

# THE GLOBAL PLAN TO STOP TB 2011–2015

Transforming the Fight  
TOWARDS ELIMINATION OF TUBERCULOSIS



# TABLE OF CONTENTS

Acknowledgements .....	<i>ii</i>
Abbreviations .....	<i>iii</i>
Foreword .....	<i>iv</i>
Preface .....	<i>v</i>
Executive summary .....	<i>vi</i>
Overview .....	1
About the Stop TB Partnership .....	20
<b>PART I: IMPLEMENTATION</b> .....	<b>24</b>
Editorial: The best reason to step up the fight against TB .....	24
1. DOTS expansion and enhancement .....	26
2. Drug-resistant TB .....	34
3. TB/HIV .....	42
4. Laboratory strengthening .....	50
<b>PART II: RESEARCH AND DEVELOPMENT</b> .....	<b>56</b>
Editorial: A quantum leap in TB research .....	56
1. Fundamental research .....	58
2. New diagnostics .....	62
3. New drugs .....	68
4. New vaccines .....	76
5. Operational research .....	84
References .....	90

## ACKNOWLEDGEMENTS

The Partnership acknowledges with gratitude everyone who has contributed to the Global Plan:

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The development of the Global Plan was coordinated by the Stop TB Partnership Secretariat, under the overall guidance of the Executive Secretary, Marcos Espinal and the Executive Secretary a.i. Giuliano Gargioni.

## ABBREVIATIONS

<b>ACSM</b>	advocacy, communication and social mobilization	<b>LPA</b>	line probe assay
<b>AFB</b>	acid-fast bacilli	<b>LTBI</b>	latent TB infection
<b>ART</b>	antiretroviral therapy	<b>MDG</b>	Millennium Development Goal
<b>BCG</b>	bacille Calmette-Guérin	<b>MDR-TB</b>	multidrug-resistant TB
<b>CDR</b>	case detection rate	<b>NGO</b>	nongovernmental organization
<b>CPT</b>	co-trimoxazole preventive therapy	<b>NIAID</b>	National Institute of Allergy and Infectious Diseases [US]
<b>CPTR</b>	Critical Path to New TB Drug Regimens (Initiative)	<b>NIH</b>	National Institutes of Health [US]
<b>DEWG</b>	DOTS Expansion Working Group	<b>NRL</b>	national reference laboratory
<b>DOTS</b>	the basic package that underpins the Stop TB Strategy	<b>NTP</b>	national TB control programme
<b>DRS</b>	drug-resistance surveillance	<b>OR</b>	operational research
<b>DST</b>	drug susceptibility testing	<b>PAL</b>	Practical Approach to Lung Health
<b>EBA</b>	early bactericidal activity	<b>PAS</b>	para-aminosalicylic acid
<b>EQA</b>	external quality assurance	<b>PK</b>	pharmacokinetic
<b>FDC</b>	fixed-dose combination	<b>PLHIV</b>	people living with HIV
<b>GCLP</b>	good clinical and laboratory practice	<b>PMTCT</b>	prevention of mother-to-child transmission [of HIV]
<b>GDF</b>	Global Drug Facility	<b>PPM</b>	public-private mix
<b>GLC</b>	Green Light Committee	<b>SNRL</b>	supranational reference laboratory
<b>GLI</b>	Global Laboratory Initiative	<b>STAG-TB</b>	WHO's Strategic and Technical Advisory Group for TB
<b>GDP</b>	gross domestic product	<b>TA</b>	technical assistance
<b>HBC</b>	high-burden [TB] country	<b>TAG</b>	Treatment Action Group
<b>HIV</b>	human immunodeficiency virus	<b>TB</b>	tuberculosis
<b>HSS</b>	health system strengthening	<b>TBTEAM</b>	TB Technical Assistance Mechanism
<b>IC</b>	infection control	<b>UNAIDS</b>	Joint United Nations Programme on HIV/AIDS
<b>ICF</b>	intensified case-finding	<b>VR</b>	vital registration
<b>IMF</b>	International Monetary Fund	<b>WG</b>	Working Group
<b>INAT</b>	Introducing New Approaches and Tools (subgroup of the DOTS Expansion Working Group)	<b>WHA</b>	World Health Assembly
<b>IPT</b>	isoniazid preventive therapy	<b>WHO</b>	World Health Organization
<b>ISTC</b>	International Standards for TB Care	<b>XDR-TB</b>	extensively drug-resistant TB
<b>LED</b>	light-emitting diode		

# FOREWORD

The Stop TB Partnership was established in 2000 as a global movement to accelerate social and political action to stop the spread of TB around the world. The Partnership's goal is to eliminate TB as a public health problem and, ultimately, to secure a world free of TB.

In 2006, the Partnership launched the *Global Plan to Stop TB 2006-2015* in Davos, Switzerland at the World Economic Forum. The plan – which provided a roadmap for scaling up prevention and treatment and for research and development, and set out the funding required – drew wide attention among broad audiences around the world. Nigerian President Olusegun Obasanjo, UK Chancellor of the Exchequer Gordon Brown and Bill Gates, Co-chair of the Bill and Melinda Gates Foundation were present at the launch and called on world leaders to rally behind the plan, whose goals included halving TB deaths compared with 1990 levels by 2015.

There have been impressive achievements to date. The incidence rate for TB worldwide is in gradual decline. Overall prevalence and death rates are falling. The number of organizations that have committed to working together to achieve the Partnership's goals has tripled since 2006 and now exceeds 1200. But there is yet a long way to go to reach the plan's targets, which comprise the TB target of the Millennium Development Goals and the Partnership's own targets for 2015.

The *Global Plan to Stop TB 2006-2015* remains both relevant and critical. In 2009, we released a report on

progress to date on the occasion of the third Stop TB Partners' Forum in Rio de Janeiro, Brazil. It was clear that some of the plan's goals, objectives and targets were in need of a fresh look in order to assess their relevance to reaching the 2015 deadline. This revised plan retains the full spirit of the *Global Plan to Stop TB 2006-2015* while providing a clearer blueprint for action.

The stakes are high: without rapid scale-up of TB prevention and treatment, some 10 million people will die of this curable disease by 2015. Addressing TB is also critical for meeting other development goals on poverty, HIV and women and children's health. Without sufficient investment in the development of new diagnostic methods, anti-TB drugs and vaccines, we will not achieve the Partnership's goal of eliminating the disease as a public health problem by 2050.

The Stop TB Partnership remains uniquely placed to promote and coordinate the actions set out in this plan. During the past five years, Stop TB Partners have clearly demonstrated their capacities to achieve results – in research and development and in providing effective TB care. We are confident that this invigorated roadmap will inspire our Partners to even greater achievements.

We urge all those currently funding activities related to TB control and research not only to sustain, but to step up your investment in the plan. Only by working together can we achieve the vision of a world free of TB.

**Marcos Espinal**  
*Executive Secretary,  
Stop TB Partnership*

# PREFACE

A pandemic, by definition, plays out on a massive scale. Controlling it requires a comparable scale of international consensus and commitment. This means having a sound roadmap that sets forth internationally agreed strategies for prevention, diagnosis and treatment, and research for improving all three; plus a clear plan for implementing those strategies worldwide. The global fight against TB benefits from broad alignment on both.

In 2006, the World Health Organization (WHO) launched the *Stop TB Strategy* as an evidence-based approach to reducing the burden of TB. Today, governments around the world have voiced their commitment to its key principles of achieving universal access to high-quality TB care, reducing human suffering, reaching out to vulnerable populations, protecting human rights and supporting the development and use of new tools.

In 2001, the Stop TB Partnership launched the *Global Plan to Stop TB 2001–2005*. In 2006, a more advanced plan for transforming these principles into action was issued: the *Global Plan to Stop TB 2006–2015*. Since then the Plan has garnered the world's confidence as a roadmap for dramatically reducing the global burden of TB by 2015.

We are now at the half-way mark, and it is a fitting moment to look at where we are and where we hope to go. This revised and updated plan further illuminates the way forward to 2015 by taking into account progress since 2006; updates on epidemiology, policy and costs related to multidrug-

resistant TB and TB/HIV; the importance of urgently giving a higher profile to laboratory strengthening; and the need to address the full spectrum of TB research in a coherent and coordinated manner.

TB is an ancient illness. By all rights – as a bacterial disease that is curable with antimicrobial drugs – it should belong to the past. In 2006, when the *Global Plan to Stop TB 2006–2015* was launched, the epidemic was still believed to be growing by about 1% each year. The fruits of implementing the *Stop TB Strategy* and the Global Plan to Stop TB are now evident. The epidemic is in a steady, although modest and slow, decline.

Nonetheless more than 9 million people still develop active TB each year and nearly 2 million die. These figures should not inspire hopelessness, but rather an acknowledgment that TB is a unique pandemic. A third of the world's population harbours latent TB infection, which can emerge at any time as an airborne and transmittable disease. Reducing this human reservoir of infection will require many years of steady and untiring effort – plus more effective tools than we have at our disposal today.

No one ever said this would be an easy fight. However, with the Global Plan to Stop TB 2011–2015 the direction is set with renewed intensity in care and control efforts, and new approaches and tools finally becoming available. We are now at the start of a road that should take us towards the achievable goal of TB elimination.

**Mario Raviglione**

*Director,*

*WHO Stop TB Department*

# EXECUTIVE SUMMARY

## ABOUT TUBERCULOSIS

Tuberculosis (TB) – an infectious airborne disease – is a major global health problem. Each year, there are around nine million new cases of TB, and close to two million deaths. All countries are affected, but 85% of cases occur in Africa (30%) and Asia (55%), while India and China alone represent 35%.

TB is closely connected with HIV. People living with HIV, representing over 10% of annual TB cases, are up to 37 times more likely to develop TB than people who are HIV-negative. In 2009, TB accounted for one in four deaths among HIV-positive people. Yet TB is, in most instances, a curable disease. More than 90% of people with drug-susceptible TB can be cured in six months using combinations of first-line drugs. Treatment of multidrug-resistant TB (MDR-TB) – there are around 0.5 million cases each year – is more challenging, requiring the use of second-line drugs that are more costly, cause more severe side-effects, and must be taken for up to two years. Cure rates for MDR-TB are lower, typically ranging from around 50% to 70%.

## THE FIGHT AGAINST TB: TARGETS AND ACHIEVEMENTS

Recognizing the scale of the problem, global targets for reductions in the TB burden have been set within the context of the Millennium Development Goals (MDGs) and by the Stop TB Partnership, a global movement made up of more than 1200 organizations working together to eliminate TB as a public health problem and, ultimately, to secure a world free of TB.

The target set within the MDGs is to halt and reverse the incidence of TB by 2015. MDG indicators for measuring progress in TB control are the incidence rate, the prevalence rate, the death rate and the proportion of cases that are detected and cured in

DOTS programmes. The Stop TB Partnership has also set two additional targets: to halve TB prevalence and death rates by 2015, compared with 1990 levels, thus paving the way for the elimination of TB (defined as less than one case of TB disease per one million population per year) by 2050.

There have been impressive achievements to date: the number of cases per capita is falling by around 1% per year, and death rates have fallen by about one third since 1990. From 1995 to 2009, 49 million TB patients were treated according to the DOTS strategy, 41 million of them successfully.

## THE GLOBAL PLAN

In 2006, the Stop TB Partnership launched the *Global Plan to Stop TB 2006–2015*, a roadmap for scaling up prevention and treatment, for research and development, and for financing. The plan's goals included halving TB deaths compared to 1990 levels by 2015 – still a target today.

The end of 2010 marks the mid-point of the *Global Plan to Stop TB 2006–2015*, and is a natural time to update the plan with a focus on the final five years leading up to the target year of 2015. There are several other reasons why the original document had to be revised. There was a need to take into account actual progress made since 2006, significant changes in policy and costs related to antiretroviral therapy, two updates to the MDR-TB component of the plan (in 2007 and 2009), one update to estimates of epidemiological burden and trends, the importance of giving a higher profile to laboratory strengthening and the necessity to address the full spectrum of research.

The Global Plan to Stop TB 2011–2015 retains the full spirit of its predecessor while providing a clearer blueprint for action, setting out what needs to be done to achieve the 2015 targets set within the context of the MDGs and by the Stop TB Partnership.

The Plan has two main parts.

The Implementation component of the Plan (Part I) sets out how to transform TB control in the years up to 2015, through scaling up existing interventions for the diagnosis and treatment of TB and introducing new technologies, notably new diagnostic tests. This component has four major elements: DOTS expansion and enhancement, drug-resistant TB, TB/HIV and laboratory strengthening.

The Research and Development component of the plan (Part II) shows what needs to be done to develop the new tools that are required to revolutionize the prevention, diagnosis and treatment of TB, as the foundation for the elimination of the disease. This component covers five major topics: fundamental research, new diagnostics, new drugs, new vaccines and operational research. The topic of fundamental research is an addition to the previous plan, reflecting the fact that it underpins the development of all new technologies. Operational research has also been included as a distinct topic because it has an essential role in improving TB control programme activities and is the interface between the development of new tools and their uptake in policy and practice within national TB control programmes.

## FUNDING

Full achievement of the Global Plan to Stop TB 2011–2015 will cost an estimated US\$ 47 billion for the five years, of which US\$ 37 billion (79%) is for Implementation and almost US\$ 10 billion (21%) is for Research and Development. The implementation of the DOTS component of the Stop TB Strategy (48% of the overall total) represents the major funding need, followed by interventions to manage drug-resistant TB (15%). Within the Research and Development component of the plan, the development of new drugs accounts for the single biggest share.

The funding required increases steadily over time, from US\$ 8 billion in 2011 to almost US\$ 11 billion in 2015. For Implementation, the requirement grows from just over US\$ 6 billion in 2011 to around US\$ 8.5 billion in 2015; for Research and Development, the amount rises from US\$ 1.9 billion in 2011 to US\$ 2.2 billion in 2015.

If current levels of domestic financing for TB control are maintained (adjusting only for inflation), about US\$ 21 billion of the US\$ 37 billion necessary for implementation could be mobilized from within the 149 low- and middle-income countries considered in the plan. Of this amount, about US\$ 11 billion would come from the large economies of Brazil, China, India, the Russian Federation and South Africa, with a further US\$ 4 billion from middle-income countries in Europe.

If domestic funding for TB control can be increased at the same rate as currently forecast by the International Monetary Fund for gross domestic product per capita, an additional US\$ 2 billion could be mobilized. In total, this suggests that about US\$ 23 billion can be mobilized from domestic sources.

The remaining US\$ 14 billion (an average of US\$ 2.8 billion per year) for Implementation would have to come from international donors in high-income countries. On an annual basis, this is about six times the level of donor funding for TB control in 2010. For comparison, international donor monies for HIV prevention, treatment and care amounted to about US\$ 8.5 billion in 2008.

It is anticipated that investment in Research and Development (almost US\$ 10 billion) will be made largely by the most developed countries. However Brazil, China, India, the Russian Federation and South Africa have already demonstrated increasing capacity for innovation and could contribute much more to the Research and Development component of this plan than has previously been the case.



Overall, high-income countries may have to put in as much as half of the necessary resources for the Implementation and Research and Development components of the Global Plan to Stop TB 2011–2015. Endemic countries, especially Brazil, China, India, the Russian Federation, South Africa and the middle-income countries of Europe would be expected to mobilize the rest internally. Political commitment, backed by the financial commitments of both endemic as well as donor countries, is critical to global efforts to stop TB.

## RESULTS

If the required funding of US\$ 37 billion for the Implementation component of the plan is mobilized, achievements will be substantial. During the five years of the plan, these include:

- diagnosis and treatment for around 32 million people with TB using the Stop TB Strategy/DOTS approach, with 28 million successfully treated;
- testing of about seven million people for MDR-TB, with one million confirmed cases of MDR-TB diagnosed and treated according to international guidelines;
- HIV testing for almost 30 million TB patients, around four million HIV-positive TB patients enrolled on both co-trimoxazole preventive treatment (to reduce TB mortality and prevent other infections) and antiretroviral therapy, and screening for TB of approximately 71 million people living with HIV.

If the required funding of US\$ 10 billion for the Research and Development component of the plan is mobilized, great strides will be made towards improved prevention, diagnosis and treatment of TB. By 2015, it is expected that we will have:

- point-of-care tests that can be used in health centres for
  - diagnosing active TB,
  - diagnosing latent TB infection and predicting the risk of progression to TB disease,
  - detecting drug resistance;
- a new, four-month TB treatment regimen for patients with drug-susceptible TB;
- at least one new drug on the market for the treatment of drug-resistant TB;
- a safer, higher-efficacy regimen for treatment of latent TB infection;
- four new TB vaccine candidates in Phase III clinical trials for safety and efficacy.

If no improvements in TB control are made from 2010 onwards, about 10 million people will die from TB by 2015.

# OVERVIEW

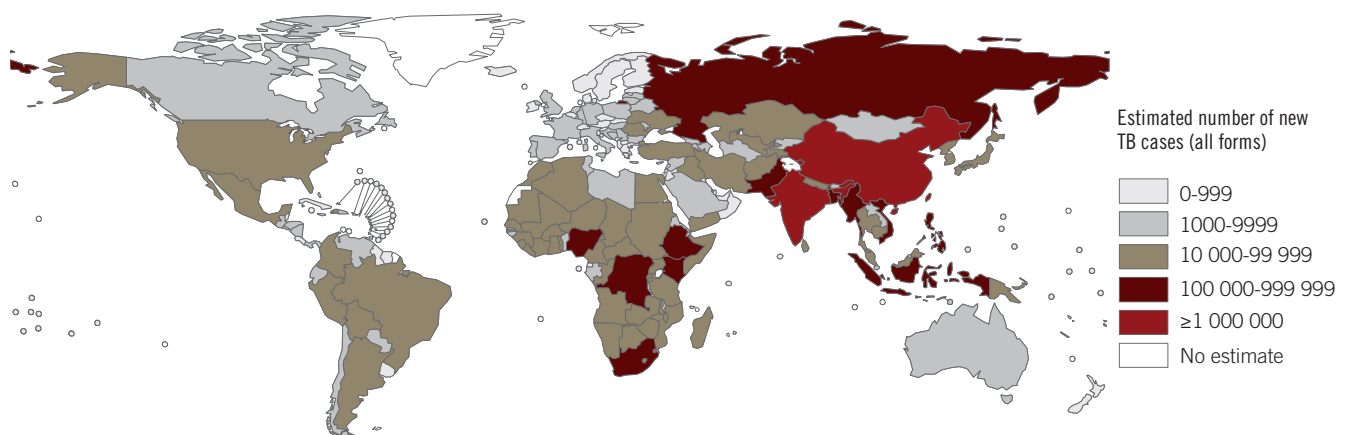
## 1. INTRODUCTION AND BACKGROUND

Tuberculosis (TB) is a major global health problem. Each year, there are around 9 million new cases of TB, and close to 2 million people die from the disease.<sup>1</sup> All countries are affected, but most cases (85%) occur in Africa (30%) and Asia (55%), with India and China alone accounting for 35% of all cases (Figure 1, Figure 2). There are 22 so-called high-burden countries (HBCs) that account for about 80% of the world's TB cases, and which have been given particular attention in TB control since around the year 2000.<sup>2</sup> Globally, the absolute number of cases is increasing slowly, although the number per capita (usually expressed as the number of cases per 100 000 population) is falling by around 1% per year. TB ranks as the eighth leading cause of death in low- and middle-income countries (seventh for men and ninth for women); among adults aged 15–59, it

ranks as the third cause of death, after HIV/AIDS and ischaemic heart disease.<sup>3</sup>

Yet TB is, in most instances, a curable disease. Using combinations of first-line drugs introduced into treatment between the 1950s and 1980s, around 90% of people with drug-susceptible TB can be cured in six months. Treatment of multidrug-resistant TB<sup>4</sup> (MDR-TB) – of which there are around 0.4–0.5 million cases each year<sup>5</sup> – is more challenging. It requires use of second-line drugs (including injectable antibiotics) that are more costly and cause more severe side-effects, and recommended regimens must be taken for up to two years. Cure rates for MDR-TB are lower, typically ranging from around 50% to 70%. Among people living with HIV, diagnosis of TB can be more difficult compared to those who are HIV-negative, and

FIGURE 1 ESTIMATED TB INCIDENCE BY COUNTRY, 2009



<sup>1</sup> *Global tuberculosis control 2010*. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.7). There were around 1.3 million deaths from TB among HIV-negative people and around 0.4 million deaths from TB among HIV-positive people.

<sup>2</sup> The 22 countries are, in alphabetical order: Afghanistan, Bangladesh, Brazil, Cambodia, China, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, the Philippines, the Russian Federation, South Africa, Thailand, Uganda, the United Republic of Tanzania, Viet Nam and Zimbabwe.

<sup>3</sup> Lopez AD et al. *Global burden of disease and risk factors*. New York, Oxford University Press and The World Bank, 2006.

<sup>4</sup> MDR-TB is defined as resistance to isoniazid and rifampicin, the two most important first-line drugs used in the treatment of TB.

