the exception of collaborative TB/HIV activities) were assumed to be for drug-susceptible TB.

For almost all countries, the total costs associated with utilization of inpatient and outpatient care were calculated using information about the typical number of days of inpatient care and outpatient visits required on a per patient basis during treatment (reported separately for drug-susceptible and MDR-TB by NTPs) combined with WHO-CHOICE unit cost estimates, multiplied by the number of patients treated in a given year (based on notification data – see **Chapter 3** for drug-susceptible TB and **Chapter 4** for MDR-TB). Multiplying quantities of visits and bed-days by their price estimates yields the total estimated cost of inpatient and outpatient services. For three countries (Belarus, Burkina Faso and the Democratic Republic of the Congo), TB inpatient and outpatient expenditures available from National Health Accounts were used in lieu of the estimated cost from this ingredients-based approach.

Unit costs were then calculated as the sum of 2014 NTP expenditures and total costs for utilization of inpatient and outpatient care, divided by the reported number of patients treated. Again, this calculation was carried out separately for drug-susceptible and MDR-TB.

FIGURE 7.5

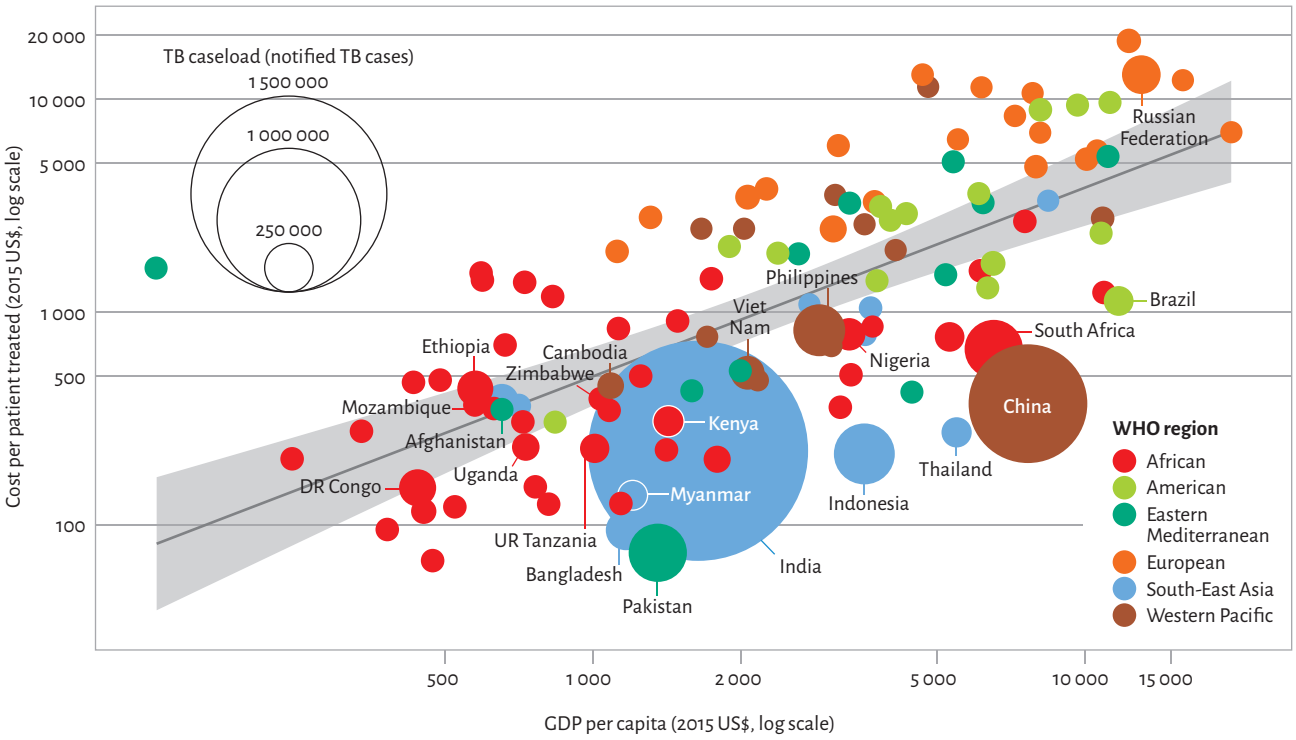
Funding gaps for TB prevention, diagnosis and treatment reported by countries, by income group and WHO region, 2006–2015 (constant 2015 US$ millions)[a]



[a] The upper-middle-income category includes three high-income countries that are in the list of TB and/or high MDR-TB burden countries: Estonia, Latvia and the Russian Federation.

FIGURE 7.6

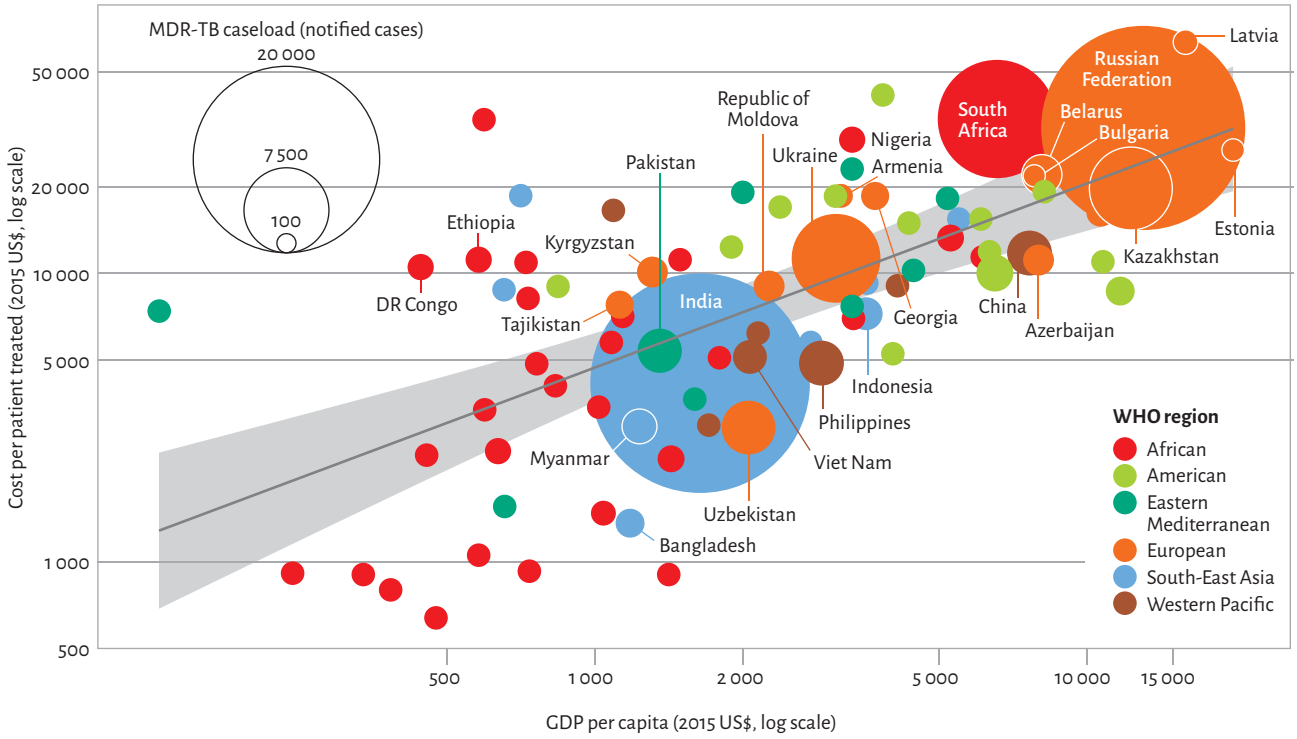
Estimated cost per patient treated for drug-susceptible TB in 117 countries, 2014[a]



[a] Limited to countries with at least 100 notified patients in 2014.

FIGURE 7.7

Estimated cost per patient treated for MDR-TB in 90 countries, 2014[a]



[a] Limited to countries with at least 20 patients on second-line treatment in 2014.

Although not yet be reflected in analyses for 2014, the Russian Federation reported hospitalization of about 65% of TB patients with drug-susceptible TB in 2015, compared with 93% in 2014.

Low-income countries spent on average US$ 516 per TB patient, while upper-middle-income or high-income countries invested an average of US$ 5 558. In the 22 HBCs, the estimated cost per patient treated for drug-susceptible TB in 2014 ranged from US$ 74 in Pakistan to US$12 988 in the Russian Federation. In all of the 22 HBCs, the cost per patient treated for drug-susceptible TB was less than gross domestic product (GDP) per capita. Six countries – China, India, South Africa, Indonesia, Bangladesh and Pakistan, which together account for 58% of the global TB burden – have costs per patient treated that are relatively low compared with their GDP per capita. While the level of GDP per capita clearly influences the cost of TB treatment, this shows that the size of the total patient caseload is also an important factor (for example, when numbers of patients treated are very large, economies of scale can be realised).

7.4.2 MDR-TB

For MDR-TB, the cost per patient treated ranged from an average of US$ 6 826 in low-income countries to an average of US$ 21 265 in upper middle-income countries in 2014. As for drug-susceptible TB, the cost per patient treated for MDR-TB was typically higher in countries of the former Soviet Union, ranging from US$ 2 935 in Uzbekistan to US$ 64 250 in Latvia (where all patients with MDR-TB are hospitalized for an average of 120 days, at an estimated cost of US$ 262 per day). This mainly reflects greater reliance on inpatient care, with admissions lasting up to an average of 240 days per patient and accounting for about 60% of the total cost of treatment.

7.5 Progress towards UHC: insights from health financing data

UHC is defined as access for all to essential preventive and treatment health care interventions, with financial protection.[1] In financing terms, the absolute level of funding for health care must be high enough to ensure that it is possible to provide essential health services to the whole population; additionally, the costs of using those services, once available, must not be prohibitive (using them should not result in financial hardship). Mandatory pre-payment financing mechanisms (such as taxation or social insurance schemes) need to form the core of domestic health financing.[2]

There are three health financing indicators for which benchmarks required to achieve UHC have been suggested and for which recent estimates are available for all countries to which the indicator applies. Analysis of data (from the WHO Global Health Expenditure database) for these three indicators can therefore provide useful insights into a country's progress towards, or achievement of, UHC. The three indicators are:

- Total government spending on health as a proportion of GDP: the suggested benchmark is 5–6%;[3,4,5]
- Government and donor-funded health expenditure per capita in low-income countries: the suggested benchmark is US$ 86 (in 2012 prices);[2]
- The share of out-of-pocket expenditures (OOP) in total health expenditures: the suggested benchmark is less than 15%.[1,6,7]

OOP expenditures are defined as direct payments made to health care providers by individuals at the time of service use, excluding prepayment for health services (for example in the form of taxes or specific insurance premiums or contributions) and, where possible, net of any reimbursements to the individual who made the payment.[8] The level of OOP expenditures provides a proxy measure of the degree to which people lack financial protection.