<sup>5</sup> *Multidrug and extensively drug-resistant TB (M/XDR-TB): 2010 global report on surveillance and response*. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.3).

mortality rates are higher. Just over 10% of the TB cases that occur each year are among people living with HIV, of which around 80% are in Africa (where around one third of TB cases are among people who are HIV-positive). The HIV epidemic caused a major upsurge in TB cases in Africa during the 1980s and 1990s, with the number of cases growing from less than 200 to more than 350 cases per 100 000 population (Figure 3). Numbers peaked in 2004, and have since begun to decline, following trends in the HIV epidemic, but with a time-lag of about six years.

The vast majority of TB cases and deaths occur in poor countries, and it is the poorest of the poor that are worst hit in all countries. This is explained by less health care access, as well as higher exposure to unhealthy and crowded living and working conditions, undernutrition, HIV infection, diabetes mellitus, smoking, alcohol and drug abuse, and several other TB risk factors<sup>6</sup>. History has shown that improved social and economic conditions can greatly facilitate TB control, while economic crises

can rapidly worsen the situation<sup>7</sup>. The clear link between HIV trends and TB trends demonstrates the importance of direct TB risk factors for TB control. Epidemics of smoking, diabetes and substance abuse could have similar effects. Improving TB prevention by tackling these determinants requires action well beyond the mandate of NTPs, and are largely dependent on macro-level political decisions and nation-wide public health efforts related to both communicable and non-communicable diseases. This plan acknowledges the importance of such preventive actions for effective future TB control. However, it is important to highlight that the plan focuses on the actions that should be pursued by NTPs. These include co-ordinated diagnosis and management of TB risk factors and co-morbidities and joint advocacy for social mobilization and development.

FIGURE 2 TB CASES BY WHO REGION, 2009

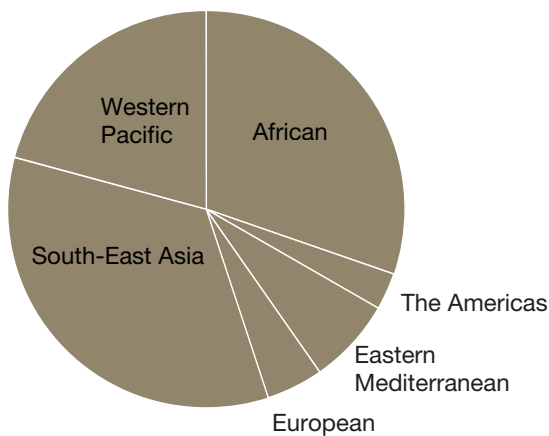
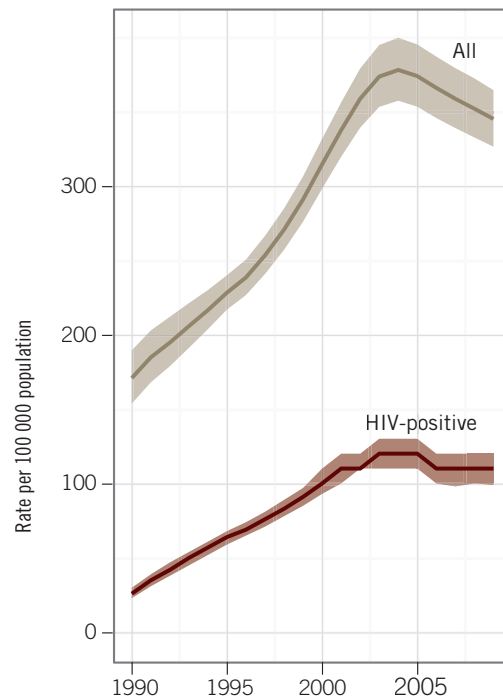


FIGURE 3 ESTIMATED TB INCIDENCE RATE IN THE AFRICAN REGION, 1990–2009<sup>a</sup>



<sup>a</sup> Shaded areas represent uncertainty bands.

<sup>6</sup>Lönnroth K, et al. *Tuberculosis control and elimination 2010-50: cure, care, and social development*. *Lancet*, 2010; 375:1814-29.

<sup>7</sup>Arinaminpathy N, & Dye C. *Health in financial crises: economic recession and tuberculosis in Central and Eastern Europe*. *J. R. Soc. Interface* 2010 doi:10.1098/rsif.2010.0072

## 1.1 GLOBAL TARGETS, THE STOP TB STRATEGY AND THE GLOBAL PLAN TO STOP TB 2006–2015

Recognizing the scale of the problem, global targets for reductions in the burden of TB disease (measured as incidence, prevalence and mortality) have been set within the context of the Millennium Development Goals (MDGs) and by the Stop TB Partnership (Box 1). The target set within the MDGs is to halt and reverse the incidence of TB by 2015. In addition, the MDGs include three other indicators for measurement of progress in TB control: prevalence and death rates, and the proportion of cases that are detected and cured in DOTS programmes (see below for a definition of DOTS).

The MDG target has been endorsed by the Stop TB Partnership. The Partnership has also set two additional targets for 2015: to halve TB prevalence and death rates by 2015, compared with 1990 levels; and, looking further into the future, the target of eliminating TB by 2050.<sup>8</sup>

### BOX 1 GOALS, TARGETS AND INDICATORS FOR TB CONTROL, 2015 AND 2050

<b>TB IN THE MILLENNIUM DEVELOPMENT GOALS (SET FOR 2015)</b>
<b>Goal 6: Combat HIV/AIDS, malaria and other diseases</b>
TARGET 6c: Halt and begin to reverse the incidence of malaria and other major diseases
INDICATOR 6.9: Incidence, prevalence and death rates associated with TB
INDICATOR 6.10: Proportion of TB cases detected and cured under DOTS
<b>STOP TB PARTNERSHIP TARGETS (SET FOR 2015 AND 2050)</b>
BY 2015: Reduce prevalence and death rates by 50%, compared with their levels in 1990
BY 2050: Eliminate TB as a public health problem, defined as a global incidence of active TB of less than one case per 1 million population per year

In 2006, the World Health Organization (WHO) launched the *Stop TB Strategy* (Box 2) as the internationally-recommended approach to reducing the burden of TB in line with global targets set for 2015. The goal of the strategy is defined as: “To dramatically reduce the global burden of TB by 2015 in line with the Millennium Development Goals and the Stop TB Partnership targets.”<sup>9</sup> The Strategy has six major components:

- pursue high-quality DOTS expansion and enhancement;
- address TB/HIV, MDR-TB, and the needs of poor and vulnerable populations;
- contribute to health system strengthening based on primary health care;
- engage all care providers;
- empower people with TB, and communities through partnership; and
- enable and promote research.

The *Stop TB Strategy* was developed as the successor to the DOTS strategy. The DOTS strategy is the basic package of five elements (see Box 2, under the first component) that underpins the *Stop TB Strategy*, and was the internationally-recommended approach to TB control from the mid-1990s up to 2006.<sup>10</sup>

<sup>8</sup> TB elimination is defined as less than one case of TB disease per 1 million population per year.

<sup>9</sup> *The Stop TB Strategy: building on and enhancing DOTS to meet the TB-related Millennium Development Goals*. Geneva, World Health Organization, 2006 (WHO/HTM/TB/2006.368).

<sup>10</sup> Further explanation of the DOTS strategy is provided in the **DOTS Expansion and Enhancement** section of this plan.

**BOX 2 THE STOP TB STRATEGY AT A GLANCE<sup>11</sup>**

<b>VISION</b>	A TB-free world
<b>GOAL</b>	To dramatically reduce the global burden of TB by 2015 in line with the Millennium Development Goals and the Stop TB Partnership targets
<b>OBJECTIVES</b>	<ul style="list-style-type: none"> <li>• Achieve universal access to high-quality care for all people with TB</li> <li>• Reduce the human suffering and socioeconomic burden associated with TB</li> <li>• Protect vulnerable populations from TB, TB/HIV and drug-resistant TB</li> <li>• Support development of new tools and enable their timely and effective use</li> <li>• Protect and promote human rights in TB prevention, care and control</li> </ul>
<b>TARGETS</b>	<ul style="list-style-type: none"> <li>• MDG 6, Target 6c: Halt and begin to reverse the incidence of TB by 2015</li> <li>• Targets linked to the MDGs and endorsed by the Stop TB Partnership: <ul style="list-style-type: none"> <li>– 2015: reduce prevalence of and deaths due to TB by 50% compared with a baseline of 1990</li> <li>– 2050: eliminate TB as a public health problem</li> </ul> </li> </ul>
<b>COMPONENTS</b>	
<p><b>1. Pursue high-quality DOTS expansion and enhancement</b></p> <p>a. Secure political commitment, with adequate and sustained financing</p> <p>b. Ensure early case detection, and diagnosis through quality-assured bacteriology</p> <p>c. Provide standardized treatment with supervision, and patient support</p> <p>d. Ensure effective drug supply and management</p> <p>e. Monitor and evaluate performance and impact</p> <p><b>2. Address TB/HIV, MDR-TB, and the needs of poor and vulnerable populations</b></p> <p>a. Scale up collaborative TB/HIV activities</p> <p>b. Scale up prevention and management of MDR-TB</p> <p>c. Address the needs of TB contacts, and of poor and vulnerable populations</p> <p><b>3. Contribute to health system strengthening based on primary health care</b></p> <p>a. Help improve health policies, human resource development, financing, supplies, service delivery, and information</p> <p>b. Strengthen infection control in health services, other congregate settings and households</p> <p>c. Upgrade laboratory networks, and implement the Practical Approach to Lung Health</p> <p>d. Adapt successful approaches from other fields and sectors, and foster action on the social determinants of health</p> <p><b>4. Engage all care providers</b></p> <p>a. Involve all public, voluntary, corporate and private providers through Public-Private Mix (PPM) approaches</p> <p>b. Promote use of the International Standards for Tuberculosis Care</p> <p><b>5. Empower people with TB, and communities through partnership</b></p> <p>a. Pursue advocacy, communication and social mobilization</p> <p>b. Foster community participation in TB care, prevention and health promotion</p> <p>c. Promote use of the Patients' Charter for Tuberculosis Care</p> <p><b>6. Enable and promote research</b></p> <p>a. Conduct programme-based operational research</p> <p>b. Advocate for and participate in research to develop new diagnostics, drugs and vaccines</p>	

<sup>11</sup> [http://www.who.int/tb/publications/2010/strategy\\_en.pdf](http://www.who.int/tb/publications/2010/strategy_en.pdf). This one-page summary is an updated version of the summary that appears in the original 2006 publication of the full strategy.

To implement the *Stop TB Strategy* and to set out the scale at which it needed to be implemented and funded to achieve the 2015 targets, the Stop TB Partnership developed a second landmark document: the *Global Plan to Stop TB 2006–2015*.<sup>12</sup> The plan included targets and indicators for each of the major components of TB control (defined in terms of the topics covered by the Working Groups of the Partnership at that time), and presented funding requirements for each of them, as well as an overall summary (Box 3). The plan was launched at the World Economic Forum in Davos in January 2006.

## 1.2 IMPLEMENTATION OF THE *GLOBAL PLAN TO STOP TB 2006–2015*: PROGRESS MADE BY MID-2010

In mid-2010, progress with respect to targets and funding for the **Implementation** component of the plan as detailed below<sup>13</sup>.

- The case detection rate for all forms of TB had reached 60–67%, with a best estimate of 63%.
- The treatment success rate for new smear-positive cases of pulmonary TB had reached 86%, and 87% in HBCs.<sup>14</sup>
- The percentage of TB patients tested for HIV had reached 26%, and 53% in the African Region. There were 55 countries in which  $\geq 75\%$  of TB patients knew their HIV status, including 16 African countries, showing that the targets in the plan can be achieved.
- The percentage of HIV-positive TB patients who were started on co-trimoxazole preventive therapy (CPT) had reached 75%, while around 140 000 HIV-positive TB patients per year were enrolled on antiretroviral treatment (ART).
- The projected number of MDR-TB patients to be treated in 2010 was around 50 000, of whom approximately 30 000 were patients to be enrolled

in projects or programmes known to be following international guidelines.

- Of the US\$ 21 billion required outside Europe in the five years 2006–2010 for implementation of TB control, approximately US\$ 14 billion was mobilized.
- In the European Region, US\$ 1.5 billion more was mobilized than was estimated to be required.

Progress with respect to targets and funding for the **Research and Development** component of the plan in mid-2010 as detailed below.

- A portfolio of new diagnostic tests was available for various levels of the health care system, enabling better and more rapid diagnosis of TB and MDR-TB at the district and first-referral levels. These tests included liquid-based culture, molecular assays (line-probe assays and automated cartridge-based DNA amplification tests), and a series of non-commercial culture methods. In addition, light-emitting diode (LED) fluorescence microscopy had become available for better case detection at the most peripheral levels of the health care system.
- The pipeline for new drugs had advanced substantially. There were two repurposed drugs in Phase III trials, investigating the safety and efficacy of a shorter (4-month) treatment regimen for drug-susceptible TB.<sup>15</sup> There were also six compounds in Phase II trials, including two novel drugs proposed for the treatment of MDR-TB.<sup>16</sup>
- Nine novel TB vaccines were in clinical trials, including five candidates in Phase I trials and four in Phase II trials. Of those in Phase II trials, two candidates were in Phase IIb ‘proof-of-concept’ trials.
- Of the US\$ 4 billion required for research and development in the first five years of the plan, approximately US\$ 2.4 billion was mobilized.

<sup>12</sup> *The Global Plan to Stop TB 2006–2015: actions for life towards a world free of tuberculosis*. Geneva, World Health Organization, 2006 (WHO/HTM/STB/2006.35).

<sup>13</sup> *Global tuberculosis control 2010*. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.7).

<sup>14</sup> Pulmonary TB – or TB of the lungs – is the most common form of TB (about 85% of TB cases notified in 2008). Typically, around 50–60% of notified patients with pulmonary TB have smear-positive TB. People with extrapulmonary TB accounted for about 15% of the TB patients notified to WHO in 2008.

<sup>15</sup> Repurposed drugs are existing drugs for which a license for treatment of other clinical condition(s) has been obtained, and that are being tested for TB treatment due to their strong anti-mycobacterial activity (such as, for example, the third generation of fluoroquinolones).

<sup>16</sup> In the context of drug trials, Phase I trials are initial studies to determine the pharmacologic actions of drugs in humans and the side-effects associated with increasing doses. Phase II trials are controlled clinical studies evaluating the efficacy of the drug in patients with the disease under study as well as the common short-term side-effects and risks. This phase can also be used to establish dose ranges and dose/response relationships. Phase IIb studies investigate the safety and efficacy in large numbers of participants (typically 200–500). Phase III trials are expanded controlled trials that gather additional information to evaluate the overall safety, efficacy and benefit-risk relationship of the drug and provide an adequate basis for the labeling of drugs.

**BOX 3 MAIN FEATURES OF THE *GLOBAL PLAN TO STOP TB 2006–2015*, WHEN LAUNCHED IN JANUARY 2006****A. GOAL AND MAIN TARGETS IN THE ORIGINAL 2006–2015 GLOBAL PLAN****Overall goal**

To achieve the MDG and Stop TB Partnership targets set for 2015

**Specific targets (according to the major components of the plan)**

- DOTS: a case detection rate (CDR) of 84% (for all cases and smear-positive cases specifically) and a treatment success rate of 87% by 2015. The CDR is the number of notified cases of TB divided by the estimated number of new (incident) cases of TB that occurred in the same year. The treatment success rate is the percentage of patients cured plus the percentage that completed treatment but for whom cure was not confirmed.
- TB/HIV: HIV testing of 85% of TB patients by 2010; provision of CPT to 95% of HIV-positive TB patients by 2010; enrolment of around 300 000 HIV-positive TB patients on ART per year by 2010; screening of close to 100% of people in HIV care services for TB on a routine basis by 2010; enrolment of around 10% of the global total of people living with HIV on isoniazid preventive therapy (IPT) by 2010.
- MDR-TB: diagnosis and treatment of 110 000 patients with MDR-TB per year by 2015, with 100% of confirmed cases treated in programmes following international guidelines.
- New diagnostics: a point-of-care test for TB by 2010; a test allowing detection of latent TB infection and to predict which people will develop active TB by 2015.
- New drugs: a novel TB drug introduced by 2010; the duration of treatment for drug-susceptible TB reduced to 3–4 months by 2010 and to 1–2 months by 2015, with regimens also active against MDR-TB and compatible with ART.
- New vaccines: two vaccines in ‘proof-of-concept’ trials by 2010 and one new safe and effective vaccine available by 2015.

**B. FUNDING REQUIREMENTS IN THE ORIGINAL 2006–2015 GLOBAL PLAN****Overall**

US\$ 56 billion over ten years, including US\$ 47 billion for implementation and US\$ 9 billion for research and development. Following the development of a more ambitious plan for MDR/extensively drug-resistant TB (XDR-TB) in 2007, the funding requirements were revised to US\$ 67 billion, including US\$ 56 billion for implementation and US\$ 11 billion for research and development. These amounts included the total funding required for implementation of all recommended interventions at country level, funding required by international agencies for technical assistance, and funding required for the development of new tools (from discovery to adoption within programmes).

**Specific funding requirements (according to the seven major components of the plan)**

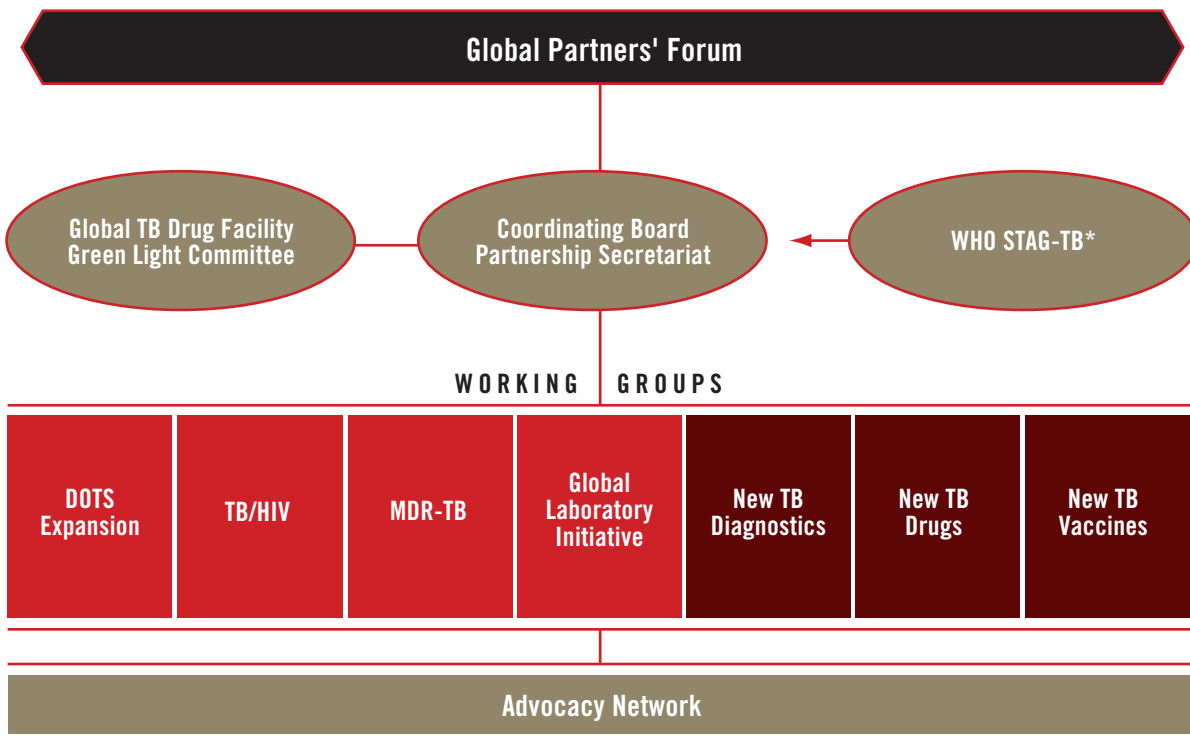
- DOTS: US\$ 28.9 billion
- MDR-TB: US\$ 5.8 billion, subsequently revised to US\$ 15 billion
- TB/HIV: US\$ 6.7 billion
- Advocacy, communication and social mobilization (ACSM): US\$ 2.9 billion
- New diagnostics: US\$ 0.5 billion, subsequently revised to US\$ 1.5 billion
- New drugs: US\$ 4.8 billion, subsequently revised to US\$ 5.8 billion
- New vaccines: US\$ 3.6 billion.

A budget of US\$2.9 billion for technical assistance was also included.

### 1.3 WHY IS AN UPDATED GLOBAL PLAN TO STOP TB NEEDED FOR 2011–2015?

The end of 2010 marks the mid-point of the *Global Plan to Stop TB 2006–2015*, and is an obvious time to update the plan with a focus on the final five years leading up to the target year of 2015. There are several other reasons why the original document needs to be updated (Box 4). Among the most important are: a need to take into account actual progress made since 2006, significant changes in policy and costs related to ART, two updates to the MDR-TB component of the plan (in 2007 and 2009), updates to estimates of epidemiological burden and trends, the importance of giving a higher profile to laboratory strengthening and the need to address the full spectrum of research (from fundamental to operational research). A further reason is changes to the structure of the Working Groups of the Stop TB Partnership as of mid-2010, such as the addition of the Global Laboratory Initiative (Figure 4).