7.5.1 Government spending on health as a proportion of GDP

The latest data on government health expenditures (GHE) are for 2013.[9] GHE was less than 6% of GDP in most countries in 2013 (149/190, 78%), including all of the 36 countries in the current lists of high TB burden and/or MDR-TB burden countries (**Figure 7.8**). Among HBCs, those at the lowest end of the range were Bangladesh, Indonesia, India, Nigeria, Myanmar, Pakistan and the Philippines (all <1.5%); those closest to the 6% threshold were Brazil, South Africa and Thailand (all at around 4.5%). Among WHO regions, the South-East Asia Region had the lowest levels of health spending as a proportion of GDP.

There were 41 countries where government spending on health exceeded 6% of GDP. Of these, only six were low or lower-middle income countries: Rwanda, Swaziland, Lesotho, Samoa, Kiribati and Micronesia.

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1 World Health Organisation, World Bank Group. *Monitoring progress towards universal health coverage at country and global levels. Framework, measures and targets*. Geneva: World Health Organization; 2014 (WHO/HIS/HIA/14.1).

2 World Health Organization. *The World Health Report 2010. Health systems financing: the path to universal coverage*. Geneva: World Health Organization; 2010.

3 World Health Organization. *The World Health Report 2010. Health systems financing: the path to universal coverage*. Geneva: World Health Organization; 2010.

4 McIntyre et al. *Fiscal Space for Domestic Funding of Health and Other Social Services*. London: Chatham House; 2014.

5 World Health Organization and Pan American Health Organization. Resolution CD53.R14 *Strategy for universal access to health and universal health coverage*. 53rd Directing Council, 66th Session of the Regional Committee of WHO for the Americas. Washington: World Health Organization and Pan American Health Organization, 2014.

6 Xu et al, Protecting Households from Catastrophic Health Spending, *Health Affairs* 2007; 26(4): 972–983.

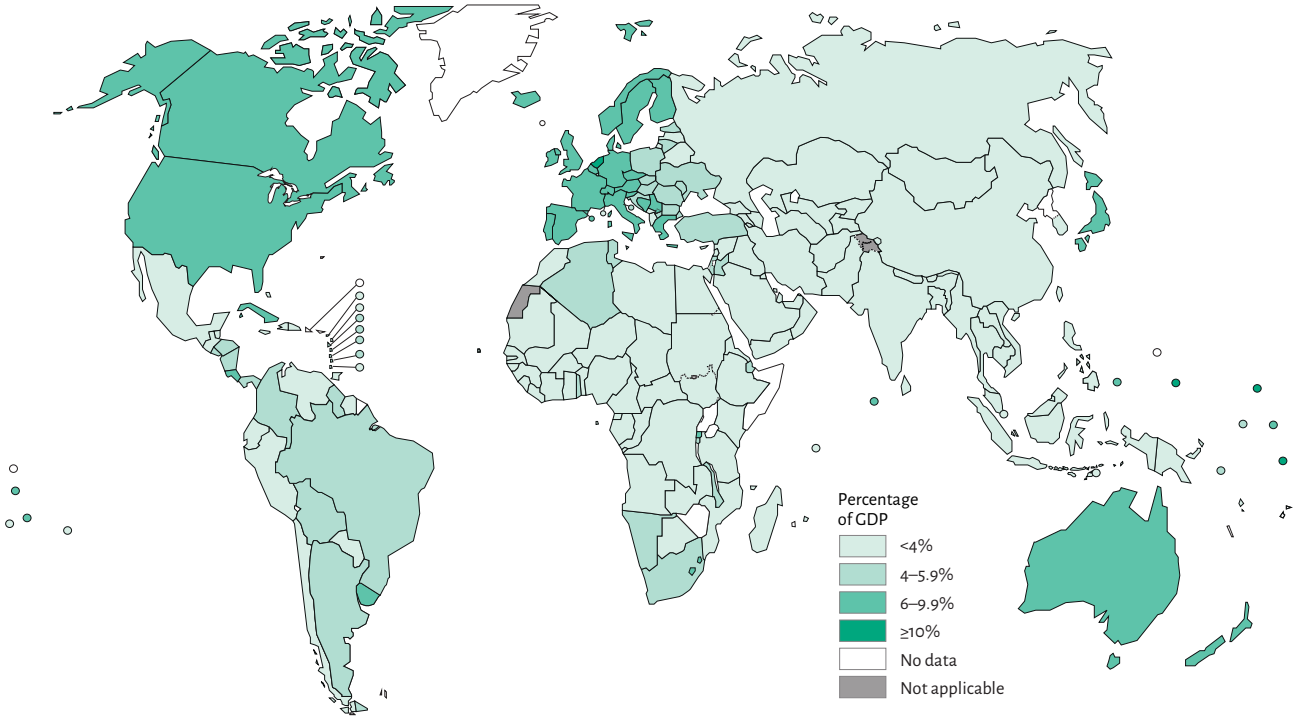
7 Xu et al., Household Catastrophic Health Expenditure: A Multicountry Analysis, *The Lancet* 2003;362: 111–117.

8 World Health Organization and World Bank. *First Global Monitoring Report on Tracking Universal Health Coverage*, 2015. http://www.who.int/healthinfo/universal_health_coverage/report/2015/en/.

9 WHO National Health Accounts database, accessed July 2015 via http://apps.who.int/nha/database

FIGURE 7.8

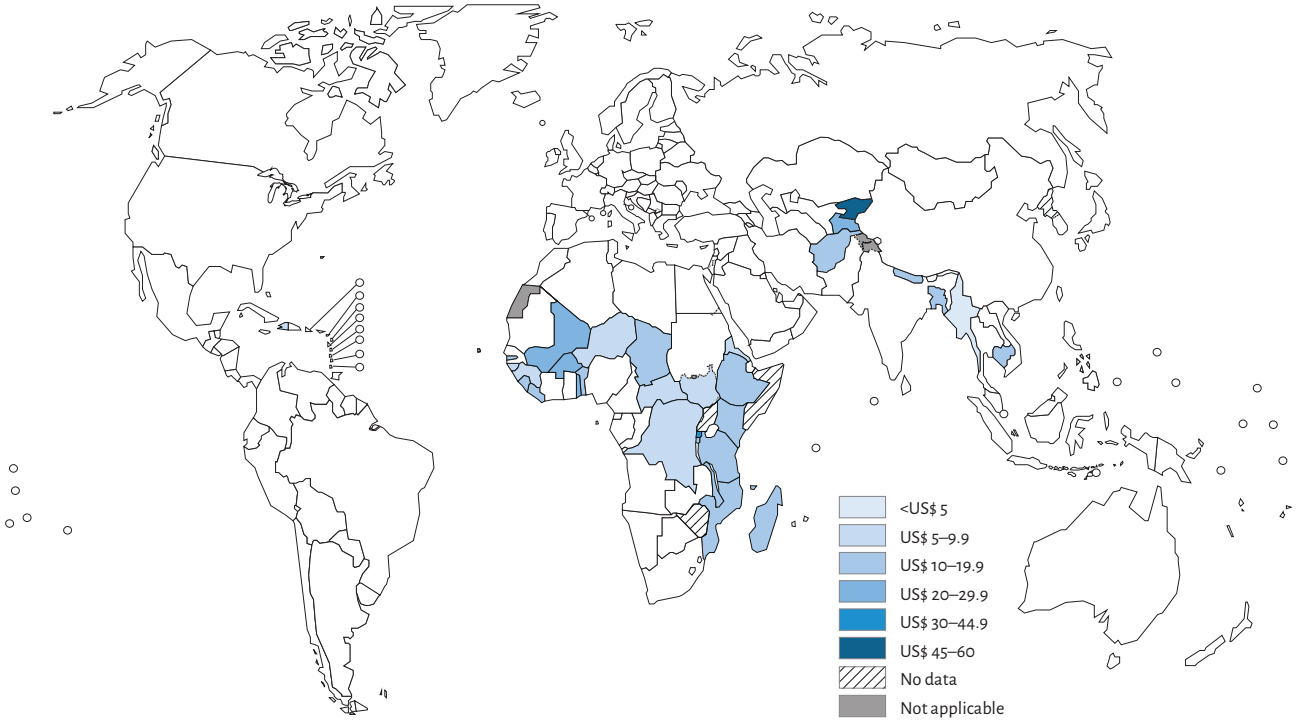
Government spending on health, as a percentage of gross domestic product (GDP), 2013[a]



[a] Data for Bahrain and Brazil are for 2012.