FIGURE 4 THE STRUCTURE OF THE STOP TB PARTNERSHIP



\* STAG-TB: Scientific and Technical Advisory Group for Tuberculosis



**BOX 4** WHY IS A GLOBAL PLAN TO STOP TB NEEDED FOR 2011–2015?

**Need to take account of actual progress made since 2006.** The plan needs to be updated to account for actual progress made since 2006. This means resetting baselines and setting out the scale-up of interventions that is required in the five years up to 2015.

**Significant changes in policy and costs related to ART for HIV-positive TB patients.** When the original plan was launched in 2006, about 50% of HIV-positive TB patients were considered eligible for ART. Since 2009, the policy recommendation is that all HIV-positive TB patients should be started on ART. In terms of costs, six months of ART is now around US\$ 500 per person. In 2005, when the original plan was developed, the cost (including all inputs required, not only antiretroviral drugs) was around US\$ 1000.

**Updates to the MDR-TB component of the plan.** A major update to the MDR-TB component of the plan was made in mid-2007, with more ambitious targets set for 27 high MDR-TB burden countries. A further update was made for these 27 countries in the context of a ministerial conference held in Beijing, China in April 2009. The prices of the regimens recommended for patients with MDR-TB have also increased in some parts of the world.

**Epidemiological projections.** The epidemiological projections need to be revised according to updated estimates of disease burden and trends, including a major update of the burden of TB among people living with HIV in 2008 and an update of the burden of MDR-TB in 2010.

**Higher profile required for laboratory strengthening and progress in diagnostics.** The original plan was structured into seven major components, following the Working Group structure of the Partnership in 2005. Laboratory strengthening did not have a prominent profile in that plan. In 2008, the Global Laboratory Initiative (GLI) was created as a new Working Group, to give a much higher profile to the crucial need to strengthen laboratories, which are essential for the diagnosis of all forms of TB. An update of the plan allows a higher profile to be given to laboratory strengthening. It also allows the plan to reflect the substantial progress in development of new diagnostics made since 2005.

**Need to intensify TB research across the continuum that extends from basic to implementation research.** The full spectrum of research must be taken into consideration, to ensure that all areas of research are being addressed in a coherent and harmonized way, and that there are no gaps in the conduct or funding of research.

**Need to give a much higher profile to fundamental research.** A major improvement in understanding fundamental TB science is urgently needed to stimulate the discovery and development of new diagnostics, drugs and vaccines. Fundamental research needs to be included as a full component of the plan in its own right.

**Need to include programme-based operational research.** Operational research (OR) is necessary to determine the best ways to implement and monitor interventions, including those based on new tools. It is also needed to adapt the Stop TB Strategy to particular contexts. OR must be included as a topic in its own right in the plan.

## 2. THE GLOBAL PLAN TO STOP TB 2011–2015

### 2.1 STRUCTURE AND CONTENT

The Global Plan to Stop TB 2011–2015 sets out what needs to be done to achieve the 2015 targets determined within the context of the MDGs and by the Stop TB Partnership (Box 1). To achieve these targets, the **Implementation** component of the plan (Part I) defines how to transform TB control in the years up to 2015 – through scaling up existing interventions for the diagnosis and treatment of TB and introducing new technologies, notably new diagnostic tests. Looking beyond the targets set for 2015, the **Research and Development** component of the plan (Part II) then shows what needs to be done to develop the new diagnostics, drugs and vaccines that are required to revolutionize the prevention, diagnosis and treatment of TB, as the foundation for the elimination of tuberculosis in the coming decades.

The **Implementation** part of the plan (Part I) is structured in four major components: DOTS expansion and enhancement; Drug-resistant TB; TB/HIV; and Laboratory strengthening. These four components reflect the Working Group structure of the Stop TB Partnership (Figure 4). Given that some components of these plans are closely related, several indicators and targets appear in more than one plan component (notably those related to laboratory strengthening). The **Research and Development** part of the plan (Part II) is structured in five major components: fundamental research; new diagnostics; new drugs; new vaccines; and operational research. The components that cover new diagnostics, new drugs and new vaccines correspond to the Stop

TB Partnership’s three ‘New Tools’ Working Groups (Figure 4). The topic of fundamental research is a new addition to the plan, to reflect the fact that it underpins the development of all new technologies (diagnostics, drugs and vaccines). Operational research has also been added as a distinct topic because it is the interface between the development of new tools and their uptake in policy and practice within national TB control programmes (NTPs), and because it can be used to improve TB control using existing tools.

The Global Plan to Stop TB 2011–2015 builds on, but is distinct from, the plan launched in 2006. A summary of what is the same and what is new in the updated plan is provided in Box 5.

**BOX 5** COMPARISON OF THE GLOBAL PLAN TO STOP TB 2011–2015 WITH THE *GLOBAL PLAN TO STOP TB 2006–2015*

**WHAT IS THE SAME?**

- **Focus on 2015 targets.** The focus of the 2011–2015 plan remains the achievement of the 2015 targets set within the MDGs and by the Stop TB Partnership.
- **Funding requirements are set out, both overall and for major components of TB control, up to 2015.**
- **A guide for planning at country level.** The indicators and targets in the implementation part of the plan, and associated objectives and activities, provide a guide to planning at country level.
- **Focus on low- and middle-income countries.** High-income countries are not considered. There were 171 low- and middle-income countries in the 2006–2015 plan; there are 149 in the 2011–2015 plan.
- **Structured according to the Working Groups of the Stop TB Partnership.** The major components of the plan are defined according to the working group structure of the Partnership.

**WHAT IS NEW?**

- **Global perspective.** The plan is for the world as a whole, and there is no attempt to set out plans for specific regions (as was done in 2006).
- **Laboratory strengthening.** This is included as one of the four major components of the Implementation part of the plan.
- **Fundamental research and operational research.** These topics have been added to the Research and Development part of the plan, even though they are not working groups of the Stop TB Partnership, to highlight the importance of addressing the full spectrum of research needed for better TB control.
- **No separate plan for advocacy, communication and social mobilization (ACSM).** In the 2006 plan, ACSM featured as a major component, reflecting the existence of a Working Group on ACSM. Since there is no longer an ACSM Working Group, ACSM is integrated within other components of this updated plan.
- **Strategic frameworks to set out each major component of the plan in a clear and consistent format.** Each plan is summarized in a two-page strategic framework. Each framework has the same structure and defines, clearly and concisely, the goal, objectives, indicators, baselines and targets for each of the major components of the plan.
- **Epidemiological and cost projections.** These have been updated using the latest data available.
- **Targets for Implementation and for Research and Development.** Targets have been updated where appropriate, taking into account baseline data for 2009 and 2010, respectively.
- **A shorter document, with only the essential information.** The plan is about 60% of the length of the 2006 plan.

## 2.2 MAJOR INDICATORS AND TARGETS

The most important indicators and targets included in the **Implementation** component of the plan are summarized in **Table 1**. Further details are available in **Part I**, notably within the two-page strategic frameworks that summarize the goal, objectives, main activities, indicators, baselines and targets for each of the four major subcomponents. **These indicators and targets, while global in scope, are designed to serve as a guide to the development of plans at country level.**

It is worth highlighting that, in contrast to the 2006 plan, the indicator of the case detection rate (CDR) is not included in the DOTS component. The CDR is defined as the number of notified cases of TB divided by the estimated number of new (incident) cases of TB that occurred in the same year. Starting around the mid-1990s, great attention was given to monitoring progress in the CDR. This reflected the fact that the two principal targets set for TB control at that time were the 1991 targets set by the World Health Assembly – to detect 70% of the new cases of smear-positive TB arising each year, and to successfully treat 85% of those cases that were detected. The targets were originally set for 2000, and later reset to 2005. Since the target year of 2005 passed, there has been a shift to measuring progress against impact targets i.e. targets for reductions in the burden of disease (measured in terms of incidence, prevalence and mortality). The *Stop TB Strategy* (**Box 2**) does not include the 70/85% targets, and nor do the MDG targets. A further reason for not including targets related to the CDR is underlying uncertainty in TB incidence. In most countries, and for the world as a whole, the CDR can only be estimated with a range of around 10–15% (for example, from 60–75%). In this plan, the indicator used to measure progress in case-finding is therefore the number of cases diagnosed, notified and treated in DOTS programmes. This can be more accurately forecast based on recent trends in notifications and the expected impact of new interventions. A fuller explanation is provided in WHO's 2010 report on global TB control.<sup>17</sup>

<sup>17</sup> *Global tuberculosis control 2010*. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.7).

**TABLE 1** SUMMARY OF MAIN INDICATORS, BASELINES AND TARGETS IN THE **IMPLEMENTATION** COMPONENT OF THE GLOBAL PLAN TO STOP TB 2011–2015

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

## 2.3 FUNDING REQUIREMENTS

The funding required to fully implement the Global Plan to Stop TB 2011–2015 is summarized in **Table 3**. The best estimate is that US\$ 47 billion is required for the five years of the plan, of which US\$ 37 billion (79%) is for implementation and almost US\$ 10 billion (21%) is for research and development.<sup>19</sup> The single biggest component is DOTS implementation (48% of the overall total), followed by interventions to

manage drug-resistant TB (15%). Within Research and Development, the development of new drugs accounts for the single biggest share of the funding needed.

The funding required increases steadily over time (**Figure 5**). For Implementation, the funding required grows from just over US\$ 6 billion in 2011 to around US\$ 8.5 billion in 2015. For Research and Development, the amount rises from US\$ 1.9 billion

<sup>18</sup> or one laboratory per country for countries with populations of less than 5 million.

<sup>19</sup> There is some uncertainty about the projections of the numbers of people that will need to receive different services (interventions) as well as some uncertainty about the unit prices of these services. This uncertainty is reflected in **Figure 5** and **Figure 6**. Uncertainty related to research and development was not modeled in this plan.

**TABLE 2** SUMMARY OF MAIN INDICATORS, BASELINES AND TARGETS IN THE **RESEARCH AND DEVELOPMENT** COMPONENT OF THE GLOBAL PLAN TO STOP TB 2011–2015

<b>PLAN COMPONENT AND INDICATORS</b>	<b>BASELINE (2010)</b>	<b>TARGET (2015)</b>
<b>Fundamental research</b>		
New funding for fundamental research, per year (US\$ millions)	98	450
<b>New diagnostics</b>		
Number of new tests for the diagnosis of active TB that can be used in district laboratories	1	2
Number of new tests for the diagnosis of active TB in peripheral-level laboratories	1	2
Number of new point-of-care tests for the diagnosis of active TB in peripheral-level health centres	0	2
Number of new tests for the diagnosis of drug-resistant TB in district laboratories	0	2
Number of new tests for the diagnosis of drug-resistant TB in peripheral-level laboratories	0	1
Number of new tests for the diagnosis of drug-resistant TB in health centres	0	1
Number of new tests for latent TB infection and prediction of the risk of progression to TB disease	0	1
<b>New drugs</b>		
Number of new and/or repurposed drugs in Phase I trials	3	21
Number of single or combination Phase II trials investigating new and/or repurposed drugs	6	34
Number of new regimens for drug-susceptible TB in Phase III trials	2	3
Number of new regimens for drug-resistant TB in Phase III trials	0	2
Duration of treatment of latent TB infection	4-6 months	2-3 months
<b>New vaccines</b>		
Number of vaccine candidates that have entered Phase I trials	5	20
Number of vaccine candidates that have entered Phase II trials	2	9
Number of vaccine candidates that have entered Phase IIb trials	2	3
Number of vaccine candidates that have entered Phase III trials	1	4
<b>Operational research</b>		
New funding for operational research, per year (US\$ millions)	35	86

in 2011 to US\$ 2.2 billion in 2015. Overall, the funding required increases from US\$ 8 billion in 2011 to almost US\$ 11 billion in 2015.

Estimates of funding needs are based on the quantities of services to be provided (for example, the number of diagnostic tests, the number of patients to be treated for drug-susceptible and drug-resistant TB, the number of HIV-positive TB patients to be enrolled on ART, the number of laboratories

to be built, the number of clinical trials to be done) and their respective unit prices. Unit prices cover all of the resources that are needed (for example, staff that manage NTPs and the multi-purpose staff who provide direct patient care or who conduct laboratory tests, first- and second-line drugs, laboratory supplies, equipment, new laboratory capacity, training, management and supervision activities, overhead costs associated with care provided in hospitals and outpatient clinics), based

on the best available data. Sources of data on unit prices included:

- a WHO global TB database. This is managed by the WHO Stop TB Department and includes data since 2002 on NTP budgets and expenditures as well as reported use of general health care services – inpatient care and outpatient visits – during TB treatment);
- a database managed by the Health Financing Department of WHO that includes estimates of the unit prices of hospital care (bed days) and outpatient visits;
- costing studies (especially of treatment for MDR-TB);
- the Joint United Nations Programme on HIV/AIDS (UNAIDS) (for the costs of ART);
- principal investigators of recent and ongoing clinical trials; and
- staff within the major partnerships engaged in TB control (for example, the Foundation for Innovative New Diagnostics; the Global Alliance for TB Drug Development; Aeras Global TB Vaccine Foundation), as well as academia, agencies and companies involved in research and development.<sup>20</sup>

**TABLE 3** SUMMARY OF ESTIMATED FUNDING REQUIRED TO IMPLEMENT THE GLOBAL PLAN TO STOP TB 2011–2015, US\$ BILLIONS

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

Comparisons with the funding requirements outlined in the 2006 plan, and the amounts since mobilized, are provided in **Box 6**.

**BOX 6** FUNDING REQUIREMENTS AND MOBILIZATION OF FUNDING: COMPARISONS WITH THE 2006–2015 PLAN

The *Global Plan to Stop TB 2006–2015* called for funding of US\$ 56 billion for its ten-year period. This was subsequently revised to US\$ 67 billion after a 2007 update to the MDR-TB component of the plan, of which US\$ 56 billion was for Implementation and US\$ 11 billion was for Research and Development (see also **Box 3**). In the first five years of the 2006–2015 plan, a total of US\$ 21 billion was intended for Implementation and US\$ 4 billion for Research and Development. Globally, the amounts actually mobilized over this period were lower. Excluding the European Region, the deficit for Implementation was almost US\$ 7 billion. In the European Region, the amount of funding mobilized was above the needs estimated in the plan. Globally, the deficit for Research and Development was US\$ 2 billion.

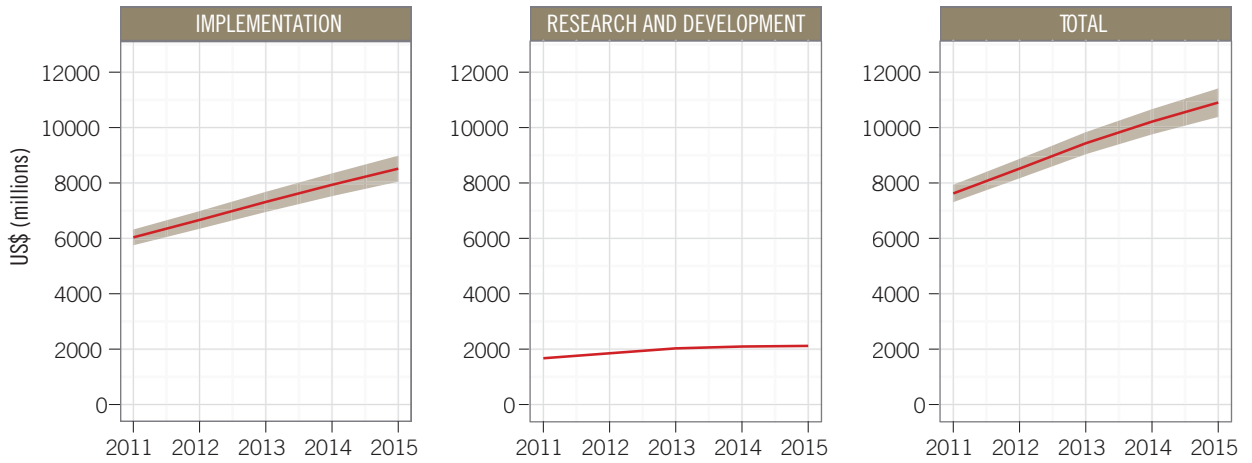
For the period 2011–2015, the original 2006 plan indicated that a total of US\$ 31 billion was needed: US\$ 26 billion for Implementation and US\$ 5 billion for Research and Development. The *Global Plan to Stop TB 2011–2015* requires an estimated US\$ 47 billion, an extra US\$ 16 billion compared with 2006 projections. Part of this increased cost can be attributed to the fact that not all of the required funding was mobilized during the period 2006–2010. The funding shortfall of US\$ 9 billion from this period must now be made up. Additional reasons are the much more ambitious scale-up of treatment for MDR-TB in the plan for 2011–2015, and recognition that investment in research and development needs to be approximately doubled.

To deliver the services necessary for the **Implementation** component of the plan, funding is needed both for NTPs (or their equivalent) and the health systems within which diagnosis and treatment are provided. In almost all countries, people with TB are diagnosed and treated by multi-purpose

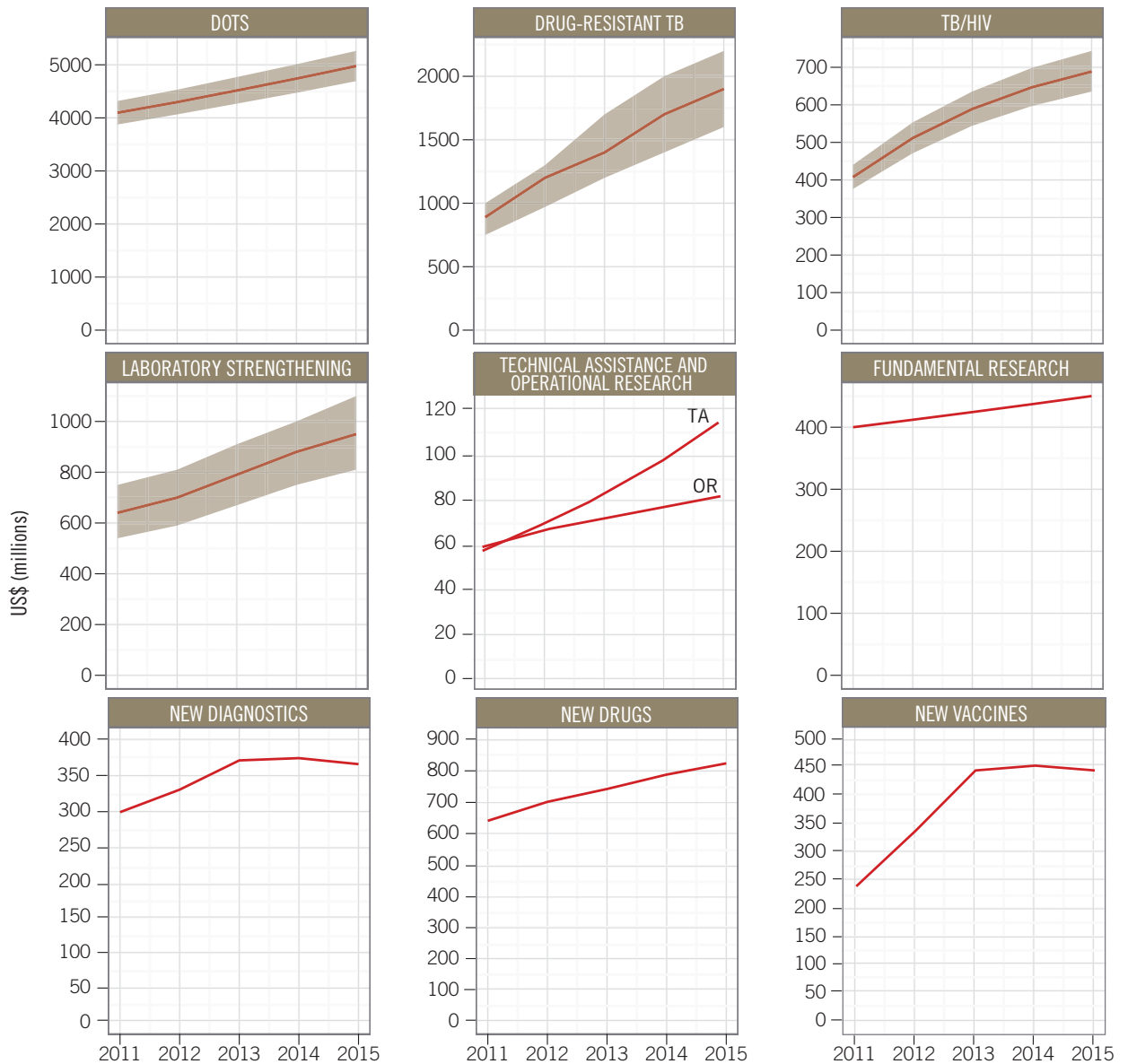
<sup>20</sup> Further details of the methods used to produce estimates of funding requirements are available from the Partnership secretariat.