FIGURE 7.9

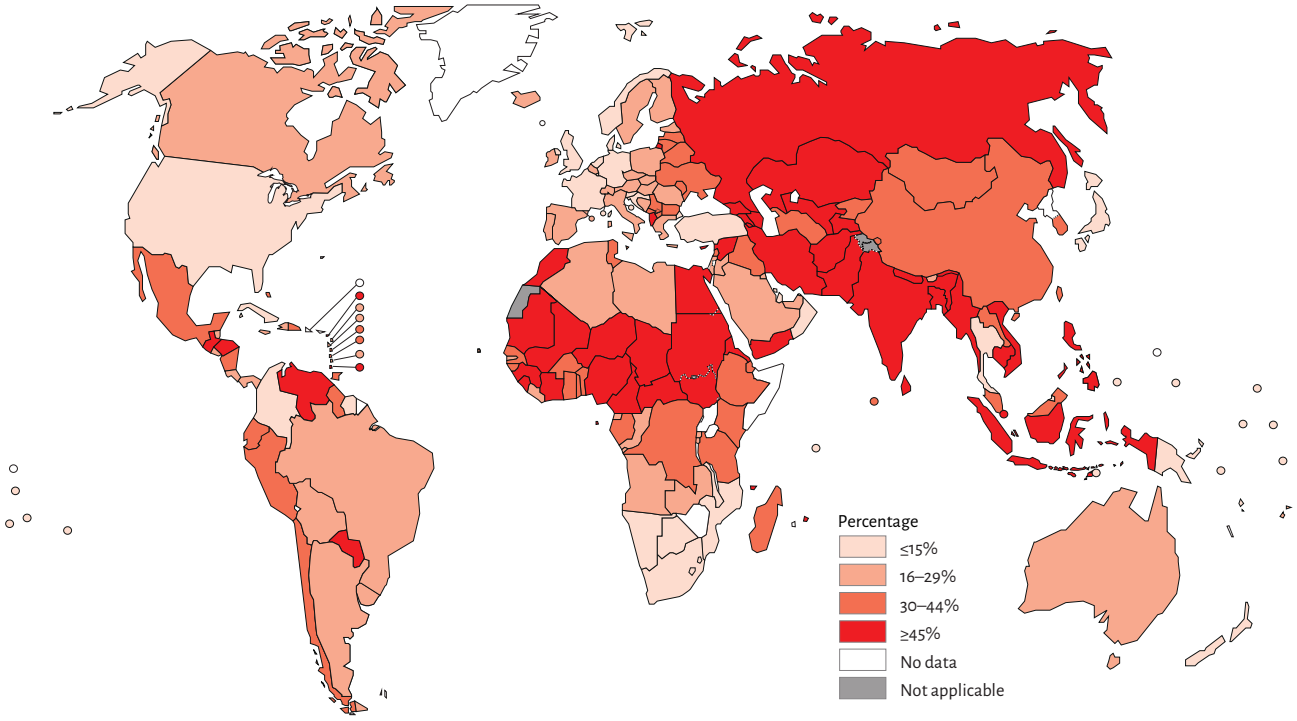
Government spending on health per capita in low-income countries (shown in blue), 2013. Middle and high-income countries are shown in white.[a]



[a] Countries are classified as per the World Bank income categories for 2013. Available at: http://data.worldbank.org/about/country-and-lending-groups

FIGURE 7.10

Out-of-pocket expenditures as a percentage of total health expenditures, 2013



7.5.2 Government spending on health per capita, low-income countries

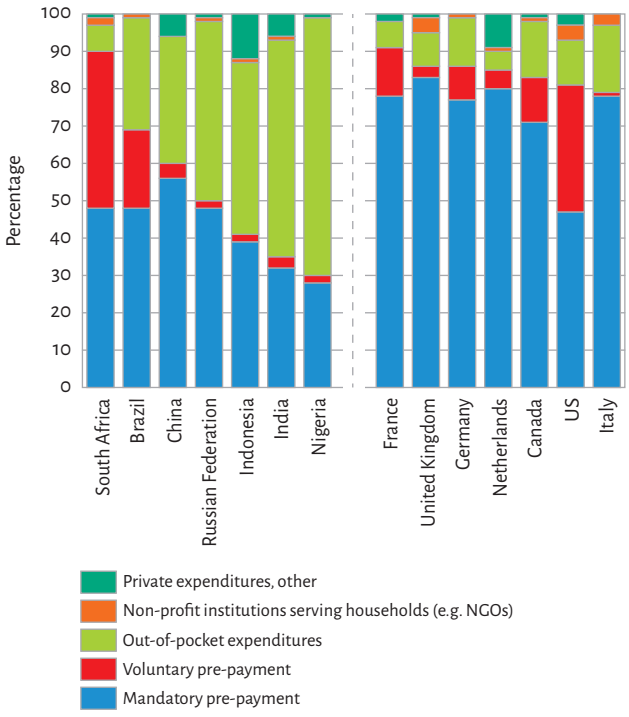
In 2013, government spending on health per capita was far below the suggested benchmark of US$ 86 per capita in all low-income countries (**Figure 7.9**). Most countries spent less than US$ 20 per capita. The countries that were closest to the benchmark were Rwanda (US$ 41 per capita) and Kyrgyzstan (US$ 51 per capita).

7.5.3 Share of out-of-pocket expenditures in total health expenditures

In 2013, OOP expenditures were less than 15% of total health spending in 43 of 190 countries for which data were available, including three HBCs: Mozambique, Thailand and South Africa (**Figure 7.10**). At the other end of the scale, there were 49 countries where OOP expenditures accounted for at least 45% of total health expenditures, including ten HBCs: Bangladesh, India, Indonesia, Cambodia, Nigeria, Myanmar, Pakistan, Philippines, Viet Nam and the Russian Federation. The global average in 2013 was 32%, a small reduction compared with 36% in 2000.[1] The breakdown of total health expenditures by source of funding, including OOP expenditures, is shown for selected high TB burden and high-income countries in **Figure 7.11**.

FIGURE 7.11

Total health expenditures by source of financing in selected high TB burden and high-income countries, 2013



[1] World Health Organization and World Bank. First Global Monitoring Report on Tracking Universal Health Coverage, 2015. http://www.who.int/healthinfo/universal_health_coverage/report/2015/en/.

7.5.4 Beyond financial risk protection

One of the three main targets in the End TB Strategy (2016–2035) is that no TB patients or their households should face catastrophic costs as a result of TB disease (**Chapter 1**). This target was specifically included because it is a key marker of financial risk protection and progress towards UHC and social protection for TB-affected households.[1] Catastrophic cost is a broader concept than catastrophic health expenditure, since it includes not only direct expenditures on health services but also (1) non-medical payments (such as transportation or lodging charges) that are directly related to accessing TB diagnosis and treatment and (2) indirect costs such as income losses (for example, related to time lost from work or loss of employment).

The proportion of patients and their households that experience catastrophic costs can be measured using periodic surveys. To support such surveys, WHO established a Task Force in 2015. The main focus of the Task Force's work in 2015 has been to develop a generic protocol and accompanying questionnaires,[2] building on methods used in previous studies of patient costs.

[1] Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias HM, et al. WHO's new End TB Strategy. *The Lancet*. 2015;385:1799-801. See in particular Panel 2 in the supplementary appendix.

[2] *Protocol for survey to determine direct and indirect costs due to TB and to estimate proportion of TB-affected households experiencing catastrophic costs – Field testing version*, 2015. Available from the Global TB Programme in WHO upon request.

CHAPTER 8

Research and development

Key facts and messages

Intensified research and development is one of the three pillars of the WHO post-2015 global TB strategy, and will play a crucial role in accelerating the reductions in TB incidence and mortality required to reach global TB targets by 2035. Efforts to develop new TB diagnostics, drugs, and vaccines intensified in the past decade, but considerable progress and investment is still needed.

The diagnostic technology landscape continues to look promising although very few technologies are at adequately advanced stages for WHO evaluation. Technologies under development include rapid tests to detect TB, drug resistance, or TB and drug resistance combined. Those based on molecular technologies such as nucleic acid amplification tests are the most advanced.

A new diagnostic platform called the GeneXpert Omni® is in development. This is intended for point-of-care testing for TB and rifampicin-resistant TB using existing Xpert MTB/RIF® cartridges. This new platform will be assessed by WHO for equivalence to the current GeneXpert platform in 2016. A next-generation cartridge called Xpert Ultra® is also in development, and is expected to replace the Xpert MTB/RIF cartridge. The Xpert Ultra assay will be assessed in 2016 in two stages, first as a replacement for the current Xpert MTB/RIF assay and second as a replacement for conventional diagnostic culture.

In 2015, three diagnostic tests were reviewed by WHO: Determine TB LAM (lipoarabinomannan), referred to as LF-LAM; and two new generic versions of line probe assays (LPAs) for first-line drugs. LF-LAM is not recommended for the diagnosis of TB (pulmonary and extrapulmonary), with the exception of people living with HIV who have low CD4 counts or who are seriously ill. WHO will update current policy recommendations for the use of LPAs in early 2016.

Two new drugs have recently been recommended for the treatment of MDR-TB under specific conditions. The first, bedaquiline, was approved by the US Food and Drug Administration (FDA) in December 2012 and the second, delamanid, was approved by the European Medicines Agency in November 2013. WHO issued interim guidance on the use of these two drugs in the treatment of MDR-TB in June 2013 and October 2014, respectively. Additionally, there are eight new or repurposed anti-TB drugs in advanced phases of clinical development. For the first time in six years, a new anti-TB drug candidate has entered a Phase I clinical trial: TBA-354, a nitroimidazole that is part of the same class of drugs as delamanid and pretomanid.

Results from three Phase III trials investigating four-month regimens for the treatment of drug-susceptible TB that include fluoroquinolones were released in 2014. These shorter regimens failed to show non-inferiority to the six-month standard of care regimen currently recommended by WHO. Several new regimens, including new and/or re-purposed drugs, are now being tested in a series of Phase II/III trials for the treatment of drug-susceptible and/or drug-resistant TB.

Two recent observational studies of the effectiveness of shorter treatment regimens for patients with MDR-TB in Niger and Cameroon have shown that a 12-month treatment regimen was effective and well-tolerated in patients not previously exposed to second-line drugs.

There are 15 vaccine candidates in clinical trials. Results of Phase II efficacy data to determine whether BCG and/or H4:IC31 can prevent infection, and M72 can prevent disease, as well as phase III data of whether M.vaccae can prevent disease, will shortly be available. Major shifts in TB vaccine research and development include the introduction of more stringent gating criteria/mechanisms for candidate entry into and progress in clinical trials; vaccine discovery that explores induction of immunity beyond conventional T cells; and support of experimental medicine studies for knowledge generation and to better connect data from animal models and human studies.

The goal of the End TB strategy endorsed by the World Health Assembly (WHA) in May 2014 is to end the global TB epidemic (**Chapter 1**). Despite major progress in TB prevention, diagnosis and treatment since the mid-1990s (**Chapters 2–7**), reaching this goal will require major technological breakthroughs from the research and development pipeline by 2025; these would make possible a major acceleration in the rate at which TB incidence declines compared with historic levels. Critical components include: the availability of affordable short, effective and well-tolerated treatments for all forms of TB (latent TB infection, drug-susceptible and drug-resistant TB disease); a point-of-care diagnostic test with capacity to identify resistance to the most important anti-TB drugs; and an effective post-exposure vaccine.