**FIGURE 5** FUNDING REQUIRED TO IMPLEMENT THE GLOBAL PLAN TO STOP TB 2011–2015 <sup>a</sup>

a) For Implementation, Research and Development and total



b) For the major components of the plan



<sup>a</sup> Shaded areas represent uncertainty bands.



staff, within general primary health care services. Funding may be channelled through ministries of health (and within these, NTPs or general health care budgets), nongovernmental organizations and other mechanisms.

Whichever mechanisms are considered most appropriate in a given context, increases in funding for TB control will help to strengthen health systems as a whole. For example, in terms of the six building blocks of health systems strengthening defined by WHO (financing, human resources, health information, working with all care providers, medical products, vaccines and technologies, and leadership and governance), the Global Plan to Stop TB 2011–2015 includes additional funding for health services and staff, strengthened laboratories, investment in better monitoring and evaluation, efforts to work with all care providers through PPM approaches, improved systems for managing commodities, increased availability of supplies of first- and second-line drugs and the development of new drugs and vaccines. The plan also recognizes that strengthening of health systems is needed to improve TB control. For example, the plan defines targets for vacancy rates in peripheral-level health care facilities (lowering these requires efforts that go far beyond NTPs) and clearly identifies the need for increased health financing.

More broadly still, it highlights the importance of strengthening vital registration systems to improve the measurement of mortality due to TB and other causes.

Potential recipients of the funding required for the **Research and Development** component of the plan include universities, research institutions, public-private partnerships that are engaged in the development of new drugs, diagnostics and vaccines, as well as international institutions and NGOs involved in translational and operational research.

If current levels of domestic funding for TB control are maintained (adjusting only for inflation), about US\$ 21 billion or 57% of the US\$ 37 billion required for implementation could be mobilized from within the 149 countries considered in the plan. Of this amount, about US\$ 11 billion could come from the large economies of the so-called BRIC countries (Brazil, China, India, the Russian Federation), and South Africa. A further US\$ 4 billion could come from middle-income countries in Europe (Scenario 1, [Table 4](#)).

If domestic funding for TB control can be increased at the same rate as currently forecast by the International Monetary Fund (IMF) for gross domestic

**TABLE 4** FUNDING REQUIRED, FUNDING AVAILABLE UNDER TWO POSSIBLE SCENARIOS AND LIKELY FUNDING GAPS, (US\$ BILLIONS)

	<b>Scenario 1.</b> Funding maintained at 2009/2010 levels <sup>a</sup>	<b>Scenario 2.</b> As for Scenario 1, but domestic funding for implementation increases at rate of per capita income growth <sup>b</sup>
<b>IMPLEMENTATION</b>		
<b>A.</b> Funding required	37	37
<b>B.</b> Domestic (endemic country) funding available	21	23
Brazil, China, India, South Africa and Europe	15	17
Rest of World	5	6
<b>C.</b> External (donor) funding available if 2010 levels maintained <sup>a</sup>	3	3
<b>D.</b> Funding gap (A-B-C)	13	11
<b>RESEARCH AND DEVELOPMENT</b>		
<b>E.</b> Funding required	10	10
<b>F.</b> Funding available if 2009 levels maintained <sup>c</sup>	3	3
<b>G.</b> Funding gap (E-F)	6	6
<b>TOTAL FUNDING GAP</b>	19	17

<sup>a</sup> Adjusted only for inflation.

<sup>b</sup> GDP per capita in international dollars (purchasing power parity), forecast for the period 2011–2015 by the International Monetary Fund (IMF).

<sup>c</sup> Based on Treatment Action Group report (referenced in footnote 39), assuming that 2009 levels maintained throughout 2011–2015, adjusted only for inflation.

product (GDP) per capita, an additional US\$ 2 billion could be mobilized (Scenario 2, [Table 4](#)).

The two scenarios outlined in [Table 4](#) suggest that between US\$ 21 and US\$ 23 billion can be mobilized from domestic sources. The remaining funding gap of US\$ 11–13 billion (or about one-third of the total) would need to be funded by international donors in high-income countries. At an average of about US\$ 2–3 billion per year, this is about six times the level of donor funding for TB control in 2010. For comparison, international donor funding for HIV prevention, treatment and care amounted to about US\$ 8.5 billion in 2008, or about 55% of the total.<sup>21</sup>

It is anticipated that investment in Research and Development (almost US\$ 10 billion) will need to be made largely by the most developed countries. However, the BRIC countries and South Africa have already demonstrated increasing capacity for innovation and could contribute much more to the Research and Development component of this plan than has been the case in the past. Funding for research and development will need to increase substantially from the estimated US\$ 0.6 billion that was available in 2009.

Overall, high-income countries may have to contribute as much as half of the necessary resources for the Implementation and Research and Development

components of the Global Plan to Stop TB 2011–2015. Endemic countries, especially the BRIC countries, South Africa and the middle-income countries of Europe, would be expected to mobilize the rest internally. **Political commitment, backed by the financial commitments of both endemic as well as donor countries, is critical to global efforts to stop TB.**

## 2.4 EXPECTED ACHIEVEMENTS IF THE PLAN IS FULLY FUNDED

If the required funding of US\$ 37 billion for the Implementation component of the plan is mobilized, achievements will be substantial ([Table 5](#)). During the five years of the plan, these include:

- **DOTS (including laboratory strengthening).** Diagnosis and treatment for around 32 million people with TB according to the DOTS approach, with 28 million successfully treated;
- **Drug-resistant TB (including laboratory strengthening).** Testing of around 7 million people for MDR-TB, with 1 million confirmed cases of MDR-TB diagnosed and treated according to international guidelines.
- **TB/HIV (including laboratory strengthening).** HIV testing for almost 30 million TB patients,

**TABLE 5** EXPECTED ACHIEVEMENTS IN DIAGNOSIS AND TREATMENT: TOTALS FOR THE PERIOD 2011–2015 (IN MILLIONS)

PLAN COMPONENT	BEST ESTIMATE	PLAUSIBLE RANGE
<b>DOTS/laboratory strengthening</b>		
People with drug-susceptible TB diagnosed, notified and treated	32.5	32.1 - 32.9
People with drug-susceptible TB successfully treated	27.9	27.8 - 28.1
<b>Drug-resistant TB/laboratory strengthening</b>		
Previously treated TB patients tested for MDR-TB	4.5	3.9 - 5.1
New TB patients tested for MDR-TB	2.6	2.4 - 2.9
Cases of MDR-TB treated according to international guidelines	1.1	0.9 - 1.2
Cases of MDR-TB successfully treated	0.8	0.7 - 0.9
<b>TB/HIV/laboratory strengthening</b>		
TB patients tested for HIV	29.9	29.7 - 30.0
HIV-positive TB patients enrolled on CPT	4.1	3.9 - 4.2
HIV-positive TB patients enrolled on ART	4.0	3.8 - 4.1
People living with HIV screened for TB at last visit to HIV care services	71.1	64.7 - 77.5

<sup>21</sup> UNAIDS Outlook Report 2010. Geneva, Joint United Nations Programme on HIV/AIDS, 2010.

around 4 million HIV-positive TB patients enrolled on both CPT and ART, and screening for TB of approximately 71 million people living with HIV.

If no improvements in TB control are made from 2010 onwards, then around 10 million people will die from TB including more than 3.5 million women and children.

If the Research and Development component of the plan is fully implemented, the following achievements can be expected as listed below.

- **In fundamental research.** Optimal characterization of human TB with identification of key molecular features of host/pathogen interactions, allowing further discovery of new biomarkers as well as new drug and vaccine candidates.
- **In new diagnostics.** A portfolio of new and improved diagnostic tests for the detection of TB in all age groups, including MDR-TB and latent TB infection, will be available. Tests will include: at least one simple, robust and affordable test that can be used for rapid and reliable diagnosis of TB at the peripheral level of health systems; a test capable of identifying people with latent TB infection who are at the greatest risk of progression to active disease; and a test for the diagnosis of MDR-TB at the peripheral level of health systems.
- **In new drugs.** A new four-month TB regimen for drug-susceptible TB (including at least one new or repurposed drug) will be approved by regulatory authorities, recommended by WHO and available for use; at least one new drug for the treatment of drug-resistant TB will be available; a nine-month regimen for treatment of MDR-TB (including at least one new drug) will be in a Phase III trial; and a safer, shorter, higher-efficacy regimen will be available for treatment of latent TB infection.
- **In new vaccines.** Four new TB vaccine candidates will have entered Phase III clinical trials for safety and efficacy; assays to determine biomarkers and correlates of immunity will be incorporated into clinical trials; and sufficient manufacturing capacity and licensing agreements will be in place to ensure an ample supply of new TB vaccines at reasonable cost.

- **In operational research (OR).** OR projects will be a full part of the evaluation plans of NTPs, to help monitor and improve programme performance. OR to collect the evidence necessary for the introduction of new tools in programme conditions will have been conducted at national and international levels.

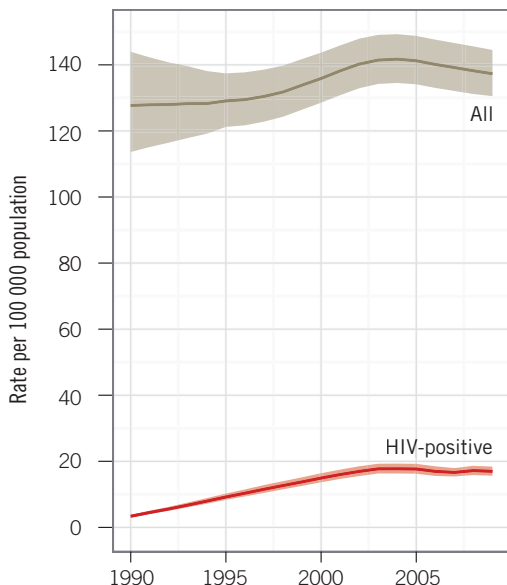
## 2.5 EXPECTED PROGRESS WITH RESPECT TO GLOBAL TARGETS SET FOR 2015

If the plan is fully funded, projections developed in 2010 suggest that the MDG target – that TB incidence should be falling by 2015 – will be achieved globally. This target will also be achieved in all six WHO regions: the African Region, the Region of the Americas, the Eastern Mediterranean Region, the European Region, the South-East Asia Region and the Western Pacific Region. Globally, incidence has been falling since 2004 (Figure 6), and improvements in TB control as set out in this plan should sustain, and ideally accelerate, the current rates of decline. Projections also suggest that the target of halving the TB mortality rate could be reached at global level (Figure 7). Projections of TB prevalence are more uncertain, but with additional data that are anticipated from surveys of the prevalence of TB disease conducted during the years 2010–2015, a robust assessment will be possible in 2015. Existing projections suggest that the target of halving TB prevalence could be achieved in all regions with the exception of the African Region and the South-East Asia Region (Figure 8).

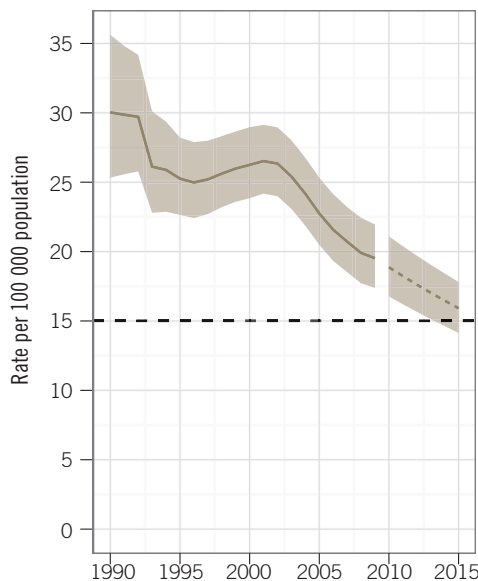
Full funding of the **Research and Development** component of the plan will provide the foundation for moving towards elimination of TB.

**Part I and Part II of the plan provide further details about the Implementation and Research and Development components of the plan.**

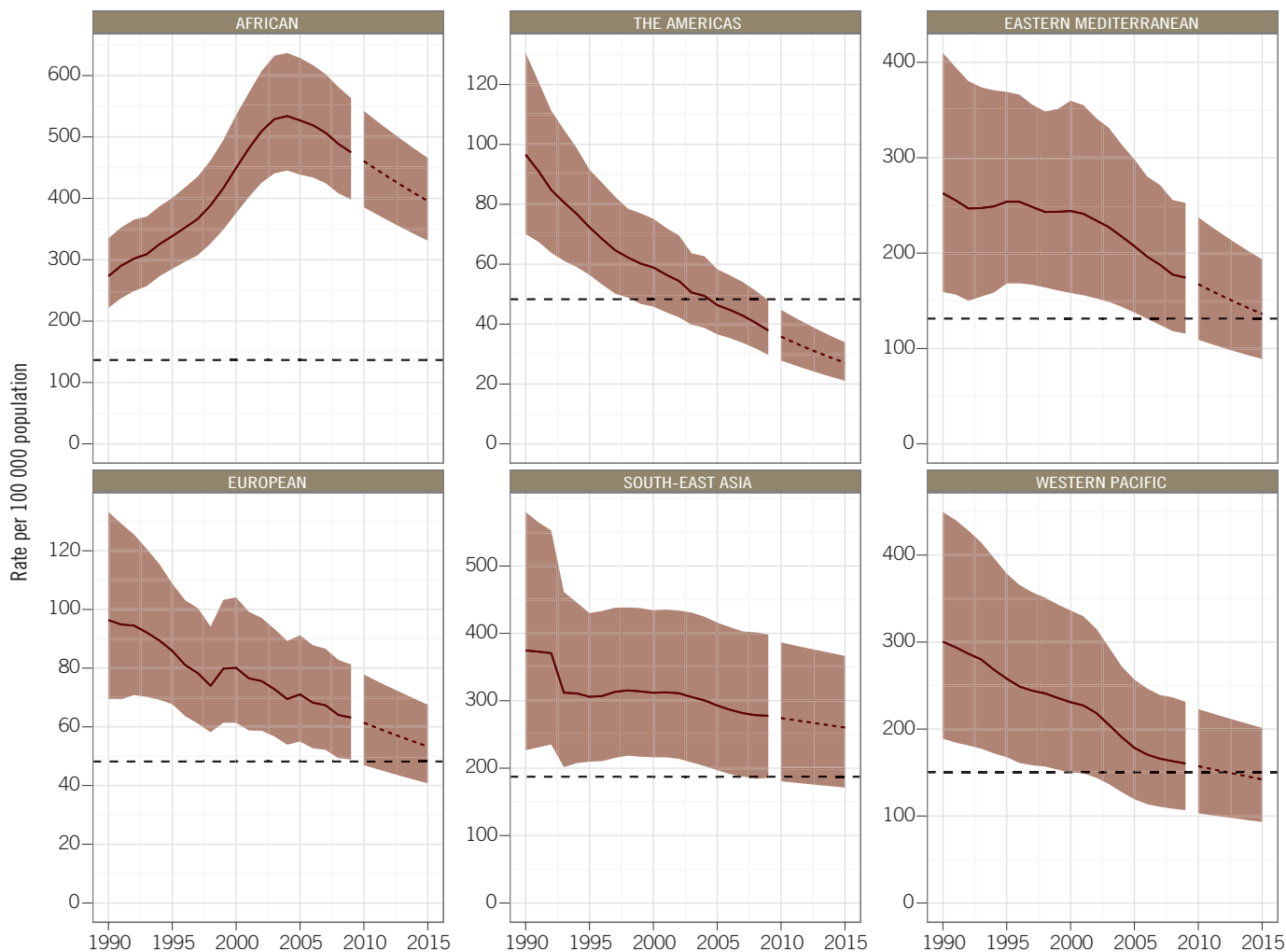
**FIGURE 6** ESTIMATED TB INCIDENCE RATE AT GLOBAL LEVEL, 1990–2009<sup>a</sup>



**FIGURE 7** ESTIMATED TB MORTALITY AT GLOBAL LEVEL, 1990–2009 AND PROJECTION UP TO 2015<sup>a</sup>



**FIGURE 8** ESTIMATED TREND IN TB PREVALENCE, BY WHO REGION<sup>a</sup>



<sup>a</sup> Shaded areas in FIGURES 6, 7 and 8 represent uncertainty bands. Horizontal dashed lines show the target for 2015; the other dashed lines show projections for 2010–2015.

# ABOUT THE STOP TB PARTNERSHIP

The Stop TB Partnership was established by the World Health Assembly (WHA) in May 2000, following the Ministerial Conference on Tuberculosis and Sustainable Development in Amsterdam, the Netherlands. It has grown steadily since then and now comprises over 1200 organizations, including donors, national and international organizations, government and nongovernmental organizations (NGOs), affected communities and academic institutions working together to reduce the toll of TB worldwide and ultimately achieve a world free of tuberculosis.

The Partnership consists of a Partners' Forum, a Coordinating Board, a Partnership Secretariat hosted by the World Health Organization (WHO) in Geneva, Switzerland, and seven Working Groups (WG):

- DOTS expansion
- TB-HIV
- Multidrug-resistant TB (MDR-TB)
- Global Laboratory Initiative
- New TB drugs
- New TB vaccines and
- New TB diagnostics.

The Partnership's mission is to:

- ensure that every person with TB has access to accurate diagnosis, effective treatment and cure;
- stop the transmission of TB;
- reduce the social and economic toll of TB;
- develop and implement new preventive, diagnostic and therapeutic tools and strategies to stop TB.

## MECHANISMS OF THE STOP TB PARTNERSHIP

The Partnership has established and maintains several mechanisms to help achieve the goals of the *Global Plan to Stop TB 2006–2015*.<sup>1</sup>

### THE GLOBAL DRUG FACILITY

The Global Drug Facility (GDF) ensures access to high-quality anti-TB drugs at the lowest possible price for countries in need. GDF has developed an innovative approach to furnishing the drugs and supplies needed to fully implement WHO's *Stop TB Strategy*, including grants of anti-TB drugs free-of-charge to countries with limited resources, a direct procurement service and expert technical assistance for managing anti-TB drugs. GDF unites these essential services under one umbrella.

GDF secures competitive prices through pooled procurement and global tendering and has developed stockpiles of first- and second-line drugs to prevent supply interruptions or 'stockouts'. It also provides diagnostics to countries for both drug-sensitive and MDR-TB.

Since its creation in 2001, GDF has delivered over 17 million patient treatments in over 115 countries and provided over 460 in-country missions to ensure successful implementation of the Stop TB strategy and increase capacity.

<sup>1</sup> *Global Plan to Stop TB 2006–2015: actions for life towards a world free of tuberculosis*. Geneva, World Health Organization, 2006 (WHO/HTM/STB/2006.35).

Between 2011 and 2015, GDF anticipates delivering 8 million anti-TB treatments. GDF services will evolve to fill the needs of the TB landscape, promoting the use of quality-assured medicines through:

- rapid response mechanisms to deal with emergencies and prevent stockouts;
- targeted grants aimed at scaling up the use of new products or formulations as per WHO treatment recommendations;
- country support through coordination with partners to provide the technical assistance needed to strengthen drug management systems and capabilities;
- market shaping to increase the affordability and production of quality-assured anti-TB medicines;
- streamlined procedures to increase effective and efficient services to countries.

## THE GLOBAL LABORATORY INITIATIVE

Since the 2006 launch of the Global Plan to Stop TB there has been growing recognition that worldwide TB laboratory capacity is insufficient to address the global pandemic, and the diagnostic challenges presented by drug-resistant and HIV-associated TB in particular. In 2007, the Stop TB Partnership Coordinating Board endorsed the creation of a Global Laboratory Initiative (GLI), with the mission to guide and coordinate a massive scale-up of laboratory capacity. In June 2008, GLI was upgraded to the status of a Stop TB Partnership Working Group with its Secretariat in WHO.

GLI has more than 100 partners including national NTPs, NGOs, technical and financial agencies, scientific and academic institutions and WHO offices at country and regional levels. GLI's vision is integrated diagnostic laboratory services delivering rapid, quality-assured tests to all who need them through a network of accredited laboratories. Its main activities include:

- global policy guidance on appropriate laboratory technology and best practices;
- effective technology transfer and coordination of technical assistance;
- laboratory-related advocacy and resource mobilization;

- laboratory capacity development;
- interfacing with other laboratory networks to ensure appropriate integration;
- standardized laboratory quality assurance;
- effective knowledge sharing, including learning by doing.

## TB TECHNICAL ASSISTANCE MECHANISM (TBTEAM)

The launch of the Stop TB Strategy in 2006 was a major stimulus for NTPs and other groups engaged in TB control to move from basic DOTS to a wider range of activities. This evolution requires new skills, which can often best be acquired by tapping into the worldwide network of TB experts dedicated to providing technical assistance (TA). The chief objective of TA is to support local TB workers and institutions to develop new approaches adapted to their resources and settings, and to build sustainable national capacity.