This is the fifth successive year in which a chapter on research and development is included in the *Global tubercu-*

FIGURE 8.1

An overview of progress in the development of molecular TB diagnostics, August 2015[a]

FOR USE IN REFERENCE -LEVEL LABORATORIES	FOR USE IN INTERMEDIATE-LEVEL LABORATORIES	FOR USE IN PERIPHERAL-LEVEL LABORATORIES
m2000 RealTime MTB assay, Abbott, USA	FluoroType MTB / FluoroType MTB RNA, Hain Lifesciences, Germany	Alere Q, Alere, USA
TruArray MDR-TB, Akkoni, USA	iCubate System, iCubate, USA	TB-LAMP, Eiken, Japan
BioFilmChip MDR-TB, AutoGenomics, USA	AdvanSure, LG Life sciences, Republic of Korea	B-SMART, LabCorp, USA
MTBC-OCTA, AutoGenomics, USA	LPA NTM/MTB DR, Nipro, Japan	Genedrive MTB/RIF ID, Epistem, UK
BD ProbeTec ET Direct TB assay, BD, USA	vereMTB, Veredus Laboratories, Singapore	HYDRA, Insilixa Inc, USA
TB drug resistance array, Capital Bio, China	SPEED-OLIGO®, Vircell, Spain	TBDx System, KGI, USA
AMTD test, Hologic Genprobe, USA	MolecuTech REBA, YD Diagnostics, Korea	Truelab/Truenat MTB, Molbio/bigtec Diagnostics, India
Cobas TaqMan MTB test, Roche, Switzerland	LATE-PCR, Brandeis University, USA	Savanna, NWGHF, USA
Anyplex™, Seegene, Korea	GeneXpert XDR cartridge, Cepheid, USA	EasyNAT TB Diagnostic kit, Ustar Biotechnologies, China
Magicplex™ MTB, Seegene, Korea	Xpert Ultra, Cepheid, USA	EOSCAPE-TB, Wave 80 Biosciences, USA
TRC Rapid®M.TB, Tosoh Bioscience, Japan	Enigma ML, Enigma Diagnostics, UK	GenePOC test, GenePOC, Canada
MeltPro®, Zeesan Biotech, China		Xpert Omni, Cepheid, USA

[a] This is not an exhaustive list of technologies in development. Those listed are the ones documented in publications by UNITAID and TAG:

UNITAID. 2014. Tuberculosis Diagnostic Technology and Market Landscape 3rd edition. Geneva: World Health Organization. Available at: http://www.unitaid.eu/images/marketdynamics/publications/UNITAID_TB_Diagnostics_Landscape_3rd-edition.pdf

Harrington M. "The tuberculosis diagnostics pipeline" in *2015 Pipeline Report: HIV, Hepatitis C Virus (HCV) and Tuberculosis Drugs, Diagnostics, Vaccines, Preventive Technologies, Research Toward a Cure, and Immune-Based and Gene Therapies in Development*. New York, Treatment Action Group, 2015. Available at: http://www.pipelinereport.org/sites/g/files/g575521/f/201507/2015%20Pipeline%20Report%20Full.pdf

losis report. The status of progress in the development of new TB diagnostics, drugs and vaccines as of August 2015 is summarized, based on recent publications and communications with and contributions from the secretariats of the relevant Working Groups of the Stop TB Partnership.

8.1 New diagnostics for TB

The End TB strategy targets set for 2035 are to reduce the absolute number of TB deaths by 95% and to reduce the TB incidence rate by 90%, compared with a baseline of 2015 (**Chapter 1**). To achieve these targets, national TB programmes (NTPs) first need to implement strategies that fully optimize the use of existing diagnostic technologies. Research and development is required so that new rapid tests that can be used at the point of care, and that accelerate access to testing for drug susceptibility for all bacteriologically-confirmed TB cases, become available.

8.1.1 An overview of the diagnostics pipeline

Although very few technologies are at an advanced stage of evaluation, the diagnostic technology landscape continues to look promising. An overview of the diagnostic pipeline for rapid molecular tests in August 2015 is shown in **Figure 8.1**. The list of technologies is not necessarily complete or exhaustive, but does reflect technologies that have been documented in recent reports published by UNITAID[1] and Treatment Action Group (TAG).[2] Tools using molecular technologies such as nucleic acid amplification tests (NAATs) are the most advanced. Technologies under development include tests to detect TB, drug resistance, or TB and drug resistance combined. These include microarray-based multiplexing diagnostic platforms for the simultaneous detection of a large number of resistance-conferring mutations. Unfortunately, most tests under development are intended for use at the reference or intermediate laboratory level only, requiring dedicated infrastructure and experienced staff.

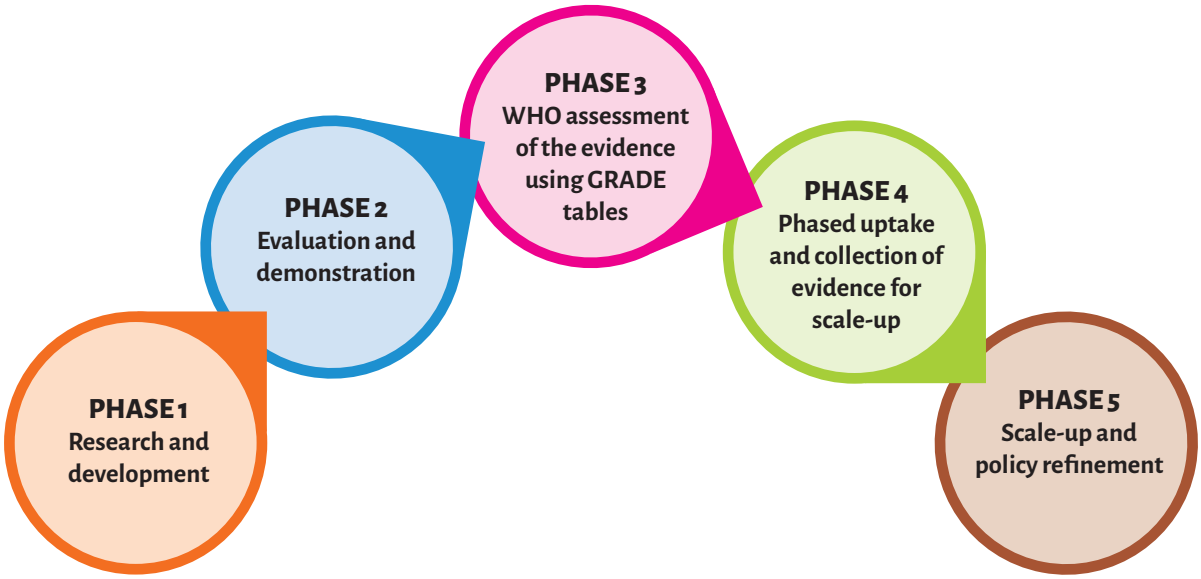
There are at least three technologies that are commercially available (Epistem Genedrive, Epistem, UK; Molbio Truelab, Molbio, India and EASYNAT, Ustar, China) that are intended for use at the microscopy level. However, to date no multicentre evaluation and/or demonstration studies in different epidemiological setting have been conducted. These are necessary to generate the performance data required by WHO to assess and produce recommendations on these technologies (**Figure 8.2**). Evaluation studies are expensive, and therefore additional funding is urgently needed, both to expedite the progress of promising new technologies through the pipeline and to conduct the necessary evaluation studies. Priority should be given to tests that are suitable for use at the lower levels of the health system. The Foundation for Innovative New Diagnostics (FIND) remains the lead organization conducting field evaluations of different

[1] UNITAID. 2014. Tuberculosis Diagnostic Technology and Market Landscape 3rd edition. Geneva: World Health Organization. Available at: http://www.unitaid.eu/images/marketdynamics/publications/UNITAID_TB_Diagnostics_Landscape_3rd-edition.pdf

[2] Harrington M. "The tuberculosis diagnostics pipeline" in 2015 *Pipeline Report: HIV, Hepatitis C Virus (HCV) and Tuberculosis Drugs, Diagnostics, Vaccines, Preventive Technologies, Research Toward a Cure, and Immune-Based and Gene Therapies in Development*. New York, Treatment Action Group, 2015. Available at: http://www.pipelinereport.org/sites/g/files/g575521/f/201507/2015%20Pipeline%20Report%20Full.pdf

FIGURE 8.2

The phases of TB diagnostics development and assessment for WHO recommendation using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) process



technologies, but the engagement of other stakeholders and adequate funding are urgently needed.

A new diagnostic platform called the GeneXpert Omni® is in development. This is intended for point-of-care testing for TB and rifampicin-resistant TB using existing Xpert MTB/RIF® cartridges. The device is expected to be smaller, lighter, and less expensive than other currently available platforms for point-of-care nucleic acid detection. The platform will come with a built-in four-hour battery; an auxiliary battery that provides an additional 12 hours of run time is also available. In 2016, this new platform will be assessed by WHO for non-inferiority to the current GeneXpert platform.

Major gaps still remain in the diagnostic pipeline, and slow progress in the evaluation of technologies in the late stages of development is the major barrier to these tools reaching the market. There are insufficient tests under development for the diagnosis of TB in children, assessment of susceptibility to drugs that may be part of new treatment regimens, prediction of progression from latent TB infection (LTBI) to active TB disease and alternatives to TB culture for treatment monitoring. The development and implementation of such tests as well as increasing access to technologies already endorsed by WHO will be essential to meet targets outlined in the End TB Strategy.

8.1.2 TB diagnostic tests reviewed by WHO in 2015

In 2015, three diagnostic tests were reviewed by WHO: Determine TB LAM (lipoarabinomannan), referred to as LF-LAM, developed by Alere, USA; and two new generic versions of line probe assays (LPAs), one developed by the Nipro Corporation, Japan and the other by Hain Lifesciences.

LF-LAM (Alere, USA)

LF-LAM is a lateral flow test that has been evaluated in several studies for the detection of active TB in people living with HIV who are severely immunocompromised. Evidence from a systematic review of the performance characteristics of the assay was considered by a Guideline Development Group convened by WHO in 2015. This group recommended that LF-LAM should not be used for the diagnosis of TB (pulmonary and extrapulmonary), with the exception of people living with HIV who have low CD4 counts or who are seriously ill. More details on these recommendations are provided in **Chapter 5**.

New generic versions of LPAs (Nipro Corporation, MTBDRplus version 2)

For new versions of technologies that WHO has already recommended, WHO requires a head-to-head comparison with the existing technology. If non-inferiority (that is, their equivalence) in performance can be demonstrated, then WHO will recommend the new version.

In 2008, WHO endorsed the use of LPAs for the rapid detection of rifampicin resistance, beginning what might be considered to be the molecular revolution in detection of drug-resistant TB. The evidence and subsequent recommendations for the utility of LPAs included an assessment of the performance of the GenoType® MTBDR*plus assay*, Hain Lifescience (Hain Version 1 assay). This assay incorporates *rpoB* probes for rifampicin resistance detection as well as *katG* probes and *inhA* probes for the determination of isoniazid resistance. Hain Lifesciences have subsequently developed an updated version of their MTBDR*plus* line probe assay (Hain Version 2 assay).

Nipro Corporation, Japan has developed an LPA that is similar to that of Hain Lifesciences, which was registered in Japan in 2012 (Nipro assay). This assay allows for the detection of rifampicin and isoniazid conferring mutations, the identification of *M. tuberculosis* complex and the identification of some common nontuberculous mycobacteria including *M. avium*, *M. intracellulare* and *M. kansasii*.

In 2014 and 2015, FIND coordinated a multi-center, blinded cross-sectional study of the diagnostic accuracy of these two tests, to compare their performance against that of the Hain Version 1 assay. A composite reference standard including phenotypic drug susceptibility testing (DST) and DNA sequencing was used. The study was divided into two distinct phases. Phase 1 was designed to evaluate the performance of the newer assays on a wide range of clinical isolates and Phase 2 to evaluate their performance on sputum specimens from patients with pulmonary TB.

The study demonstrated non-inferiority of the newer LPA assay versions (Hain Version 2 and Nipro) in comparison with the Hain Version 1 assay; these assays showed comparable performance for the detection of *M. tuberculosis* and rifampicin resistance conferring mutations in acid-fast bacilli smear-positive samples and isolates of M. tuberculosis. WHO will update current policy recommendations for the use of LPAs and review new evidence about the clinical utility of the Hain Lifescience GenoType MTBDR*sl* assay and will assess the role of sequencing in detecting resistance to second-line drugs in 2016.

8.1.3 Technologies scheduled for field evaluation studies in 2016

There are two technologies scheduled for field evaluation in 2016.

Xpert Ultra, Cepheid

A new version of the Xpert MTB/RIF assay, called Xpert Ultra®, is in development. The aim is to improve the sensitivity and specificity of the current assay in detection of TB and rifampicin resistance, respectively. In 2016, FIND will initiate a two-step evaluation process. The first step is a rapid non-inferiority study that will compare the new Xpert Ultra assay with the current Xpert MTB/RIF assay. If non-inferiority is demonstrated, the Xpert Ultra assay will be recommended as a replacement for the current Xpert MTB/RIF assay. The second step will be multi-country evaluation studies. It is anticipated that these studies will demonstrate that the Xpert Ultra assay has superior performance (for example, about 95% sensitivity in detecting smear-negative, culture-positive TB from a single sputum specimen). The Xpert Ultra assay will be developed for use on the Omni platform (described above).

Alere Q, Alere

The Alere™ q TB diagnostic system is being developed with funding support from the Bill & Melinda Gates Foundation. It is a rapid and sensitive test for detection of TB, followed by an immediate reflex test for a full analysis of drug resistance for people found to have TB. A sputum sample is collected in a cup that is then screwed onto the test cartridge, which contains all reagents. The inoculated cartridge is subsequently placed into a battery-powered stand-alone device that allows for sample processing, DNA amplification, detection and result interpretation and reporting in approximately 20 minutes. This technology is a major step towards achieving universal DST for all TB cases. Multi-centre evaluation studies are planned for 2016–2017.

8.1.4 Tests that predict progression from latent to active TB

Most people with LTBI have no signs and symptoms of TB disease. People with LTBI are not infectious, but they are at risk for developing active disease and becoming infectious. On average, 5–15% of those infected will develop active TB during their lifetime, typically within the first 2–5 years after the initial infection. Current tests for LTBI (i.e. interferon gamma release assays, IGRAs; and the tuberculin skin test, TST) are immunity-based and have very limited ability to identify which individuals are likely to progress to active TB. They also have limited sensitivity in people with HIV infection, and are not able to differentiate between recent and remote infection or to distinguish if a person has been re-infected if re-exposed.

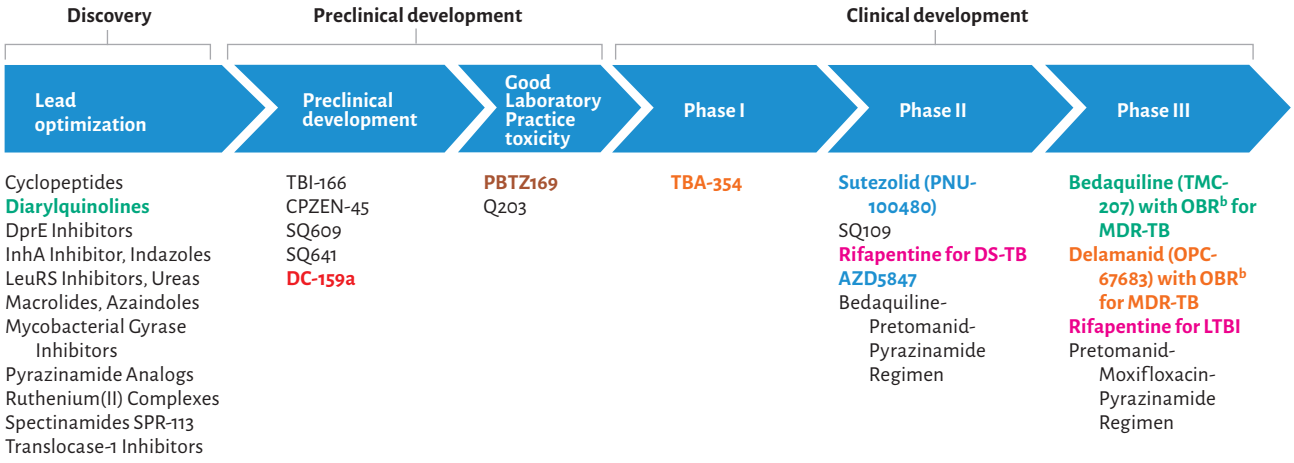
In May 2015, WHO hosted a meeting on behalf of FIND and the New Diagnostics Working Group of the Stop TB Partnership to review a set of minimal and optimal performance characteristics and develop a target product profile (TPP) for a biomarker-based test to predict the risk of progression to active TB from LTBI and rule out active TB. The meeting was attended by representatives from the diagnostic development industry, universities, clinicians and technical partners. Following the meeting, the process to define the TPP for a test for progression of LTBI has continued alongside the development of standardized study protocols that could be used to evaluate the performance of such tests.

8.2 New drugs and drug regimens to treat TB

Much progress has been made during the last ten years in the treatment of TB. The body of knowledge about the use of various drugs in combination regimens, as well their potential interaction with ARVs and the optimum timing of ART in the treatment of HIV-positive TB patients, has grown substantially. However, TB treatment remains centred on the standard 6 month regimen of isoniazid, rifampicin, pyrazinamide and ethambutol. Ensuring adherence to treatment remains a challenge, and drug-resistant TB remains a major threat to global TB prevention, diagnosis and treatment (**Chapter 4**). This section provides an overview of the latest status of the development of new TB drugs and new TB treatment regimens.

FIGURE 8.3

The development pipeline for new TB drugs, August 2015[a]



[a] Details for projects listed can be found at http://www.newtbdrugs.org/pipeline.php and ongoing projects without a lead compound series identified can be viewed at http://www.newtbdrugs.org/pipeline-discovery.php

[b] OBR = Optimized Background Regimen

Source: Working Group on New TB Drugs, 2015 – www.newtbdrugs.org

8.2.1 The pipeline of new and re-purposed anti-TB drugs

The status of the pipeline for new and repurposed anti-TB drugs in August 2015 is shown in **Figure 8.3**. There are eight drugs in Phase I, Phase II or Phase III trials for the treatment of drug-susceptible, multidrug-resistant TB (MDR-TB) or LTBI. Two of these compounds (AZD5847 and Sutezolid) do not appear to have progressed in the last two years. However, for the first time in six years, a new anti-TB drug candidate has entered a Phase I clinical trial: TBA-354, a nitroimidazole that is part of the same class of drugs as delamanid and pretomanid (formerly PA-824).[1] In addition, more diversified fundamental research is being conducted to better understand the diversity of the metabolic stages of *M. tuberculosis* and associated host responses, and to identify novel targets against which therapeutic chemicals can be directed. This is important to ensure that drugs are effective throughout the various stages of TB – from acute disease through treatment of chronic bacterial carriage to cure.

Rifapentine for drug-susceptible TB

Investigation of the potential effectiveness of rifapentine in the treatment of drug-susceptible TB, is continuing based on the results of the TB Trial Consortium (TBTC) Study 29 that showed comparable efficacy of daily rifapentine (10 mg/kg) and rifampicin (10 mg/kg) when provided alongside standard doses of isoniazid, ethambutol and pyrazinamide. The outcome of interest is culture conversion at two months in smear-positive pulmonary TB patients.[2] A further study (Study 29X), aimed at investigating the effect of various dosages of rifapentine (10, 15 or 20 mg/kg, given seven days a week with food supplements), showed that the substitution of high-dose daily rifapentine for rifampicin improved the antimicrobial activity of combination chemotherapy during the intensive phase of treatment, and that this activity was driven by rifapentine exposure.[3] The observed safety and tolerability combined with the high levels of antimicrobial activity observed in the groups that received higher doses of rifapentine provide support for the evaluation of high-dose daily rifapentine-containing regimens of less than six months duration in Phase III clinical trials.

Rifampicin

Assessment of whether higher doses of rifampicin could reduce treatment duration for drug-susceptible TB has continued. Results from the PanACEA MAMS-TB-01 trial presented at the Conference on Retroviruses and Opportunistic Infections (CROI) in March 2015 showed that daily dosing with 35 mg/kg of rifampin (in addition to standard doses of isoniazid, ethambutol, and pyrazinamide) reduced the time

[1] ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (U.S.). 2000. Identifier NCT02288481, A phase 1 study to evaluate the safety, tolerability, and pharmacokinetics of TBA-354 in healthy adult subjects; 2014 November 7. https://clinicaltrials.gov/ct2/show/NCT02288481

[2] Dorman S et al. Substitution of Rifapentine for Rifampin During Intensive Phase Treatment of Pulmonary Tuberculosis: Study 29 of the Tuberculosis Trials Consortium. *J Infect Dis.* 2012, 206 (7): 1030–1040.