TA covers the set of skills required to help the uptake of innovative approaches and new tools to improve TB control while integrating their activities within national health plans. TA includes specialized activities (such as laboratory strengthening, infection control and management of drug-resistant or HIV-associated TB) requiring close interaction with technical experts and specialist input. It also covers the skills required to expand the management responsibilities of national TB programmes, including the flows of external funding from agencies such as the Global Fund to fight AIDS, Tuberculosis and Malaria and other donors. National coordination of TA is essential to ensure that the needs of NTPs are addressed efficiently, without overloading NTP staff.

TA can best be coordinated and appropriately delivered when countries have comprehensive national plans for it. TA plans address needs or gaps clearly identified in the NTP's strategic plan, covering issues such as DOTS expansion, MDR-TB, TB/HIV, laboratory strengthening, management, health systems strengthening, and monitoring and evaluation. The plans need to include both short- and long-term TA, with the involvement of all relevant stakeholders.

At present there is a serious shortage of people able to provide high-quality TA on TB and support the build-up of technical capacity at country level. There is an urgent need to scale up training of experts (both national staff and external TA providers) in all relevant technical areas with particular attention to infection control, MDR-TB, laboratory strengthening and funding processes (proposal preparation, grant negotiation and implementation).

In 2005, the Stop TB Partnership’s Coordinating Board agreed that a coalition of major technical partners should join forces so that TA could be provided in a coordinated manner. TBTEAM was established in 2007 to fulfil this role. TBTEAM, with a secretariat housed at WHO in Geneva, is a global coalition of partners, countries and funding agencies. It promotes national planning for TA by countries, facilitates identification of needs and coordination of TA at country level and the supply, coordination and quality assurance of TA providers. Quality assurance is proving to be a challenge, but includes a review of a person’s curriculum vitae by members of the relevant Working Groups before they are included in the TBTEAM roster of experts, and performance evaluation by senior staff in the requesting country.

Another important role of TBTEAM is to provide regular assessment of TA funding requirements and to conduct related advocacy. This implies efforts to harmonize advocacy for TB-related TA and associated financing with similar initiatives in other parts of the health sector.

In most countries heavily affected by TB there is now a clear understanding of the critical importance of TA. The demand for skilled TA recently reached an all-time high, in accordance with emerging national plans and proposals for their implementation.

By 2015, it is anticipated that 149 countries will have comprehensive national TA plans that are aligned with at least part of national strategic plans for TB control. A total of US\$ 416 million will be needed from 2011–2015 for Stop TB partners to provide essential TA for countries to fully implement their national plans.

## THE GREEN LIGHT COMMITTEE INITIATIVE

The Green Light Committee (GLC) Initiative was set up by WHO in 2000 and has supported countries in the fight against MDR-TB. Under this initiative, countries meeting WHO standards for TB control have benefited from quality-assured second-line anti-TB drugs at reduced prices and corresponding technical assistance.

Between 2000 and 2010, GLC approved treatment for almost 85 000 people in 85 countries. The initiative has provided assurances to funding agencies that their investments supported MDR-TB treatment programmes that conform to WHO standards. The initiative’s three components are:

- a group of technical experts advising WHO, with the role of reviewing proposals for second-line treatments;
- GDF, which has served as the initiative’s procurement arm, arranging the supply of second-line anti-TB drugs at reduced cost;
- a secretariat hosted by WHO.

At the time of publication of this plan, the global framework for addressing MDR-TB – in which the GLC Initiative has played a key role – was being reviewed with the goal of rapidly scaling up access to diagnosis and treatment.

## TB REACH

Launched in January 2010, TB REACH is a fast-track funding initiative focused on reaching people who have limited or no access to TB services, with the main objective of promoting early and increased detection of infectious TB cases and ensuring their timely treatment.

TB REACH encourages the development and application of innovative, ground-breaking and efficient techniques, interventions, and activities that result in increased TB case detection, reduced transmission and prevention of drug-resistant TB.

TB REACH has US\$ 110 million available for 2009–2013 to fund programmes in eligible countries with the clear purpose of detecting and treating at least 200 000 additional new smear-positive TB cases.

Under the first wave of funding, 30 selected government and NGO projects are receiving US\$ 18.5 million, with the objective of detecting and treating 45 000 additional smear-positive TB cases in one year.

### **CHALLENGE FACILITY FOR CIVIL SOCIETY**

The Challenge Facility targets grass-roots and other civil society organizations that seek to help shape policy at a local level by giving a voice to people living with TB and those involved in its prevention, treatment and care. Proposals are reviewed and grants awarded by an independent committee composed of 10 representatives from the community affected by TB, NGOs from developing and developed countries and multilateral or technical agencies.

The activities of grant recipients result in resources for TB control, active community case-finding and referral by the community, engagement with cured people to encourage TB patients to complete treatment and tracing of people who have interrupted their treatment.

In the third grant round (June 2010), the Partnership announced that 22 civil society organizations across Africa, Asia, Eastern Europe and Latin America were to receive grants ranging from US\$ 5000 to US\$ 20 000.

### **THE RESEARCH MOVEMENT**

The establishment of the Stop TB Partnership Research Movement in 2006 reflects the Partnership's increasing focus on promoting and enabling TB research. The overall goal of the Research Movement is to stimulate, support and expand research to ensure the global elimination of TB in the world by 2050, through the mobilization of a broad alliance of researchers, research institutions, donor organizations and civil society involved in TB research and development.

The Research Movement has three overarching objectives:

- to lead on efforts to increase resources for TB research;
- to provide a forum for TB researchers and funders of TB research to coordinate their priorities and actions;
- to develop and implement a coherent and comprehensive global TB research roadmap to TB elimination.

The initiative seeks to strengthen the wide community of researchers engaged in the broad fields of fundamental research, development of new drugs, diagnostics and vaccines and operational research to ensure discovery of new tools and ensure that these are accessible to those who need them.



# PART I

# IMPLEMENTATION

## THE BEST REASON TO STEP UP THE FIGHT AGAINST TUBERCULOSIS

What does being ill with TB mean for a person? If he or she has access to prompt diagnosis and care, it means treatment and a high chance for cure. Without prompt access, it generally means many weeks, months or years of being seriously ill with a disease that causes an unrelenting cough, weakness and fever and that may ultimately result in death.

What does it mean to a family when the mother or father is ill with TB and goes without effective diagnosis or treatment? The family may well be driven into poverty because a breadwinner is unable to work. Children may have to leave school to work themselves or care for a sick parent. And if a parent dies, they must face life as an orphan.

These situations are intensified if the person with TB has a multidrug-resistant (MDR) form of the disease or is also living with HIV. People living with HIV who develop TB but do not receive effective TB and HIV care have only a one-in-ten chance of surviving for three months or more. A person with MDR-TB faces up to two years of treatment with drugs that have severe side-effects including vomiting, vertigo and tingling in the hands and feet.

What does it mean to countries when they have a high burden of TB? Because TB takes so many people out of the workforce it has a strong impact on the economic fate of entire nations. But there is good evidence that fighting TB is highly cost-effective. A 2007 World Bank study found that the 22 countries

that are most heavily burdened by TB could earn on average ten times more than they spend on TB diagnosis and treatment if they fully implemented the *Global Plan to Stop TB 2006–2015*.

There are many other reasons to urgently scale up TB control. TB is an airborne, potentially lethal infectious disease, and in a world where millions of people are crossing borders and even continents every day, global security is at stake. The emergence of drug-resistant forms of the disease – some of them virtually untreatable – poses an additional and unacceptable risk.

But from our viewpoint, the most compelling reason to fight TB is that every person with TB has a face, a name and a life that is as precious to her or to him as it is to any of us. All women, men and children who need TB diagnosis and care have a right to it – no matter who they are or where they live – and they should be able to access TB services free of charge and in a manner that respects their dignity.

This Global Plan to Stop TB sets forth an ambitious agenda for reaching more people than ever with accurate TB diagnosis and effective treatment. Currently there is a shortfall of more than US\$ 10 billion in the funding required to meet these goals between now and 2015, but consider the human cost if the world fails to achieve them.

Over 10 million people will lose their lives to this preventable, curable disease; around 3 million of them will be women and 2 million of them will be people living with HIV. Millions of children will be orphaned needlessly. Over 2 million cases of MDR-TB will emerge.

There are many barriers to reaching the roughly 3 million people who are currently failing to access quality TB care each year. One of the most daunting challenges – the inability of a great many countries to provide accurate and rapid diagnosis, particularly for drug-resistant and HIV-associated TB – is addressed by this plan.

The Global Plan to Stop TB 2011–2015 sets specific objectives for building and renovating laboratories, training laboratory staff and introducing recently developed rapid TB tests. It also highlights the activities of a new Stop TB Partnership Working Group, GLI, which was launched in 2008. GLI provides policy guidance on appropriate laboratory technology and best practices and oversees global initiatives aimed at helping countries build or scale up laboratories that efficiently and effectively provide services for TB as well as other diseases.

It is absolutely clear that reaching the unreached millions in need of TB diagnosis and care requires accessible laboratory facilities with quality services, effective anti-TB drugs and, one day, an effective vaccine. But this is not enough.

TB is an infectious disease, but we will need more than medical treatment to conquer it. The title of this new plan, *Transforming the fight*, speaks to that challenge. TB is a social issue, primarily affecting the world's poorest and most marginalized communities. It will take an entirely new level of empowerment and engagement in affected communities, and commitment by the international community, for us to win the fight.

**Jeremiah Chakaya**

*Chair, Working Group on DOTS Expansion*

**Diane Havlir**

*Chair, Working Group on TB/HIV*

**John Ridderhof**

*Chair, Global Laboratory Initiative*

**Catharina Van Weezenbeek**

*Chair, Working Group on MDR-TB*

## 1. DOTS EXPANSION AND ENHANCEMENT

### INTRODUCTION: DEFINITIONS, TARGETS AND PROGRESS TO DATE

An estimated 9.4 million new cases of TB occur each year. TB exists in all parts of the world, but there are 22 HBCs<sup>1</sup> that account for around 80% of the world's TB cases. Globally, the highest rates of TB per capita are in the African Region (Figure 9). Most people who develop TB have drug-susceptible forms of TB (more than 95% of all cases worldwide): that is, TB that can be treated and cured with six months of chemotherapy using 'first-line' drugs.<sup>2</sup>

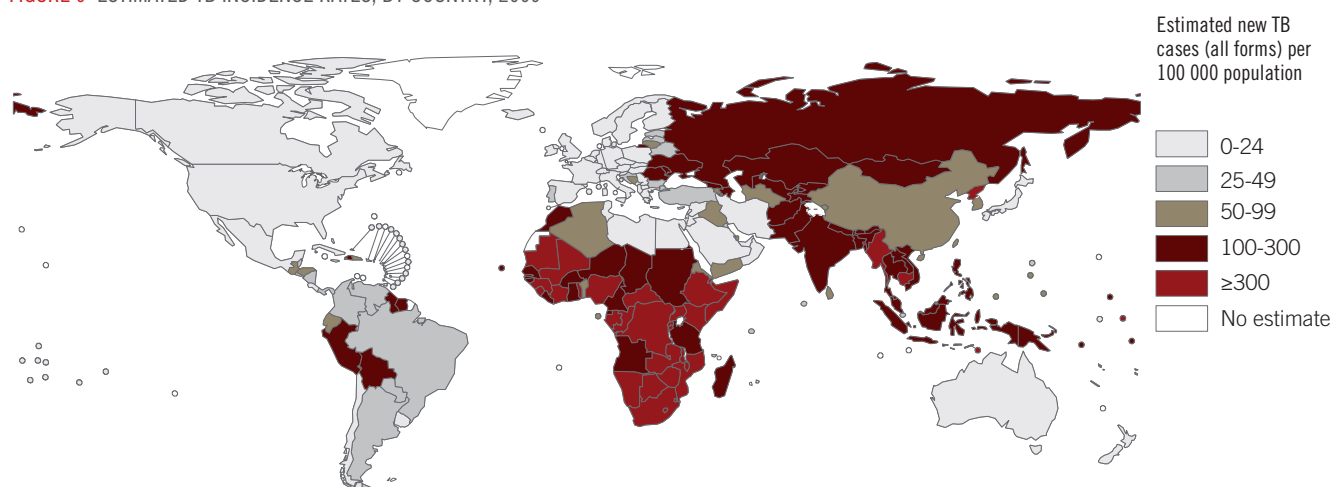
The so-called 'DOTS' strategy was developed in the mid-1990s as the internationally-recommended approach to TB control, and was subsequently expanded worldwide. The strategy was built on model programmes developed in African countries from the late 1980s, and has five components:

**1. Political commitment.** This is the foundation of the strategy. One indicator of political commitment is the percentage of funding for TB control that is provided from domestic sources.

**2. Early case detection through quality-assured diagnosis.** Initially, great emphasis was given to diagnosis of the most infectious cases of TB (i.e. sputum smear-positive cases of pulmonary TB), detected using sputum smear microscopy. More recently, there has been increasing emphasis on the role of diagnosis based on culture and molecular tests as well as smears, as highlighted in the **Laboratory strengthening** component of the Global Plan.

**3. Standardized treatment with supervision, and patient support.** The recommended treatment for drug-susceptible TB is a short-course (six months) regimen of four drugs: isoniazid and rifampicin, the two most powerful first-line anti-TB drugs, plus pyrazinamide and ethambutol. For patients with drug-susceptible TB, these regimens will cure around 90% of TB cases when treatment is fully adhered to and drugs are quality-assured. Treatment and patient support can usually be provided on an outpatient basis, with no need for hospital admission, within general primary health care services.<sup>3</sup>

FIGURE 9 ESTIMATED TB INCIDENCE RATES, BY COUNTRY, 2009



<sup>1</sup> These countries, in alphabetical order, are: Afghanistan, Bangladesh, Brazil, Cambodia, China, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, the Philippines, the Russian Federation, South Africa, Thailand, Uganda, the United Republic of Tanzania, Viet Nam and Zimbabwe. Combined, India and China account for an estimated 35% of the world's cases of TB.

<sup>2</sup> Diagnosis and treatment of patients with drug-resistant strains of TB, in particular multidrug-resistant TB (MDR-TB), is covered in the **Drug-resistant TB** component of the plan.

<sup>3</sup> A small number of countries provide treatment on an inpatient basis for two months or more, sometimes in specialist TB hospitals. A small proportion of TB patients with severe forms of TB need to be managed in hospitals in many countries.

**4. Drug supply and management system.** A reliable supply of quality-assured first-line drugs is fundamental to high-quality treatment. GDF was established by the Stop TB Partnership in 2001 to help ensure the availability of quality-assured drugs at affordable prices.<sup>4</sup>

**5. Monitoring and evaluation.** Routine monitoring of the performance of TB control is crucial. The main indicators to monitor DOTS implementation are the number of cases diagnosed and notified, and the percentage of patients who are successfully treated.

A critical milestone in DOTS implementation was a high-level ministerial conference held in Amsterdam, the Netherlands in 2000. At this conference, the 22 HBCs committed to achieving global targets set for TB control for 2005, through implementation of the DOTS strategy.<sup>5</sup> The global targets were: (i) to detect 70% of new smear-positive cases of pulmonary TB (i.e., to diagnose 70% of the estimated number of new cases of smear-positive pulmonary TB<sup>6</sup> that occur each year, a target known as the CDR); and (ii) to successfully treat 85% of detected cases. These targets were first set by the Forty-fourth World Health Assembly in 1991,<sup>7</sup> for the year 2000, and were subsequently reset to 2005. In line with these commitments and targets, the first *Global Plan to Stop TB 2001–2005*,<sup>8</sup> gave particular emphasis to implementation of DOTS and achievement of the 70/85% targets in the 22 HBCs.

Building on the success of the DOTS strategy, but recognizing the need to broaden its scope, WHO launched the *Stop TB Strategy* in 2006<sup>9</sup> (see **Box 2** in the **Overview** of this plan). DOTS is the first component (of six) and the foundation of the *Stop TB Strategy*. The *Global Plan to Stop TB 2006–2015*, launched in the same year, set out the scale at which DOTS (and other components of the strategy) should

be implemented. The major targets were to reach a CDR of 84% by 2015 and a treatment success rate of 87% by 2015.

There has been enormous progress in DOTS implementation in the past 15 years. The total number of countries implementing DOTS reached 180 in 2003 (up from around 70 in 1995), and has since remained stable at around this level. All 22 HBCs have implemented the DOTS strategy since 2000. By 2008, more than 99% of the TB cases reported to WHO by NTPs were being treated through the DOTS approach. Of the 5.8 million cases of TB (new cases and relapse cases) that were treated by NTPs in 2009, 2.6 million (45%) were new smear-positive cases of pulmonary TB, 2.0 million (35%) were new smear-negative cases of pulmonary TB (including cases for which smear status was unknown), 0.9 million (15%) were new cases of extrapulmonary TB and 0.3 million (5%) were relapse cases.

The percentage of new cases of smear-positive TB detected (the CDR) was 56–68% in 2008, with a best estimate of 62%. Globally, the treatment success rate reached 86% in the 2007 and 2008 cohorts, and 87% in HBCs.

In the fifteen years from 1995 to 2009, 49 million TB patients were treated according to the DOTS strategy, 41 million successfully. The TB incidence rate (per 100 000 population) peaked in 2004, and has since fallen each year. By 2009, the mortality rate at global level had fallen by 35% compared with a baseline of 1990.

Building on the achievements of the last 15 years, the DOTS component of the *Global Plan to Stop TB 2011–2015* sets out how TB control can be further improved, reaching more people with TB and achieving higher rates of treatment success. This

<sup>4</sup> For more information about the Global Drug Facility, see the section of this plan that explains the mechanisms of the Stop TB Partnership.

<sup>5</sup> [http://www.stoptb.org/assets/documents/events/meetings/amsterdam\\_conference/decla.pdf](http://www.stoptb.org/assets/documents/events/meetings/amsterdam_conference/decla.pdf)

<sup>6</sup> Pulmonary TB – or TB of the lungs – is the most common form of TB (about 85% of TB patients treated in 2008). Typically, around 50–60% of notified patients with pulmonary TB have smear-positive TB. TB patients with extrapulmonary TB accounted for about 15% of TB patients notified to WHO in 2008.

<sup>7</sup> [www.who.int/tb/publications/tbresolution\\_wha44\\_8\\_1991.pdf](http://www.who.int/tb/publications/tbresolution_wha44_8_1991.pdf)

<sup>8</sup> [www.stoptb.org/assets/documents/global/plan/GLOBAL\\_PLAN\\_TO\\_STOP\\_TB\\_2001\\_2005.pdf](http://www.stoptb.org/assets/documents/global/plan/GLOBAL_PLAN_TO_STOP_TB_2001_2005.pdf)

<sup>9</sup> *The Stop TB Strategy: building on and enhancing DOTS to meet the TB-related Millennium Development Goals*. Geneva, World Health Organization, 2006 (WHO/HTM/TB/2006.368).

includes giving attention to elements of TB control that are more broadly related to health system strengthening (HSS). The six building blocks of HSS, as defined by WHO, are as follows: health financing; human resources; health information systems; working with all care providers; medical products, vaccines and technologies; and leadership and governance.<sup>10</sup> The plan for DOTS includes objectives and targets related to human resource development, infection control in health care facilities, monitoring and evaluation (including strengthening of notification and vital registration systems), engagement of all care providers through public-private mix (PPM) approaches, and the share of funding that is provided from domestic sources.

## OVERVIEW OF PLAN GOALS, OBJECTIVES, TARGETS AND ACTIVITIES, 2011–2015

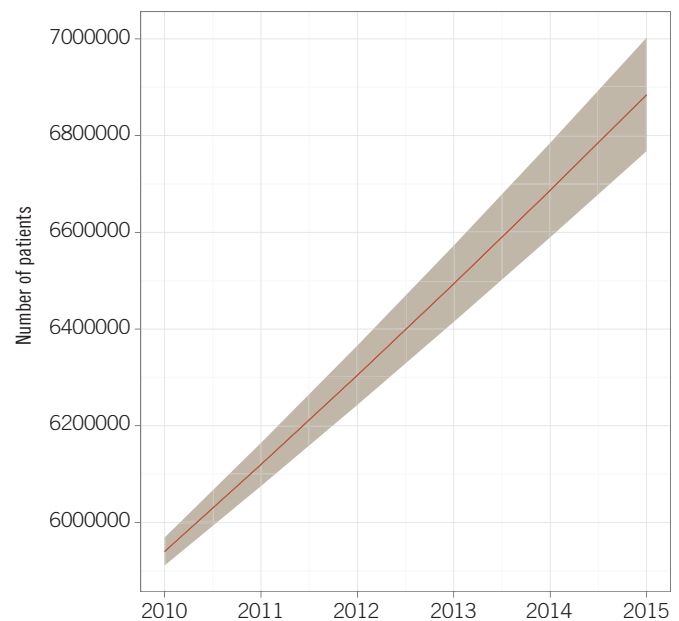
The main goal of the DOTS component of the Global Plan is to reduce the global burden of TB in line with the targets set for 2015 as part of the Millennium Development Goals (MDGs) and by the Stop TB Partnership, through early TB diagnosis, high-quality treatment of all cases, and prevention of TB transmission. As explained in the [Overview](#) section of this plan, the MDG target is that incidence should be falling by 2015; the Stop TB Partnership targets are to halve mortality and prevalence rates by 2015, compared with a baseline of 1990. The main target highlighted in the strategic plan for DOTS is the reduction of TB mortality by 50% by 2015, compared with 1990.