[3] Dorman S et al. Daily Rifapentine for Treatment of Pulmonary Tuberculosis: A Randomized, Dose-Ranging Trial. *Am J Respir Crit Care Med* 2015, 191; 333–343.

to stable culture conversion when measured over 12 weeks on liquid media, but not on solid media, compared to the standard six month regimen.[1] In the same trial, a second arm in which 20 mg/kg of rifampin + moxifloxacin was provided showed a non-significant improvement in the time to culture conversion on liquid media over 12 weeks, but no improvement when measured using solid media. Both arms appeared safe and well tolerated, but a slightly higher percentage of patients (14% versus 10%) experienced grade 3 adverse events compared with the control arm. There were potentially higher rates of hepatic adverse events that resulted in a change of treatment in the 35 mg/kg rifampin arm. Final analysis of results is underway. Further research about the safety and efficacy of higher dosages of rifampicin, with or without moxifloxacin, and its capacity to shorten treatment, is needed.

Fluoroquinolones

The results from three Phase III trials of four-month combination regimens for the treatment of drug-susceptible TB, all of which included a fluoroquinolone, were published in late 2014. These were: (i) the OFLOTUB trial, in which gatifloxacin was substituted for ethambutol;[2] (ii) the ReMOX trial, in which moxifloxacin was substituted for either ethambutol or isoniazid;[3] and (iii) the Rifaquin trial, in which moxifloxacin was substituted for isoniazid in the intensive phase of treatment and rifapentine was used in the continuation phase of treatment.[4]

Disappointingly, all of these trials showed that the shortened regimen cannot be recommended for the treatment of uncomplicated smear-positive pulmonary TB. Moreover, the inclusion of a third-generation fluoroquinolone as a substitute for either ethambutol or isoniazid was associated with a higher risk of relapse compared with the standard regimen of six months.

Bedaquiline

In December 2012, bedaquiline was approved by the US Food and Drug Administration (FDA) for treatment of MDR-TB as part of combination therapy for adults with pulmonary TB when other alternatives are not available. The drug is being introduced in several countries for the treatment of severe forms of MDR-TB (**Chapter 4**), following interim guidance issued by WHO in 2013.[5]

The safety and efficacy of bedaquiline in combination with short MDR-TB regimens of six and nine months duration is currently being investigated as part of the Phase III STREAM trial. These shorter regimens are being compared with the current standard of care for MDR-TB recommended by WHO.

Delamanid

In November 2013, a conditional marketing authorization for delamanid was granted by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA). Delamanid was authorized for use as part of a combination regimen for pulmonary MDR-TB in adult patients "when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability". Interim guidance on the use of delamanid was issued by WHO in October 2014.[6]

Delamanid is currently being tested in a Phase III clinical trial, as an addition to an optimized background regimen (OBR) for the treatment of MDR-TB. The trial is comparing six months of treatment with delamanid plus the OBR with a placebo plus OBR. It is anticipated that the trial will be completed in 2016.

Two other trials are evaluating the use of delamanid in the treatment of children with MDR-TB. The first trial is a 10-day open label pharmacokinetic (PK) study of delamanid plus an OBR. Patients who successfully complete this trial may then be enrolled in a second, open-label study (Trial 242-12-233) to assess the safety, tolerability, PK, and efficacy of delamanid plus an OBR over a six-month treatment period. These trials are scheduled for completion in 2017.

Pretomanid

Pretomanid is a nitroimidazole developed by the Global Alliance for TB drug development. It is being tested as part of three potential combination regimens for the treatment of both drug-susceptible and drug-resistant TB (further details are provided in **section 8.2.2**).

SQ109

Preliminary results from the PanACEA MAMS-TB-01 trial presented at CROI in March 2015 showed that there was no benefit of including SQ109 instead of ethambutol in standard therapy for drug-susceptible TB, in terms of time to culture conversion measured over 12 weeks.[1]

8.2.2 Trials of new regimens for the treatment of drug-susceptible and/or drug-resistant TB

Besides individual compounds, new combinations of drugs are being tested in several Phase II or Phase III trials.

The **NC-002** Phase IIb trial, conducted by the Global Alli-

[1] Boeree M, Hoelscher M. High-dose rifampin, SQ109 and moxifloxacin for treating TB: the PanACEA MAMS-TB trial. Paper presented at: 22nd Conference on Retroviruses and Opportunistic Infections; 2015 February 23–26; Seattle, WA.

[2] Merle CS et al. A Four-Month Gatifloxacin-Containing Regimen for Treating Tuberculosis. *N Engl J Med* 2014;371:1588–98.

[3] Gillespie SH et al. Four-Month Moxifloxacin-Based Regimens for Drug-Sensitive Tuberculosis. *N Engl J Med* 2014;371:1577–87.

[4] Jindani A et al. High-Dose Rifapentine with Moxifloxacin for Pulmonary Tuberculosis. *N Engl J Med* 2014;371:1599–608.

[5] *The use of bedaquiline in the treatment of multidrug-resistant tuberculosis: Interim policy guidance*. Geneva: World Health Organization; 2013 (WHO/HTM/TB/2013.6). Available at: http://apps.who.int/iris/bitstream/10665/84879/1/9789241505482_eng.pdf

[6] *The use of delamanid in the treatment of multidrug-resistant tuberculosis: Interim policy guidance*. Geneva: World Health Organization; 2014(WHO/HTM/TB/2014.23). Available at: http://apps.who.int/iris/bitstream/10665/137334/1/WHO_HTM_TB_2014.23_eng.pdf

ance for TB Drug Development (referred to in this text as "TB Alliance") in South Africa and the United Republic of Tanzania, investigated the efficacy, safety and tolerability of the combination of moxifloxacin + pretomanid + pyrazinamide (MPaZ) after eight weeks of treatment in 207 adult patients with newly diagnosed drug-susceptible or smear-positive pulmonary MDR-TB.[1] Two doses of pretomanid were tested (100 mg and 200 mg); the 26 MDR-TB patients received only the higher dose. The primary endpoint was the rate of change in colony forming units (CFUs) from sputum on solid culture over eight weeks. Results of this trial showed that the MPaZ regimen had active bactericidal activity against both drug-susceptible and MDR-TB over two months and that this bactericidal activity was significantly greater than that of isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE) therapy in patients with drug-susceptible TB when the MPa(200mg)Z regimen was used. The frequency of adverse events was similar to standard treatment in all groups. The combination of moxifloxacin, pretomanid, and pyrazinamide thus appeared to be safe, well-tolerated, and showed superior bactericidal activity for treatment of drug-susceptible TB during the first eight weeks of treatment.

On the basis of the results from the Phase IIb trial, a Phase III trial was launched in February 2015. Known as the STAND trial, it will be implemented in 16 countries and is a partially randomized clinical trial. Treatments are assigned to five parallel groups: Pa(100mg)-M-Z for 4 months for 350 patients with drug-susceptible TB; Pa(200mg)-M-Z for four months for 350 patients with drug-susceptible TB; Pa(200mg)-M-Z for six months for 350 patients with drug-susceptible TB; HRZE for six months for 350 patients with drug-susceptible TB; and Pa(200mg)-M-Z for six months for 350 patients with drug-resistant TB.

The **NC-003** trial tested the 14 day early bactericidal activity (EBA) of various combinations of clofazimine, bedaquiline, pretomanid and pyrazinamide in patients with drug-susceptible TB.[2] Following the results from this trial, a Phase IIb trial, **NC-005**, has been launched. This is testing all-oral combination regimens that include bedaquiline (two different doses), pretomanid, and pyrazinamide for patients with drug-susceptible TB, and these drugs in combination with moxifloxacin for patients with MDR-TB. The trial is measuring the decline in CFUs over eight weeks, and the time to positivity based on results from pooled sputum sampling every 16 hours. This study started in October 2014, and results are expected in mid-2016.

The **NiX-TB** study, implemented by the TB Alliance in South Africa, started in April 2015. It is investigating the safety and efficacy of a six month combination of bedaquiline, pretomanid and linezolid (all compounds that are new or to which there is little pre-existing resistance due to limited use) for TB patients with XDR-TB. The primary endpoint is the incidence of bacteriologic failure or relapse or clinical failure, with follow-up for 24 months after the end of treatment. Alongside the Nix-TB study, the TB Alliance is undertaking a study of the response to different doses of linezolid in patients with drug-susceptible TB over two weeks. This study will inform dosing adjustments that may need to be made for linezolid in the NiX-TB trial or other regimens that include linezolid.

There are two clinical trials scheduled to start around the end of 2015. The first is called the endTB trial. It is a Phase III trial funded by UNITAID and implemented by Partners in Health and Médecins Sans Frontières. It will evaluate five new all-oral short regimens for the treatment of MDR-TB. These regimens contain one new anti-TB drug (either bedaquiline or delamanid), moxifloxacin or levofloxacin, and pyrazinamide plus linezolid or clofazimine or both, in various combinations. They will be compared with the current WHO standard of care. Potential sites include Georgia, Kazakhstan, Kyrgyzstan, Lesotho and Peru. The second is the TB-PRACTECAL trial. This is a randomized, controlled, open-label, Phase II/III adaptive trial that will evaluate the safety and efficacy of six-month regimens that contain bedaquiline, pretomanid and linezolid with or without moxifloxacin or clofazimine for the treatment of adults with MDR-TB or XDR-TB. The trial is funded by Médecins Sans Frontières and will be conducted in Uzbekistan and Swaziland.

In addition to trials, two recent observational studies investigating the effectiveness of shorter treatment regimens for patients with MDR-TB in Niger[3] and Cameroon[4] have shown that a 12-month treatment regimen was effective and well-tolerated in patients not previously exposed to second-line drugs.

8.2.3 Treatment of latent TB infection (LTBI)

Since the publication of WHO guidelines on the treatment of LTBI in 2015,[5] new evidence about the benefits of isoniazid preventive therapy (IPT) when provided in addition to antiretroviral therapy (ART) to HIV-positive people with very high CD4 counts has become available from the TEMPRANO ANRS 12136 trial.[6] This trial included 2056 patients in Côte

[1] Dawson R et al. Efficiency and safety of the combination of moxifloxacin, pretomanid (PA-824), and pyrazinamide during the first 8 weeks of antituberculosis treatment: a phase 2b, open-label, partly randomised trial in patients with drug-susceptible or drug-resistant pulmonary tuberculosis. *Lancet* 2015

[2] Everitt D et al. 14 Day EBA study of clofazimine alone and in combination. 44th Union World Conference on Lung Health, Late-breaker session, Paris, 2013

[3] Piubello A, Harouna SH, Souleymane MB et al. High Cure Rate with Standardised Short-Course Multidrug-Resistant Tuberculosis Treatment in Niger: No Relapses. *Int J Tuberc Lung Dis* 2015;18:1188–94.

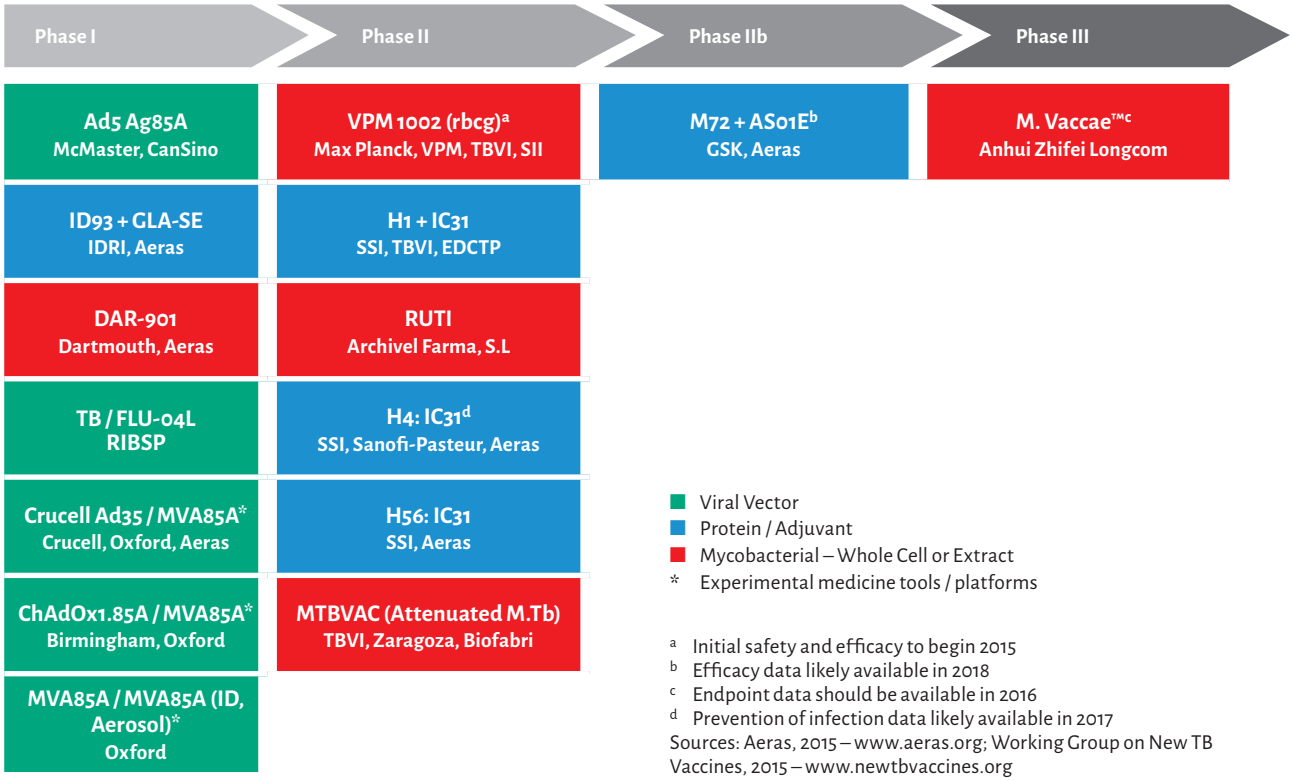
[4] Kuaban C, Noeske J, Rieder HL et al. High Effectiveness of a 12-Month Regimen for MDR-TB Patients in Cameroon. The International Journal of Tuberculosis and Lung Disease. *Int J Tuberc Lung Dis* 2015;19: 517–24.

[5] World Health Organization. *Guidelines on the management of latent tuberculosis infection*. Geneva: World Health Organization; 2015. Available at: http://www.who.int/tb/publications/ltbi_document_page/en/

[6] The TEMPRANO ANRS 12136 Study Group. A Trial of Early Antiretrovirals and Isoniazid Preventive Therapy in Africa. *N Engl J Med* 2015; 373:808–822.

FIGURE 8.4

The development pipeline for new TB vaccines, August 2015



Sources: Aeras, 2015 – www.aeras.org; Working Group on New TB Vaccines, 2015 – www.newtbvaccines.org

d'Ivoire and found that IPT and ART provided together had a higher efficacy in preventing TB disease than ART alone. The study also found lower rates of severe illness when ART was started immediately alongside 6 months of IPT, compared with deferred ART and no IPT. This was true overall and among patients with CD4 counts of ≥500 cells/mm³. Study authors also highlighted that isoniazid can be prescribed safely when given early in the course of HIV disease.

8.3 New vaccines to prevent TB

The slow decline in TB incidence globally (**Chapter 2**) and the persistent threat of MDR-TB both highlight the critical need for new effective TB vaccines. It is estimated that at least US$ 8 billion is required each year for TB diagnosis and treatment using currently available interventions (**Chapter 7**). A recent modelling study showed that developing at least one new TB vaccine over the next 10–15 years would cost about US$ 0.8–1 billion, approximately 1% of diagnosis and treatment costs, and that an adolescent and adult vaccine with 60% efficacy delivered to 20% of the population-at-risk could avert as many as 30–50 million new cases of TB by 2050.[1] Recent modelling also indicates that targeting adolescents will prevent morbidity and mortality in infants and young children, and is a more effective strategy to protect them from TB than direct vaccination of infants with a similar vaccine.[2]

The potential for an adult/adolescent vaccine to have a meaningful impact on the global TB epidemic, compared with the limited impact of an infant vaccine, has shifted the focus of TB vaccine development. The new paradigm emphasises the development of a diverse pipeline of new TB vaccine candidates that target the prevention of active TB in these older age groups.

Scientific advances have also enabled the pursuit of more sophisticated approaches to vaccine design. The global pipeline of TB vaccine candidates in clinical trials is more robust than at any previous period in history, now including recombinant BCGs, attenuated M. tuberculosis strains, recombinant viral-vectored platforms, protein/adjuvant combinations, and mycobacterial extracts.

The status of the pipeline for new vaccines in August 2015 is shown in **Figure 8.4**. These vaccines aim either to prevent infection (pre-exposure) or to prevent primary progression to disease or reactivation of latent TB (post-exposure). Further details are provided below.

[1] Aeras, *TB Vaccine Research and Development: A Business Case for Investment*. Rockville: Aeras; 2014. Available at: http://bit.ly/1EodJBj

[2] White, R. *Indirect effects in infants on the force of TB disease from vaccinating adolescents and adults*. London: TB Modelling Group, TB Centre, Centre for the Mathematical Modelling of Infectious Diseases; 2015.

8.3.1 Phase II and Phase III clinical trials

There are currently eight vaccines in Phase II or Phase III trials.

M72/AS01E (made by GlaxoSmithKline (GSK)) is a recombinant fusion protein of the *M. tuberculosis* antigens 32A and 39A with the AS01E adjuvant. A large randomized placebo-controlled Phase IIb trial (NCT01755598, conducted by GSK and Aeras) is enrolling pulmonary TB-negative, IGRA-positive, HIV-negative adults in Kenya, South Africa and Zambia. The aim is to enroll 3506 adults; by July 2015, 2096 participants had been enrolled. The primary endpoint will be the protective efficacy of two doses of M72/AS01E against pulmonary TB disease. Secondary endpoints include safety and immunogenicity.

Three vaccines are *protein subunits with adjuvants*, initially developed by the Statens Serum Institute (SSI) in Copenhagen, Denmark. These are:

- **H1:IC31®** is an adjuvanted subunit vaccine combining the *M. tuberculosis* antigens Ag85B and ESAT-6 with Valneva's IC31 adjuvant. The H1:IC31® vaccine was the first TB vaccine to commence clinical development by SSI, and Aeras subsequently joined this effort. The H1:IC31® vaccine has been evaluated in three Phase I trials, which showed the vaccine to be safe and immunogenic in HIV-negative adults who were either *M. tuberculosis* naïve, BCG vaccinated or latently infected, in low- and high TB burden settings. A Phase II double-blind and placebo controlled trial in HIV-positive individuals with or without LTBI confirmed that the vaccine was safe and immunogenic.[1] Recently, a large Phase II trial investigating the influence of dose, schedule and LTBI status on the immunogenicity of H1:IC31® in 240 adolescents in South Africa was finalized; H1:IC31® was the first TB vaccine to be tested in a large trial in this important target population. A paper in which results will be published is in preparation. In parallel, the H1:IC31® subunit vaccine construct has been improved with the addition of a third antigen, Rv2660c, becoming H56:IC31®. Clinical data on H1:IC31® will support the further development of H56:IC31®. No further clinical trials with H1:IC31® are planned.
- **H4:IC31** is being developed as a booster vaccine to BCG with Sanofi Pasteur. The vaccine candidate contains a fusion protein of Ag85B and TB10.4 formulated with IC31 adjuvant. H4:IC31 is currently being evaluated in Phase II studies in African infants with Sanofi and SSI (and also with the International Maternal Pediatric Adolescent AIDS Clinical Trials Group (IMPAACT) network and the HIV Vaccine Trials Network (HVTN) in conjunction with NIAID). In addition, the H4:IC31 candidate is being assessed in a Phase II proof-of-concept study for its ability to prevent de novo infection with *M. tuberculosis* among IGRA-negative, HIV-uninfected South African adolescents at high risk of acquiring *M. tuberculosis* infection. An intensive immunogenicity study of H4:IC31 in South African adolescents is underway.
- **H56:IC31**. This is an adjuvanted subunit vaccine that combines three *M. tuberculosis* antigens (Ag85B, ESAT-6, and Rv2660c) with Valneva's IC31 adjuvant. It is being developed by SSI and Aeras. A Phase I study to evaluate the safety and immunogenicity profile of H56:IC31 in HIV-negative adults with and without LTBI and no history or evidence of TB disease has been completed. Two Phase I studies are currently ongoing to determine the safety and immunogenicity profile of H56:IC31 in HIV-negative, BCG-vaccinated adults with and without LTBI and in patients who have recently been treated for pulmonary TB disease, respectively. A study to determine the efficacy of H56:IC31 in preventing TB infection in LTBI negative adolescents is planned for 2016.

VPM 1002, originally developed at the Max Planck Institute of Infection Biology with further development by Vakzine Projekt Management, the Tuberculosis Vaccine Initiative (TBVI), and Serum Institute of India, is a live recombinant vaccine. It has been derived from the Prague strain of BCG into which the listerolysin gene from *Listeria monocytogenes* has been cloned, and the urease gene deleted, to potentially improve immunogenicity. A Phase IIa trial of this vaccine has been completed in South Africa. The Phase II trial (in planning) will assess the safety and immunogenicity of the vaccine in HIV exposed and unexposed newborns.