To achieve this goal, there are six critical objectives and associated targets, which are explained below.

**Objective 1: Ensure early diagnosis of all TB cases.** By 2015, approximately 7 million people should be receiving accurate diagnosis of TB and effective treatment ([Figure 10](#)), an increase of more than 1 million compared with 2009.<sup>11</sup> To facilitate this, diagnosis should be easily accessible, with no

or minimal financial and geographic barriers to care. All countries should have at least one laboratory able to conduct sputum smear microscopy per 100 000 population (see also the [Laboratory strengthening](#) component of the Global Plan), and access to care needs to be improved through strengthening and expansion of basic health-care services (especially for hard-to-reach populations, as in [TBREACH](#)<sup>12</sup> projects). Particular efforts including outreach activities and selective active case finding are needed to detect TB in vulnerable groups, which can include pregnant women and young children, the urban poor, contacts of TB cases, migrants, prisoners, alcohol users, drug users, displaced people, smokers and people with diabetes. In addition, NTPs need to establish links and collaborate with the full range of care providers through PPM approaches. There is good evidence that PPM approaches can increase the percentage of people who are diagnosed and receive high-quality treatment by between one quarter and one third, with health care providers such as pharmacists, traditional healers and private practitioners often the first point of contact for

**FIGURE 10** DOTS: NUMBER OF PATIENTS TO BE TREATED, 2011–2015<sup>a</sup>



<sup>a</sup> Shaded areas represents uncertainty band.

<sup>10</sup> *Everybody's business: Strengthening health systems to improve health outcomes*. Geneva, World Health Organization, 2007.

<sup>11</sup> The target has been set in terms of the number of people diagnosed and treated, as opposed to the CDR. This is because of uncertainty in estimates of the CDR (given uncertainty in the underlying incidence of TB) and because progress in the numbers diagnosed and treated can be directly measured as well as projected more reliably from existing numbers of notified cases.

<sup>12</sup> For more information about [TBREACH](#), see the section of this plan that explains the mechanisms of the Stop TB Partnership.

people with symptoms of TB. Educating health workers about the Practical Approach to Lung Health (PAL)<sup>13</sup> including smoking cessation and coordinated management of respiratory illnesses can also increase case detection, as can raising awareness about TB among the general population.

**Objective 2: Ensure high-quality treatment of all diagnosed cases of TB.** The global treatment success rate should reach 90% by 2015, a level that has already been achieved in several HBCs and other countries. This will require drug management and rational use of anti-TB drugs that meet the pre-qualification standards established by WHO, according to international guidelines for all patients (including paediatric formulations). Procurement through GDF is an excellent way to ensure that first-line drugs meet these standards. Use of fixed-dose combinations (FDCs) of drugs should be encouraged and interruptions to drug supplies must be avoided at all costs. High rates of treatment success also depend on provision of care and support in health care facilities and the community, including use of enablers and incentives where appropriate, effective programme management and supervision and engagement of all care providers through PPM and the International Standards for TB Care (ISTC).<sup>14</sup> Ensuring good health outcomes among TB patients also requires that relevant co-morbidities and risk factors (such as HIV, smoking, respiratory illnesses, diabetes, undernutrition, and substance abuse) are identified and managed optimally, in collaboration with other health programmes. Community engagement can improve the quality of care through direct patient support, and have a very positive and immediate impact on adherence to TB treatment.

**Objective 3: Strengthen monitoring and evaluation including impact measurement.** Monitoring and evaluation is the fifth component of the DOTS strategy, and is essential to document progress and to show whether TB control is having the expected impact on the burden of disease. By 2015, all countries should be reporting treatment outcomes for all cases (not just those with smear-positive pulmonary TB, which was the original emphasis in recording and reporting when the DOTS strategy was launched in

the mid-1990s). This should be done using electronic systems for recording and reporting of data wherever possible. Following the recommendations agreed by the WHO Global Task Force on TB Impact Measurement,<sup>15</sup> systematic assessments of the quality and coverage of notification and vital registration (VR) data need to be undertaken on a regular basis, using the framework and associated tools developed by the Task Force; vital registration systems need to be developed or strengthened and surveys of the prevalence of TB disease are needed in selected countries (the Task Force has identified 21 so-called ‘global focus’ countries where surveys are strongly recommended). Prevalence of TB risk factors and comorbidities should also be monitored, as well as indicators of implementation of actions to address them.

**Objective 4: Strengthen human resource development for TB control in the context of overall health workforce development.** Expanding access to TB care relies heavily on the availability of well-trained health workers within the primary health care system. NTPs need to coordinate with the human resource (or equivalent) departments in ministries of health to promote the availability of sufficient levels of staffing, of both multipurpose health care workers and staff who work full-time (or for most of their time) on TB control. In most countries, diagnosis and treatment of TB is integrated into general health care services, with some full-time staff working in the NTP (these staff typically focus on activities such as policy guidance, supervision and monitoring and evaluation, rather than direct patient care).

**Objective 5: Scale-up measures to ensure appropriate infection control.** To prevent TB transmission in health care settings, countries should implement the recommended package of measures for infection control. These include use of protective masks by health care workers, administrative controls (for example, in waiting areas for people attending outpatient services) and environmental measures such as ventilation systems. Some of these measures are simple yet effective: for example, use of natural ventilation and separation of potentially infectious patients from other people in outpatient

<sup>13</sup> For more information, see [http://www.who.int/tb/health\\_systems/pal/](http://www.who.int/tb/health_systems/pal/).

<sup>14</sup> *International standards for tuberculosis care: diagnosis, treatment, public health*. The Hague, Tuberculosis Coalition for Technical Assistance, 2006.

<sup>15</sup> For further details, see the Task Force website at [http://www.who.int/tb/advisory\\_bodies/impact\\_measurement\\_taskforce/en/index.html](http://www.who.int/tb/advisory_bodies/impact_measurement_taskforce/en/index.html)

settings. The best indicator to assess the quality of infection control is the ratio of the notification rate of TB among health care workers to the notification rate among the general population. This ratio should be around one. Infection control is also of specific importance in settings where the prevalence of HIV is high and in settings where there is a risk of transmitting drug-resistant TB.

**Objective 6: Coordinate global-level efforts of the DOTS Expansion Working Group.** Major activities include maintaining the operations of the Working Group, advocacy, facilitating the provision of appropriate technical assistance (through **TBTEAM** and other mechanisms) and resource mobilization.

Further details are shown in the corresponding strategic framework (see pp32-33).

In addition, new diagnostic methods and shorter treatment regimens are now on the horizon (see the **New diagnostics** and **New drugs** components of this plan, in **Part II**). Rapid adoption and scale-up of their use will help to achieve earlier diagnosis and contribute to improved TB care and treatment outcomes.

## FUNDING REQUIREMENTS

The total cost of DOTS implementation according to the targets described above (and in the strategic framework) is estimated to be US\$ 22.6 billion for the five years 2011–2015. This amount is equivalent to almost two-thirds of the total funding required for the implementation of TB control (i.e. two-thirds of the total funding required for the DOTS, TB/HIV, Drug-resistant TB and Laboratory strengthening components of the Global Plan). The amount of funding required annually will increase from around US\$ 4 billion in 2011 to US\$ 5 billion in 2015 (**Figure 11**).

The total of US\$ 22.6 billion includes all resources needed for treatment of DOTS patients. The cost of diagnosis is accounted for in the section on laboratory strengthening; the amount specific to DOTS implementation is US\$ 1.7 billion. Together, the diagnosis and treatment costs take into account:

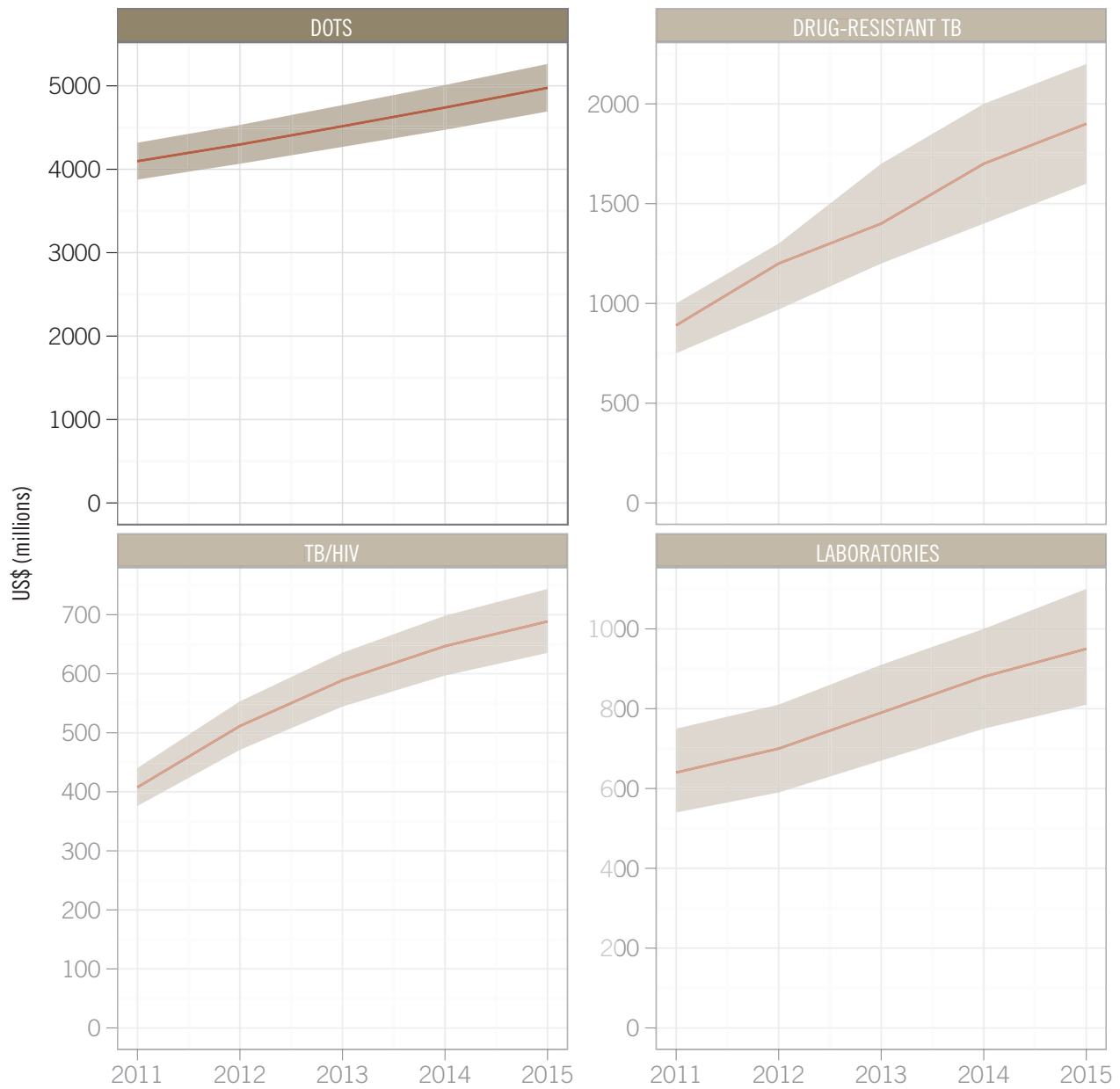
- inputs and activities managed directly by NTPs and that are often funded through NTP budgets in high-burden or high-incidence countries. These include first-line drugs, staff who work full-time on TB control at national and sub-national levels, programme management and supervision activities, laboratory supplies and equipment for smear microscopy and PPM;
- the costs of using resources that are part of the general health system – notably, multi-purpose staff in hospitals and outpatient clinics who spend time on TB diagnosis and patient management, and a share of the infrastructure and other overhead costs required for such care.

About 25% of the total for DOTS is for NTP staff, another 25% is associated with the cost of using general health system resources (multipurpose staff and infrastructure) during hospital admissions and outpatient visits.

The target is that at least 70% of the required funding should be mobilized from domestic sources – this was the global-level average of funding provided from domestic sources in the period 2006–2009.<sup>16</sup> Domestic funding can be mobilized from multiple sources including government budgets, loans and social insurance schemes.

<sup>16</sup> *Global tuberculosis control 2010*. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.7).

**FIGURE 11** FUNDING REQUIRED FOR DOTS IMPLEMENTATION, IN THE CONTEXT OF THE OTHER “IMPLEMENTATION” COMPONENTS OF THE PLAN <sup>a</sup>



<sup>a</sup> Shaded areas represent uncertainty bands.



## DOTS: STRATEGIC FRAMEWORK, 2011–2015

### VISION: UNIVERSAL ACCESS TO HIGH-QUALITY TB CARE AND PREVENTION, MAKING A MAJOR CONTRIBUTION TO TB ELIMINATION

GOAL AND OBJECTIVES	MAJOR ACTIVITIES	INDICATOR(S)	BASELINE (2009)	TARGET FOR 2015
<p><b>Goal:</b> To reduce the global burden of TB in line with the 2015 MDG and Stop TB Partnership targets through early TB diagnosis, high-quality treatment of all cases and prevention of TB transmission</p>	<p>Provision of diagnostic services (smear and/or culture and molecular tests plus chest X-rays, as appropriate) for all those with signs and symptoms suggestive of TB, with laboratory tests conducted in quality-assured laboratories; decentralization of these services to increase access; elimination of user fees that affect both access to care and the timing of access to care; promotion of the use of guidelines on the management of childhood TB; programme management and supervision; contact investigations; active case finding in selected high risk groups; engagement of all care providers through PPM and use of the international standards for TB care (ISTC); scale-up of PAL (including smoking cessation and prevention) and ACSM.</p>	<p>Percentage reduction in global TB mortality relative to 1990 baseline</p> <p>% total annual funding needs financed from domestic sources</p> <p>Global annual notifications of TB</p> <p>Number of HBCs (n=22) in which diagnosis of TB is provided free-of-charge or is fully reimbursable via health insurance</p> <p>Number of countries with <math>\geq 1</math> AFB microscopy laboratory per 100 000 population**</p> <p>Number of countries among the 22 HBCs and 27 high MDR-TB burden countries with <math>\geq 1</math> culture laboratory per 5 million population**</p> <p>Proportion of notified cases reported from non-NTP care providers, in selected countries</p> <p>Treatment success rate (global) among notified cases of smear-positive pulmonary TB</p>	<p>35%*</p> <p>70%</p> <p>5.8 million</p> <p>4</p> <p><math>\geq 75</math></p> <p>18–21</p> <p>n/a***</p> <p>86%</p>	<p>50%</p> <p><math>\geq 70\%</math></p> <p>6.9 million</p> <p>22</p> <p>149</p> <p>36</p> <p>15–20%</p> <p>90%</p>
<p><b>Objective 1:</b> Ensure early diagnosis of all TB cases (pulmonary, both smear-positive and -negative; extrapulmonary; adults and children)</p>	<p>Provision of diagnostic services (smear and/or culture and molecular tests plus chest X-rays, as appropriate) for all those with signs and symptoms suggestive of TB, with laboratory tests conducted in quality-assured laboratories; decentralization of these services to increase access; elimination of user fees that affect both access to care and the timing of access to care; promotion of the use of guidelines on the management of childhood TB; programme management and supervision; contact investigations; active case finding in selected high risk groups; engagement of all care providers through PPM and use of the international standards for TB care (ISTC); scale-up of PAL (including smoking cessation and prevention) and ACSM.</p>	<p>Percentage reduction in global TB mortality relative to 1990 baseline</p> <p>% total annual funding needs financed from domestic sources</p> <p>Global annual notifications of TB</p> <p>Number of HBCs (n=22) in which diagnosis of TB is provided free-of-charge or is fully reimbursable via health insurance</p> <p>Number of countries with <math>\geq 1</math> AFB microscopy laboratory per 100 000 population**</p> <p>Number of countries among the 22 HBCs and 27 high MDR-TB burden countries with <math>\geq 1</math> culture laboratory per 5 million population**</p> <p>Proportion of notified cases reported from non-NTP care providers, in selected countries</p> <p>Treatment success rate (global) among notified cases of smear-positive pulmonary TB</p>	<p>35%*</p> <p>70%</p> <p>5.8 million</p> <p>4</p> <p><math>\geq 75</math></p> <p>18–21</p> <p>n/a***</p> <p>86%</p>	<p>50%</p> <p><math>\geq 70\%</math></p> <p>6.9 million</p> <p>22</p> <p>149</p> <p>36</p> <p>15–20%</p> <p>90%</p>
<p><b>Objective 2:</b> Ensure high-quality treatment of all diagnosed cases of TB (pulmonary, both smear-positive and -negative; extrapulmonary; adults and children)</p>	<p>Drug management and rational use of anti-TB drugs according to international guidelines for all patients (including paediatric formulations); treatment in health care facilities and the community, including provision of enablers and incentives, and management of co-morbidities and risk factors where appropriate; programme management and supervision; engagement of all care providers through PPM and the ISTC; ACSM.</p>	<p>Percentage reduction in global TB mortality relative to 1990 baseline</p> <p>% total annual funding needs financed from domestic sources</p> <p>Global annual notifications of TB</p> <p>Number of HBCs (n=22) in which diagnosis of TB is provided free-of-charge or is fully reimbursable via health insurance</p> <p>Number of countries with <math>\geq 1</math> AFB microscopy laboratory per 100 000 population**</p> <p>Number of countries among the 22 HBCs and 27 high MDR-TB burden countries with <math>\geq 1</math> culture laboratory per 5 million population**</p> <p>Proportion of notified cases reported from non-NTP care providers, in selected countries</p> <p>Treatment success rate (global) among notified cases of smear-positive pulmonary TB</p>	<p>35%*</p> <p>70%</p> <p>5.8 million</p> <p>4</p> <p><math>\geq 75</math></p> <p>18–21</p> <p>n/a***</p> <p>86%</p>	<p>50%</p> <p><math>\geq 70\%</math></p> <p>6.9 million</p> <p>22</p> <p>149</p> <p>36</p> <p>15–20%</p> <p>90%</p>

\* The baseline shown here is based on the latest time-series of estimates published by WHO. Time-series from 1990 onwards are updated each year and thus the baseline figure shown here may be updated in future years.  
 \*\* This indicator is also included in the strategic framework for **Laboratory strengthening**. Among the 149 countries (all countries except high-income countries) included in the Global Plan that reported data to WHO in 2009, 75 had at least 1 AFB laboratory per 100 000 population while 26 did not report data, and 48 had less than 1 AFB laboratory per 100 000 population. Among the 27 high MDR-TB burden countries, 18 countries had at least 1 culture laboratory per 5 million population and 3 did not report data.  
 \*\*\* Abbreviations and notes: ACSM - Advocacy, communication and social mobilization; AFB - acid-fast bacilli; HBC - high burden country; ISTC - International Standards for TB Care; PAL - Practical Approach to Lung Health; PPM - public-private mix; n/a - not available. A baseline for PPM is not available because too few countries have reported data.

OBJECTIVES (CONTINUED)	MAJOR ACTIVITIES	INDICATOR(S)	BASELINE (2009)	TARGET FOR 2015
<b>Objective 3:</b> Strengthen monitoring and evaluation including impact measurement	Assessments of the quality and coverage of notification and vital registration data according to the framework developed by the WHO Global Task Force on TB Impact Measurement and associated tools; development and strengthening of vital registration (VR)* systems; prevalence surveys in selected countries; monitoring of risk factors and co-morbidities and interventions to address them.	<p>Number of countries that have conducted a recent assessment of the quality and coverage of notification and VR data</p> <p>Number of countries that meet VR quality and coverage criteria</p> <p>Number of countries that have successfully completed a national survey of the prevalence of TB disease between 2008 and 2015, among the 21 countries where such a survey is strongly recommended</p> <p>Number of countries reporting treatment outcomes for all cases (not just smear-positive cases)</p> <p>Number of countries with electronic and case-based recording and reporting systems</p>	63  46  1	119  60  21
<b>Objective 4:</b> Strengthen human resource development for TB control in the context of overall health workforce development	Training and continued education of all health care workers (including community health workers)** involved in TB control; coordination between the NTP and Human Resources for Health (or equivalent) departments regarding staffing, filling of vacancies, and retention packages; supportive supervision; TB screening among health care workers (including community health workers).	<p>Number of HBCs (n=22) with &lt;15% vacancy rates** at peripheral-level health care facilities</p> <p>Number of countries in which 100% of health care workers with job descriptions that include tasks related to TB control in peripheral-level health care facilities have been trained by the NTP in the past five years</p>	5  ≥10**	22  149
<b>Objective 5:</b> Scale-up measures to ensure appropriate infection control	Implementation of infection control (IC), including administrative, personal protection and environmental measures, in TB hospital wards, outpatient settings where TB is diagnosed and treated, and congregate settings, according to international and national guidelines; monitoring.	Ratio of TB notification rate among health care workers to notification rate among general population	n/a	~1
<b>Objective 6:</b> Coordinate global-level efforts of the DOTS Expansion Working Group	Development and monitoring of DOTS Expansion Working Group (DEWG) plan; meetings; conference calls; advocacy efforts.	Number of countries participating in DEWG	22	30

\* Abbreviations: IC - infection control; VR - vital registration; n/a - not available.