RUTI® is a non-live and polyantigenic vaccine based on fragmented and detoxified *M. tuberculosis* bacteria. The product is a liposome suspension of the Drug Substance with a charge excipient. **RUTI®** is being developed by Archivel Farma as an immunotherapeutic vaccine. A Phase II trial in South Africa was completed recently and other clinical trials are in the planning stages.

MTBVAC is being developed by the University of Zaragosa, Institut Pasteur, BIOFABRI and TBVI. It is a live *M. tuberculosis* strain attenuated via deletions of the *pho*P and *fad*D26 genes. It is the first live attenuated *M. tuberculosis* vaccine to enter a Phase I trial, which was recently completed. The next trial will be a Phase I/II trial among adults in South Africa. The vaccine is being developed both as a BCG replacement vaccine and as a potential boost vaccine in adolescents and adults.

M. Vaccae™ is a specified lysate developed by the pharmaceutical company Anhui Zhifei Longcom Biologic Pharmacy Co., Ltd. and licensed by the China Food and Drug Administration as an immunotherapeutic agent to help shorten TB treatment for patients with drug-susceptible TB. It is in a Phase III trial to assess its efficacy and safety in preventing TB disease in people with LTBI. The trial is being conducted in collaboration with the Guangxi Center for Disease Con-

[1] Reither K, Katsoulis L, Beattie T et al. Safety and Immunogenicity of H1/IC31®, an Adjuvanted TB Subunit Vaccine, in HIV-Infected Adults with CD4+ Lymphocyte Counts Greater than 350 cells/mm³: A Phase II, Multi-Centre, Double-Blind, Randomized, Placebo-Controlled Trial. *PLoS ONE*. 2014;9(12):e114602.

trol and Prevention in China. It is the largest TB vaccine trial undertaken in the last decade, including 10 000 people aged 15–65 with a PPD>15mm. The trial is scheduled to be completed by April 2016.

Of note, MVA85A, the attenuated vaccinia virus-vectored vaccine candidate expressing Ag85A of *M. tuberculosis* designed at Oxford University as a booster vaccine for BCG vaccinated infants, has now completed a Phase II safety and immunogenicity study.[1] The study was conducted in 650 BCG-vaccinated, HIV-positive participants in Senegal and South Africa. As in the infant study[2], the vaccine was well tolerated and immunogenic, but no efficacy against *M. tuberculosis* infection or disease was demonstrated (although the study was not powered to detect an effect against disease). Current and future clinical approaches focus on evaluating MVA85A delivered by aerosol, alone or in a prime-boost combination with a second virally vectored vaccine, ChAdOx1.85A (see below).

8.3.2 Phase I clinical trials

There are seven vaccines in Phase I clinical trials.

ID93 + GLA-SE, developed by the Infectious Disease Research Institute (IDRI) in collaboration with Aeras, comprises three *M. tuberculosis* immunodominant antigens (Rv2608, Rv3619 and Rv3620), one *M. tuberculosis* latency-associated antigen (Rv1813), and the adjuvant GLA-SE. A Phase I trial in 60 adults in the United States to assess safety and immunogenicity was recently completed. The vaccine was found to have an acceptable safety profile, and T cell responses were seen at all of the dose levels that were studied. A further Phase I trial in South Africa is being conducted to describe the safety and immunogenicity profile of ID93 + GLA-SE in BCG-vaccinated, QuantiFERON TB-Gold negative and positive healthy adults. A Phase IIa trial in South Africa, with the support of the Wellcome Trust, is evaluating safety and immunogenicity in patients that have recently completing treatment for pulmonary TB disease. A Phase IIb trial to assess whether the vaccine can prevent recurrence of TB disease in patients who have recently and successfully completed TB treatment is being planned by IDRI and South African collaborators in the same population.

Ad5 Ag85A is an adenovirus serotype 5 vector expressing Ag85A. It has been developed by McMaster University with support from CanSino, a Chinese biotechnology company. Ad5Ag85A was evaluated in 24 healthy human volunteers (both BCG-naïve and previously BCG-immunized) for safety and immunogenicity following a single intra-muscular injection in a Phase I clinical study completed at McMaster University, Canada. Immunization of Ad5Ag85A was safe and well-tolerated in both trial volunteer groups, with only reactions at the injection site. Pre-existing Ad5 antibodies did not appear to affect the immune response. Ad5Ag85A was immunogenic in both groups and stimulated polyfunctional T cell responses, but it more potently boosted both CD4+ and CD8+ T cell immunity in previously BCG-vaccinated volunteers compared with BCG-naïve individuals.

DAR 901 is a heat-inactivated *M. obuense*. It has been developed by investigators at Dartmouth University, USA, and manufactured by Aeras. Enrolment in a Phase I safety and immunogenicity study in 60 BCG-vaccinated, HIV-infected and -uninfected individuals was recently completed in the USA. The study remains blinded while subjects continue to be followed. No serious adverse events have been reported and plans are underway to complete in-depth immunologic evaluations by the end of 2015, using data for the first people enrolled in the trial.

TB/FLU-04L is a recombinant influenza vectored vaccine candidate developed by the Research Institute for Biological Safety Problems and the Research Institute on Influenza in the Russian Federation, with support and assistance from international experts. The influenza virus strain A/Puerto Rico/8/34 (H1N1) was used as a parent strain for construction of an attenuated replication-deficient vector expressing *M. tuberculosis* antigens Ag85A and ESAT-6. It was designed as a mucosal "boost" vaccine for infants, adolescents and adults. A Phase I trial in BCG-vaccinated QuantiFERON TB-Gold negative healthy adult volunteers using intranasal administration was recently completed, and a Phase IIa trial is planned.

ChAdOx1.85A is a simian adenovirus expressing antigen 85A that was developed at the University of Oxford. ChAdOX1.85A is being evaluated in a Phase I trial in BCG-vaccinated adults, both alone and as part of a prime-boost strategy with MVA85A. In this first-in-humans study, ChAdOx1.85A is being administered intramuscularly. Future plans include evaluation of the aerosol route of delivery of ChAdOx1.85A.

Crucell Ad35/AERAS-402 and MVA85A are now being tested in combination, to try and induce both CD4+ and CD8+ T cells. One or two doses of Crucell Ad35 followed by a dose of MVA85A is being compared with 3 doses of Crucell Ad35 in a Phase I/II trial in adults in the United Kingdom. The trial is being implemented by Oxford University, Aeras and Crucell.

MVA85A (Aerosol) is an aerosolized MVA85A candidate developed by Oxford that recently underwent a Phase I double-blind trial to compare the safety and immunogenicity of aerosol-administered and intradermally administered MVA85A in 24 BCG-vaccinated adults in the United Kingdom. The study concluded that aerosol vaccination with MVA85A appeared to be a safe and feasible vaccination that produced stronger CD4+ T-cell response than intradermal MVA85A. Further studies assessing the aerosol route are necessary.

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[1] Ndiaye BP, Thienemann F, Ota M, et al. Safety, immunogenicity, and efficacy of the candidate tuberculosis vaccine MVA85A in healthy adults infected with HIV-1: a randomised, placebo-controlled, phase 2 trial. *Lancet Respir Med* 2015;3:190–200.

[2] Tameris MD, Hatherill M, Landry BS, et al. Safety and efficacy of MVA85A, a new tuberculosis vaccine, in infants previously vaccinated with BCG: a randomised placebo-controlled phase 2b trial. *Lancet* 2013;381:1021–28

8.3.3 Early stage, translational research

As documented above, there is a reasonably robust pipeline of vaccine candidates, including those based on whole cell approaches, antibody-inducing vaccines and nucleic acid-based (DNA and RNA) vaccines. This may help to diversify the clinical portfolio and fill the scientific gaps that currently exist.

To supplement existing efforts, there is also a re-prioritized focus on early stage, translational research. This will test hypotheses about immunological mechanisms, delivery methods, and candidate biomarkers, and help to broaden preclinical scientific approaches, antigen selection strategies, and evaluation strategies, with the overall goal of ensuring that a more diverse pipeline of new TB vaccine candidates can move forward into clinical trials.[1] Discussions about relevant clinical endpoints, beyond immunological measures that indicate prevention of disease or infection, and how these endpoints may be assessed through biomarkers early in clinical trials or pre-clinically to select the most promising candidate vaccines/adjuvants, are also underway.

8.4 The End TB Strategy: the critical role of research and development

The End TB Strategy includes "Intensified Research and Innovation" as one of three fundamental pillars (Chapter 1). This has two essential and complementary components:

(1) Discovery, development and rapid uptake of new tools, interventions and strategies; and
(2) Research to optimize implementation and impact.

The overall aim of the pillar is that intensified research will result in revolutionary new technologies, strategies and models of service delivery that will transform the way in which TB is diagnosed, treated and prevented. As highlighted at the beginning of this chapter, such changes are necessary by 2025, so that the rate at which TB incidence falls can be accelerated beyond the best-ever historic performance and targets that correspond to ending the global TB epidemic by 2035 can be achieved.

A massive increase in funding for research is required. This includes funding to create or expand research-enabling environments for the next generation of scientists in low and middle-income countries with the largest burden of TB, so that they can play a lead role in research based on domestic investments, alongside established global expertise. Increased domestic investments in research in countries with a high burden of TB will be facilitated by advocacy from key players including national public health authorities, researchers, care providers, and civil society. It is also important that high-income countries and their institutions, international agencies and philanthropic organizations increase their investments in TB research and training, in close collaboration with high-burden countries.

Once new technologies and innovative approaches are developed, they need to be translated into policies and practices, and then adapted to particular country contexts as appropriate. This will require expanded efforts to disseminate research results, particularly to policy makers.

To foster and intensify high-quality research at national and international levels, WHO has developed a *Global Action Framework for Research towards TB Elimination* that covers the period 2016–2025. This plan shows how to operationalize Pillar 3 of the End TB Strategy, including through the development of country-specific TB research strategic plans, capacity strengthening, and development/reinforcement of networks at country level, and through regular meetings and the development of international networks for research, capacity building and advocacy at global and regional levels.

[1] Brennan MJ and Thole J, Eds. Tuberculosis vaccines: A strategic blueprint for the next decade. *Tuberculosis*. 2012; 92: Supplement 1; S6–S13.