\*\* The World Health Report 2006 defined health workers as: a) those who are directly involved in delivering health care services (e.g. physicians and nurses) and b) those who are indirectly involved in providing these services (e.g. health management and support workers such as accountants and administrative officers). Vacancy rates and the status of training will be monitored for four groups of staff: 1) medical officers; 2) nurses (including registered nurses, enrolled midwives, enrolled nurses and enrolled midwives); 3) health assistants/medical assistants/clinical officers; 4) laboratory technicians/microscopists. The baseline number is an underestimate, due to lack of reporting of data by 99 countries.

## 2. DRUG-RESISTANT TB

### INTRODUCTION: DEFINITIONS, TARGETS AND PROGRESS TO DATE

Multidrug-resistant TB and extensively drug-resistant TB (MDR-TB and XDR-TB) are major threats to TB control, with all countries at risk. MDR-TB is defined as resistance to isoniazid and rifampicin, the two most important first-line drugs that are used in the treatment of TB. XDR-TB is defined as MDR-TB plus resistance to additional drugs - a fluoroquinolone and, at least, one second-line injectable drug.<sup>17</sup> The standard six-month treatment with first-line anti-TB drugs is not effective for people with MDR-TB and XDR-TB. Instead, they must be treated with drugs that are less efficacious, more toxic and much more costly (typically, US\$ 2000–5000 per patient). The treatment time is up to two years.

WHO estimates that in 2008, 440 000 MDR-TB cases emerged and 150 000 deaths were caused by MDR-TB.<sup>18</sup> The proportion of TB cases that have MDR-TB is highest in eastern Europe and central Asia (Figure 12), while around half of the world's cases of MDR-TB occur in China and India. As of August 2010, 59 countries had reported at least one case of XDR-TB. In some settings, over a quarter of

all new TB patients are now being diagnosed with MDR-TB.

One of the most important constraints to rapid expansion of diagnosis and treatment for MDR-TB is laboratory capacity. In 2009, diagnostic testing for drug susceptibility (DST) among new cases of TB was almost entirely confined to the European Region and the Region of the Americas. Among previously treated cases, DST was done for 36% of cases in the Region of the Americas and for 16% in the European Region, with figures of less than 10% in all other regions.

The need to scale-up the diagnosis and effective treatment of MDR-TB was clearly recognized in the *Global Plan to Stop TB 2006–2015*. At the time the plan was launched, only a few thousand people were being diagnosed with and treated for MDR-TB in programmes or projects following international guidelines each year. The plan set a target to increase this number to around 100 000 per year by 2015, with all diagnosed patients to be enrolled in programmes following international guidelines. A more ambitious target was established in the 2007 Global MDR/XDR Response Plan<sup>19</sup>: to reach 85% of MDR-TB cases with accurate diagnosis and effective treatment in 2015.

FIGURE 12 ESTIMATED PERCENTAGE OF MDR-TB AMONG NEW TB CASES, 2008<sup>a</sup>



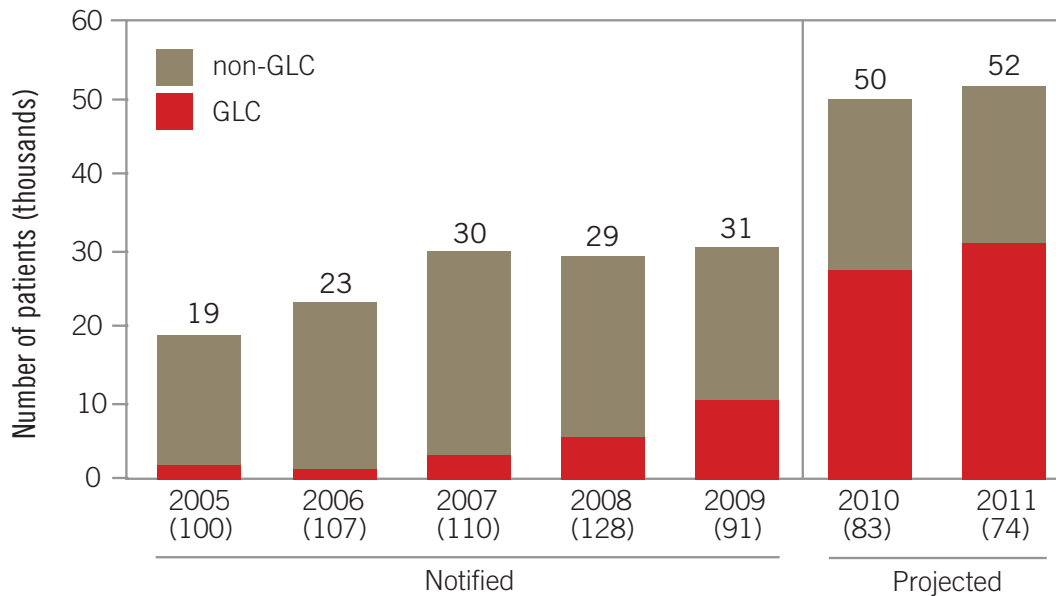
<sup>a</sup> Values derived from surveillance data from 1995–2008 and modelled estimates where data were missing.

<sup>17</sup> Amikacin, kanamycin and/or capreomycin.

<sup>18</sup> *Multidrug and extensively drug-resistant TB (M/XDR-TB). 2010 global report on surveillance and response*. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.3).

<sup>19</sup> *The Global MDR-TB and XDR-TB response plan, 2007–2008*. Geneva, World Health Organization, 2007 (WHO/HTM/TB/2007.387).

**FIGURE 13** REPORTED MDR-TB CASES, 2005-2009 AND PROJECTED NUMBER OF PATIENTS TO BE ENROLLED ON TREATMENT, 2010-2011 <sup>a</sup>



<sup>a</sup> The numbers in parentheses under each bar show the number of countries reporting data

Further momentum and commitment to address the problems of MDR and XDR-TB were generated in 2009. A ministerial conference held in Beijing, China in April 2009 brought together high-level representatives from the 27 high MDR-TB burden countries<sup>20</sup> that collectively account for around 85% of the world's cases of MDR-TB, and led to a Call to Action on the part of governments and international agencies. Less than two months after the Beijing meeting, a resolution on MDR-TB was passed at the 62nd World Health Assembly in May 2009. This called on all countries to implement the measures needed to achieve universal access to diagnosis and treatment of MDR-TB by 2015, including strengthening of basic TB control, development of laboratory capacity for diagnosis, establishment of comprehensive patient management and care programmes, effective collaboration with HIV programmes, strengthening of health information and surveillance systems and acceleration of research and development related to new tools for prevention, diagnosis and treatment.

Globally, progress in diagnosing MDR and XDR-TB is being made. The latest data available in mid-2010<sup>21</sup> showed that around 30 000 cases of MDR-TB were diagnosed and notified in 2009 (Figure 13), mostly by European countries and South Africa. The number of notified cases enrolled on treatment in projects or programmes that meet international standards is also increasing, and reached 5000 in 2008. Country plans suggested that this would rise to around 30 000 in 2010. There are also several models that show how MDR-TB can be successfully managed, even in settings where rates are high. These include Estonia, Latvia and the Russian oblasts of Orel and Tomsk, where levels of MDR-TB were rising for several years but where the numbers of cases are now falling.

Building on the momentum and commitments of 2009, a substantial and rapid expansion of diagnosis and treatment for MDR-TB is required in the next five years.

<sup>20</sup> The 27 high MDR-TB burden countries are, in alphabetical order: Armenia, Azerbaijan, Bangladesh, Belarus, Bulgaria, China, the Democratic Republic of the Congo, Estonia, Ethiopia, Georgia, India, Indonesia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Myanmar, Nigeria, Pakistan, the Philippines, the Republic of Moldova, the Russian Federation, South Africa, Tajikistan, Ukraine, Uzbekistan and Viet Nam.

<sup>21</sup> *Global tuberculosis control 2010*. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.7).

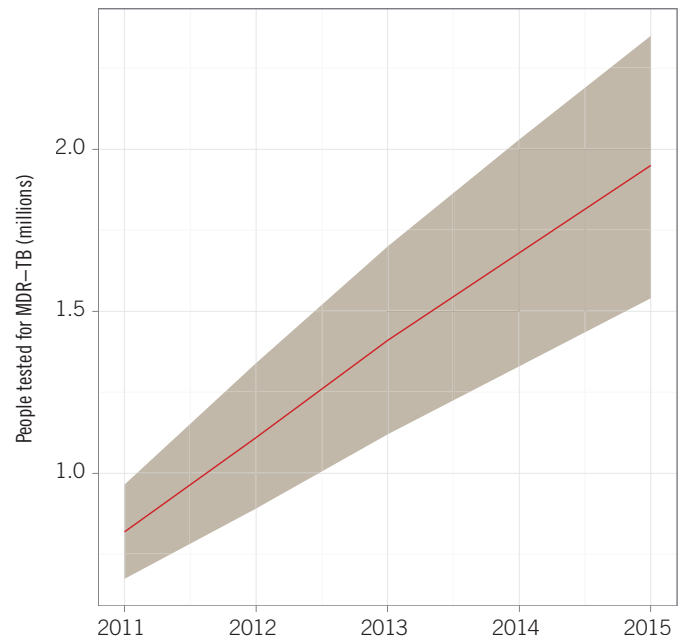
## OVERVIEW OF PLAN GOALS, OBJECTIVES, TARGETS AND ACTIVITIES, 2011–2015

The goal of the plan is to reduce the global burden of drug-resistant TB. The target is that the incidence of MDR-TB should be declining by 2015.<sup>22</sup>

To achieve this goal, there are six major objectives. These objectives, and associated targets and activities, are explained below.

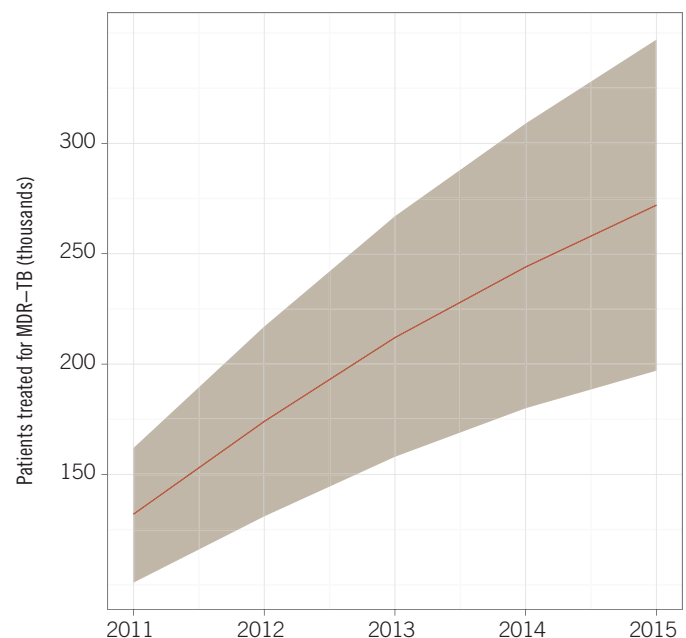
**Objective 1: Scale up access to testing for resistance to first-line anti-TB drugs among TB patients.** Scaling up testing for susceptibility to first- and second-line drugs is a fundamental first step in most countries. Limited laboratory capacity is the main reason why only 5% of the estimated 440 000 people who became ill with MDR-TB in 2008 were diagnosed. By 2015, 100% of people who have been previously treated for TB (and are thus considered at higher risk of having MDR-TB) should be tested for MDR-TB, using either conventional or new molecular-based diagnostics. People who have developed TB for the first time should also be tested for MDR-TB if they have a specific risk, such as contact with a person with confirmed MDR-TB. In total, the number of people tested for MDR-TB should increase from around 0.8 million in 2011 to 1.9 million in 2015 (Figure 14). This will require a substantial strengthening of laboratory capacity, including use of newer, molecular technologies for the detection of drug resistance (see also the **Laboratory strengthening** component of this plan).

**FIGURE 14** DRUG SUSCEPTIBILITY TESTING AMONG TB PATIENTS, 2011–2015<sup>a</sup>



<sup>a</sup> Shaded area represents uncertainty band.

**FIGURE 15** PATIENTS TREATED FOR MDR-TB, 2011–2015<sup>a</sup>



<sup>a</sup> Shaded area represents uncertainty band.

<sup>22</sup> When launched in January 2006, the Global Plan did not include a target for reducing the level of MDR-TB among TB cases. Targets were limited to the number of cases of MDR-TB to be diagnosed and treated.

**Objective 2: Scale up access to testing of susceptibility to second-line anti-TB drugs, as well as HIV testing among confirmed cases of MDR-TB.** All people who are found to have MDR-TB should receive testing for susceptibility to second-line drugs, so as to diagnose or rule out XDR-TB. They should also be offered HIV testing.

**Objective 3: Scale up access to effective treatment for drug-resistant TB.** All patients with confirmed MDR-TB should be treated according to international standards.<sup>23</sup> The number of patients to be treated for MDR-TB should reach around 270 000 in 2015.<sup>24</sup> The total number of people to be treated in the five years 2011–2015 is approximately 1 million (Figure 15). The treatment success rate among patients with confirmed MDR-TB should increase from the 2009 baseline of 60% to  $\geq 75\%$  by 2015. The key activities required to scale-up treatment are: procurement and supply of second-line drugs, provision of treatment in hospitals, outpatient clinics and community-based programmes, management of adverse events, human resource development including training, programme management and supervision, data management and technical assistance (harmonized wherever possible through TBTEAM).<sup>25</sup>

**Objective 4: Scale up TB infection control in MDR-TB hospital wards and outpatient clinics.** Infection control is crucial to prevent the spread of MDR-TB from person to person. Countries with a high burden of MDR-TB should have instituted a recommended package of infection control measures in hospital wards and outpatient clinics where patients with MDR-TB are treated.<sup>26</sup>

<sup>23</sup> *Guidelines for the programmatic management of drug-resistant tuberculosis*. Emergency update. Geneva, World Health Organization, 2008 (WHO/HTM/TB/2008.402).

<sup>24</sup> The total of 270 000 is less than the estimated total number of cases of MDR-TB (for which the best estimate was 440 000 in 2008). This is because the plan recognizes that not all cases of MDR-TB will be reached by TB programmes (total notifications are projected to reach around 7 million, which is less than the estimated 9 million or so cases that occur each year), and because the plan recognizes that not all cases of MDR-TB can be detected with current technologies.

<sup>25</sup> For more information about TBTEAM, see the section of this plan that explains the mechanisms of the Stop TB Partnership.

<sup>26</sup> It should be noted that since infection control is a cross-cutting issue, it is also included in the DOTS, TB/HIV and Laboratory strengthening components of this plan.

**Objective 5: Strengthen surveillance, including recording and reporting, of drug-resistant TB.**

The quality and geographical coverage of drug-resistance surveillance (DRS) data must be increased by 2015, such that high-quality data are available for 110 non-high-income countries instead of the 78 for which data were available in 2009. This will require more surveillance of drug resistance through routine testing of TB patients as well as surveys, the development and implementation of electronic recording and reporting systems, advocacy at country level and among international technical and financial partners, training workshops, and periodic updating and implementation of guidelines and standard operating procedures. Many countries are likely to require technical assistance as they establish surveillance of drug resistance among TB cases through routine testing of patients and/or surveys.

**Objective 6: Expand country capacity to scale up the management of drug-resistant TB through global advocacy and policy guidance.**

Major activities include maintaining the operations of the Working Group on MDR-TB, advocacy for access to and effective treatment of drug-resistant TB, facilitating the provision of appropriate technical assistance, and resource mobilization.

Further details are shown in the corresponding strategic framework (see pp40-41).

**FUNDING REQUIREMENTS**

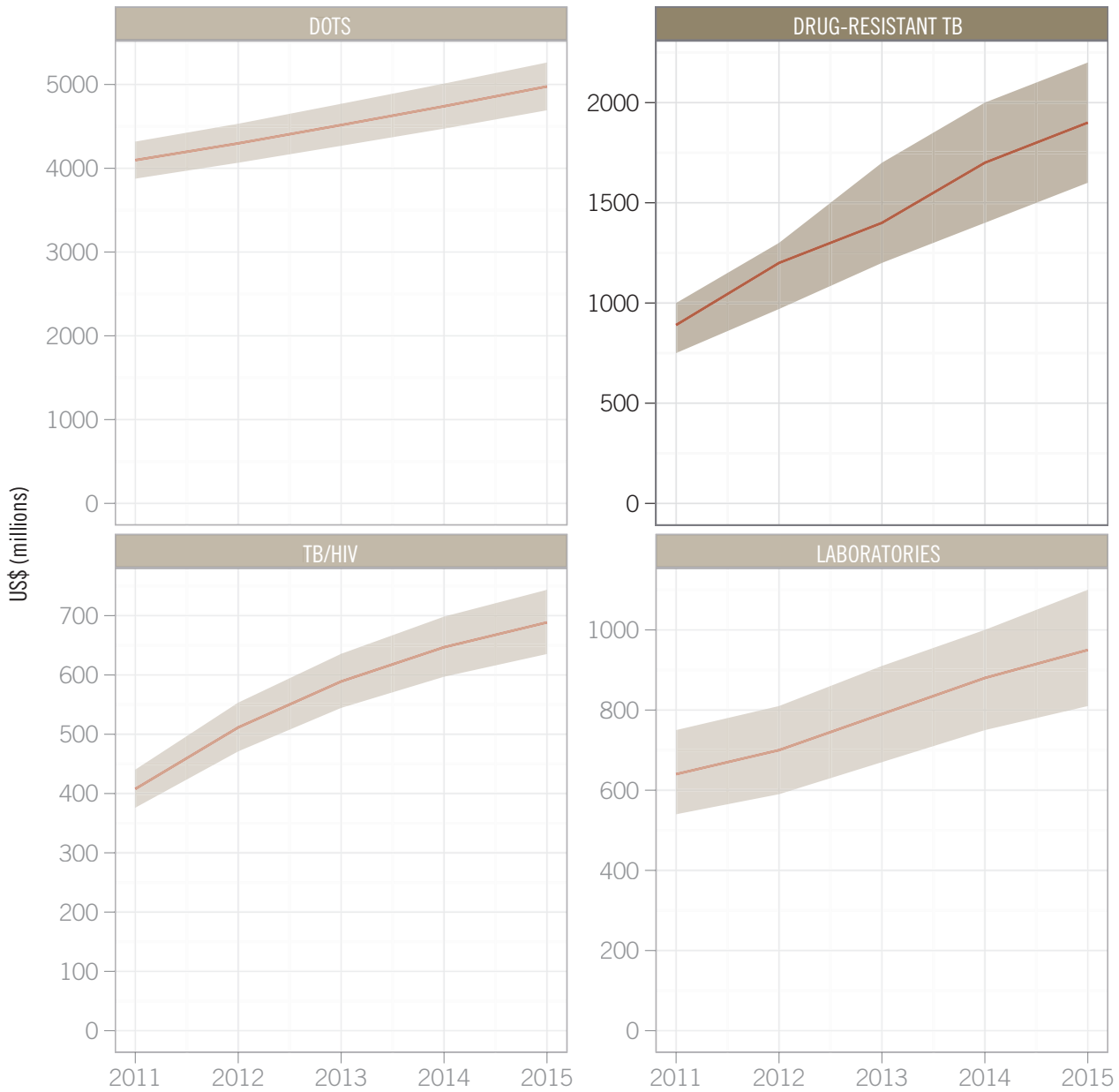
The total cost of implementing the plan for MDR and XDR-TB is US\$ 7.1 billion for the five years 2011–2015. The annual funding required increases from US\$ 0.9 billion in 2011 to US\$ 1.9 billion in 2015 (Figure 16).

These estimates of required funding include all resources needed for treatment. An additional US\$ 0.3 billion required for diagnostic tests is included in the **Laboratory strengthening** component of the plan.

Together, the costs of diagnosis and treatment cover inputs and activities managed directly by NTPs and that are typically funded through NTP budgets (for example, in high MDR-TB burden countries these could include second-line drugs, programme management and supervision activities, laboratory supplies and equipment for culture and DST, or equivalent molecular tests). They also include the costs of using resources that are part of the general health system (for example, staff who work in hospital wards in which patients with MDR-TB are treated, multipurpose staff who work in outpatient clinics and spend part of their time on TB diagnosis and patient management, and a share of the infrastructure and other overhead costs required for hospital and outpatient care).

The cost of second-line drugs represents around 50–60% of the total funding required. These costs could be reduced as the scale of production increases, and if the costs of particular drugs that have a major influence on the cost of recommended regimens can be lowered (notably, para-aminosalicylic acid [PAS]).

**FIGURE 16** FUNDING REQUIRED FOR MDR-TB, IN THE CONTEXT OF THE OTHER “IMPLEMENTATION” COMPONENTS OF THE PLAN <sup>a</sup>



<sup>a</sup> Shaded areas represent uncertainty bands.



## DRUG-RESISTANT TB: STRATEGIC FRAMEWORK, 2011–2015

### VISION: DRUG-RESISTANT TB ELIMINATED AS A THREAT AT GLOBAL, REGIONAL AND COUNTRY LEVELS

GOAL AND OBJECTIVES	MAJOR ACTIVITIES	INDICATOR(S)	BASELINE (2009)	TARGET FOR 2015
<p><b>Goal:</b> To reduce the global burden of drug-resistant TB</p> <p><b>Objective 1:</b> Scale up access to testing for resistance to first-line anti-TB drugs among TB patients</p>	<p>Testing for MDR-TB using culture and DST* and molecular technologies (e.g. LPAs).</p>	<p>Trend in the incidence of MDR-TB</p> <p>Percentage of new bacteriologically-positive TB patients tested for resistance to first-line drugs</p> <p>Percentage of previously treated TB patients tested for resistance to first-line drugs</p> <p>Number of countries among the 22 HBCs and 27 high MDR-TB burden countries with <math>\geq 1</math> culture laboratory per 5 million population</p>	<p>n/a</p> <p>7%</p> <p>7%</p> <p>18–21**</p>	<p>Declining</p> <p>20%**</p> <p>100%</p> <p>36</p>
<p><b>Objective 2:</b> Scale up access to testing of susceptibility to second-line anti-TB drugs, as well as HIV testing among confirmed cases of MDR-TB</p>	<p>Testing for susceptibility to second-line drugs using culture and DST; testing for HIV.</p>	<p>Percentage of confirmed MDR-TB patients who had a second-line DST result</p>	<p>15%</p>	<p>100%</p>
<p><b>Objective 3:</b> Scale up access to effective treatment for drug-resistant TB</p>	<p>Procurement and supply of second-line TB drugs; provision of treatment in hospitals and outpatient clinics, including use of incentives and enablers where appropriate; management of adverse events; training; programme management and supervision; data management; technical assistance.</p>	<p>Percentage of cases with confirmed MDR-TB started on treatment in programmes that follow international guidelines</p> <p>Treatment success rate among patients with confirmed MDR-TB</p>	<p>36%</p> <p>60%</p>	<p>100%</p> <p><math>\geq 75\%</math></p>
<p><b>Objective 4:</b> Scale up TB infection control in MDR-TB hospital wards and outpatient clinics</p>	<p>Development of national plan on infection control as part of a national plan for MDR-TB; assessments of the current status of infection control; training; implementation of administrative, personal protection and environmental measures, based on results of assessments.</p>	<p>Ratio of TB notification rate among health care workers to notification rate among general population</p>	<p>n/a</p>	<p><math>\sim 1</math></p>

\* Abbreviations: DST - drug susceptibility testing; LPA - line probe assay; n/a - not available.

\*\* 20% is the estimated proportion of new cases that would meet criteria for being considered at high-risk of having MDR-TB and who should be tested. Among the 36 that are in the list of 22 HBCs and/or the 27 high MDR-TB burden countries, 18 countries had at least 1 culture laboratory per 5 million population and 3 did not report data.

OBJECTIVES (CONTINUED)	MAJOR ACTIVITIES	INDICATOR(S)	BASELINE (2009)	TARGET FOR 2015
<p><b>Objective 5:</b> Strengthen surveillance, including recording and reporting, of drug-resistant TB</p>	<p>Surveillance of drug resistance (DRS) among TB cases through routine testing of patients and/or surveys; provision of international technical assistance for DRS and the development and implementation of recording and reporting systems; advocacy at country level and among international technical and financial partners; training workshops; development and implementation of electronic tools, and associated guidelines and standard operating procedures.</p>	<p>Number of countries reporting results from drug resistance surveys and/or Class A* continuous surveillance</p> <p>Number of high MDR-TB burden countries with an electronic case-based database for MDR-TB patients on treatment at national level</p> <p>Percentage of countries reporting <math>\geq 50\%</math> of the MDR-TB cases that are expected to exist among notified TB cases</p> <p>Percentage of countries reporting treatment outcomes for all confirmed cases of MDR-TB</p> <p>Number of high MDR-TB burden countries reporting treatment outcomes for all confirmed cases of MDR-TB</p>	<p>78</p> <p>10</p> <p>23%</p> <p>21%</p> <p>2</p>	<p>110, including the 36 countries that are among the 22 HBCs and/or 27 high MDR-TB burden countries</p> <p>27</p> <p>100%</p> <p>100%</p> <p>27</p>
<p><b>Objective 6:</b> Expand country capacity to scale up the management of drug-resistant TB through global advocacy and policy guidance</p>	<p>Operations of the Working Group on MDR-TB, including meetings, advocacy for access to and effective treatment of drug-resistant TB; resource mobilization.</p>	<p>Number of partners attending meetings of the Working Group</p> <p>Number of high burden of MDR-TB</p>	<p>15</p> <p>1</p>	<p>30</p> <p>10</p>

\*Abbreviations and notes: DRS - drug-resistance surveillance. Class A continuous surveillance: data from ongoing surveillance of drug resistance are representative of the patient caseload (criteria to be met are defined in the following publication: WHO/HTM/TB/2010.3, see page 36).

### 3. TB-HIV

#### INTRODUCTION: DEFINITIONS, TARGETS AND PROGRESS TO DATE

People living with HIV are 20 to 37 times more likely to develop TB disease during their lifetimes than people who are HIV-negative.<sup>27</sup> HIV and TB are so closely connected that the term ‘co-epidemic’ or ‘dual epidemic’ is often used to describe their relationship, which is also referred to as TB/HIV (or HIV/TB).

Of the 9.4 million people who became ill with TB in 2009, an estimated 1.0–1.2 million (11–13%) were HIV-positive, with a best estimate of 1.1 million (12%).<sup>28</sup> Of these HIV-positive TB cases, approximately 80% were in the African Region. Throughout the 1990s and up to 2004, the HIV epidemic led to a dramatic increase in the number of TB cases in the African Region, from less than 200 to more than 350 cases per 100 000 population. The African Region is thus the part of the world in which interventions to prevent TB in HIV-positive people, and to reduce the illness and mortality associated with HIV infection in HIV-positive TB patients, are most needed. Within the African Region, the highest rates of HIV infection

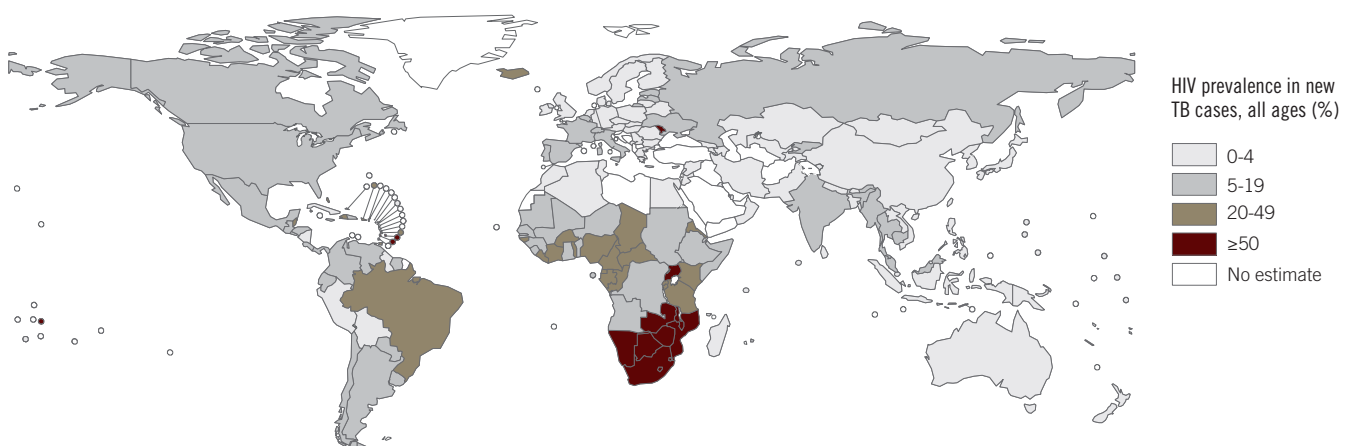
among TB patients are in countries in southern and eastern Africa, where more than 50% of TB patients are estimated to be infected with HIV (Figure 17).

An estimated 0.4 million HIV-positive people died of TB in 2009, equivalent to about one in four of the deaths that occur among HIV-positive people each year.

In 2004, WHO defined a set of collaborative TB/HIV activities that are essential to ensure that HIV-positive TB patients are identified and treated appropriately, and to prevent TB in HIV-positive people.<sup>29</sup> These activities include establishing mechanisms for collaboration between TB and HIV programmes; infection control in health care and congregate settings; HIV testing of TB patients; CPT and ART for those TB patients infected with HIV, to reduce illness and mortality; and intensified TB case-finding among people living with HIV followed by isoniazid preventive therapy (IPT) for those without active TB. All HIV-positive TB patients are considered eligible for ART according to the latest WHO guidelines on provision of ART.

Currently, testing TB patients for HIV and providing CPT for HIV-positive TB patients are typically the responsibility of NTPs. National HIV programmes

FIGURE 17 ESTIMATED HIV PREVALENCE IN NEW TB CASES, 2009



<sup>27</sup> *Global tuberculosis control 2010*. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.7).

<sup>28</sup> *Ibid.*

<sup>29</sup> *Interim policy on collaborative TB/HIV activities*. Geneva, World Health Organization, 2004 (WHO/HTM/TB/2004.330; WHO/HTM/HIV/2004.1).

are usually responsible for initiating intensified case-finding among HIV-positive people and provision of IPT to those without active TB. Provision of ART to HIV-positive TB patients is often the responsibility of national HIV programmes. In future, all these services should be provided as part of an integrated package of care, and at the same time and place wherever possible.

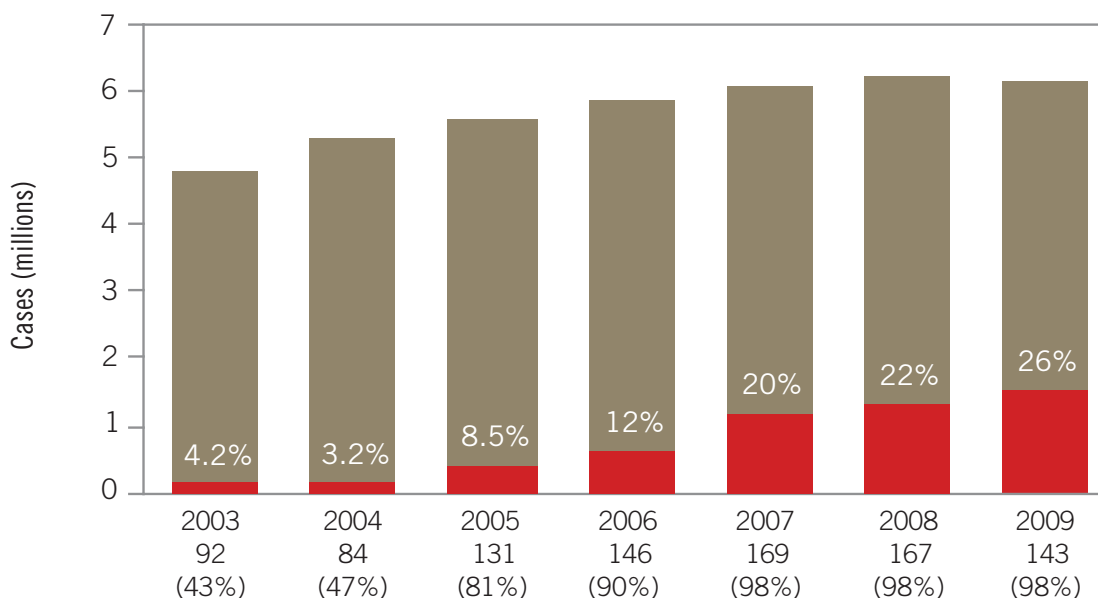
The *Global Plan to Stop TB 2006–2015* set out the scale at which TB/HIV interventions should be implemented, in the context of the goal of universal access to treatment by 2010. The major targets were to test 85% of TB patients for HIV by 2010, and to sustain this level of testing up to 2015; to provide 95% of HIV-positive TB patients with CPT by 2010; and to enrol around 300 000 HIV-positive TB patients on ART by 2010. Ambitious targets for TB screening among people living with HIV and provision of IPT to HIV-positive people without active TB disease were also set. These were to screen close to 100% of people in HIV care services for TB on a routine basis, and to enrol approximately 10% of the global total of people living with HIV on IPT by 2010.

Since monitoring of progress in the scale-up of collaborative TB/HIV activities began in 2003, considerable progress has been made.<sup>30</sup> By 2009, 1.6 million TB patients knew their HIV status, equivalent to 26% of notified cases, up from 4% in 2003 (Figure 18). In the African Region, 53% of TB patients knew their HIV status in 2009. In the same year, there were 55 countries in which  $\geq 75\%$  of TB patients knew their HIV status, including 16 African countries, showing that the targets in the Global Plan can be achieved. Of the TB patients who were known to be HIV-positive, 75%, or just over 250 000, were enrolled on CPT, and 37% or almost 140 000 were enrolled on ART (see Figure 19, Figure 20, Figure 21).

Screening for TB among HIV-positive people and provision of IPT to those without active TB more than doubled between 2007 and 2009. The number of HIV-positive people screened for TB increased from 0.6 million to 1.7 million, and the number of people who were provided with IPT grew from under 30 000 in 2007 to around 80 000 in 2009. Despite these improvements, progress falls short of what is

**FIGURE 18** HIV TESTING FOR TB PATIENTS, ALL COUNTRIES, 2003–2009

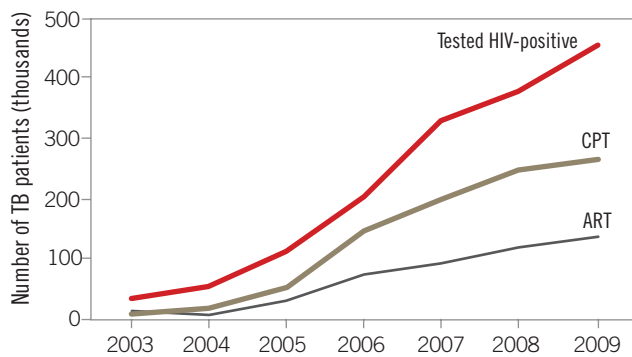
The number of notified new and retreatment cases is shown in brown and the number of cases for which the HIV status was recorded in the TB register is shown in red. The percentage of notified TB cases with known HIV status is indicated above the red bars.<sup>a</sup>



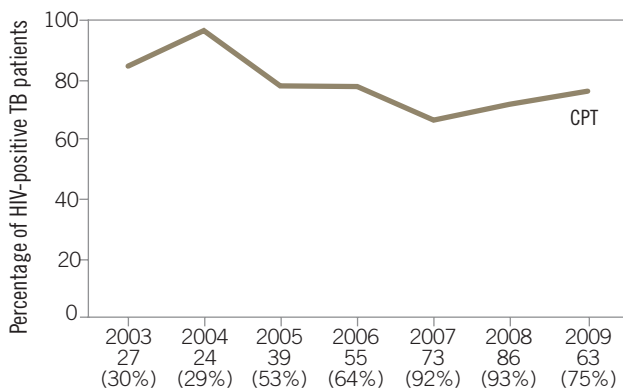
<sup>a</sup> The numbers under each year show the number of countries reporting data on HIV testing followed by the percentage of total estimated HIV-positive TB cases accounted for by reporting countries.

<sup>30</sup> *Global tuberculosis control 2010*. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.7).

**FIGURE 19** CPT AND ART FOR HIV-POSITIVE TB PATIENTS, 2003–2009

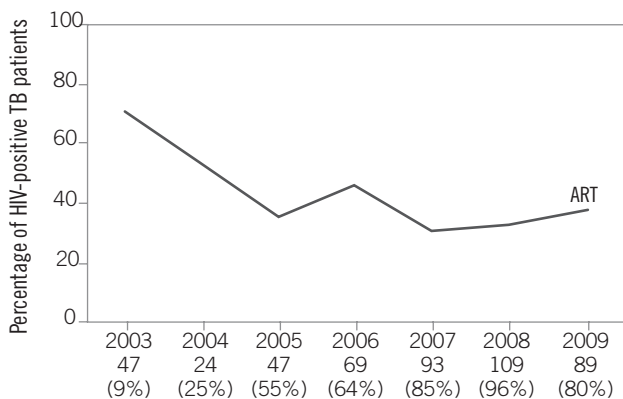


**FIGURE 20** CPT FOR HIV-POSITIVE TB PATIENTS, 2003–2009<sup>a</sup>



<sup>a</sup> Numbers under years show the number of countries reporting data followed by the percentage of total estimated HIV-positive TB cases accounted for by reporting countries.

**FIGURE 21** ART FOR HIV-POSITIVE TB PATIENTS, 2003–2009<sup>a</sup>



<sup>a</sup> Numbers under years show the number of countries reporting data followed by the percentage of total estimated HIV-positive TB cases accounted for by reporting countries.

needed. The numbers screened were equivalent to about one-third of those on ART and around 10% of the numbers estimated to be in need of ART. The number of people living with HIV who have been started on IPT is less than 1% of the people living with HIV worldwide.

Building on the achievements of the last few years, the TB/HIV component of the Global Plan to Stop TB 2011–2015 sets out how interventions need to be further expanded and improved, reaching more HIV-positive TB patients and more people living with HIV in whom TB can either be diagnosed earlier or prevented altogether.

### OVERVIEW OF PLAN GOALS, OBJECTIVES, TARGETS AND ACTIVITIES, 2011–2015

The goal for 2015 is to reduce deaths from TB among HIV-positive people by 50% compared to 2004 levels. In turn, this will help to achieve the Stop TB Partnership target of halving TB mortality by 2015, compared with a baseline of 1990. The target for reduction of TB deaths among HIV-positive people is set with respect to 2004 because this is the year in which HIV-associated rates of TB incidence and mortality peaked.

To achieve this goal, the TB/HIV plan includes eight major objectives, and associated targets and activities, which are explained below.

**Objective 1: Scale up access to HIV testing among TB patients.** By 2015, the target is that 100% of TB patients should be tested for HIV. It is estimated that about 30 million TB patients will need to be tested between 2011 and 2015. Countries need to institute national policies for HIV testing in people with active TB or those suspected of having TB (if these do not yet exist), and ensure that training on HIV testing and counselling is provided.

**Objective 2: Scale up access to CPT for HIV-positive TB patients according to international guidelines.** By 2015, all HIV-positive TB patients should be treated with CPT, equivalent to about 0.9 million people in that year.

**Objective 3: Scale up access to ART for HIV-positive TB patients according to international guidelines.** Provision of ART needs to be expanded, such that by 2015 all HIV-positive TB patients – estimated at almost 1 million people in 2009 – are enrolled on ART. ART can reduce the incidence of TB among people living with HIV by up to 90% at the individual level, and by 60% at the population level. National policies need to be updated so that all HIV-positive TB patients are eligible for ART and to ensure that access to TB and HIV services is promoted among the populations that are most at-risk.

**Objective 4: Scale up TB screening among people living with HIV, according to international guidelines.** By 2015, 100% of people receiving HIV care should be screened for TB using a symptom-based clinical algorithm.

**Objective 5: Scale up access to IPT among people living with HIV and who do not have active TB according to international guidelines.** All those who are screened for TB and do not have active TB are eligible for IPT. By 2015, all those who are in HIV care and without active TB should be offered IPT.

**Objective 6: Scale up the implementation of measures for TB infection control in health care facilities providing services to people living with HIV.** People living with HIV are at higher risk of developing TB. In health care facilities where people living with HIV are receiving care, a high priority is to prevent the transmission of TB. The scale and efficacy of TB infection control measures in health care facilities providing services to people living with HIV can be assessed according to the ratio of new TB cases per 100 000 health care workers to the notification rate of TB in the general population: the

ratio should be around one. Measures to reduce the spread of TB in health care settings should include annual surveillance for TB disease among health care workers, and implementation of an infection control plan.

**Objective 7: Scale up implementation of interlinked patient monitoring systems for TB/HIV and recording of TB deaths among people living with HIV.** Development of interlinked monitoring systems is critical to measurement of progress and strategic planning.<sup>31</sup> A specific target is that all of the 63 countries that have been identified as priorities for TB/HIV at global level should be reporting TB deaths among people living with HIV by 2015.

**Objective 8: Coordinate global-level efforts to reduce the burden of HIV-related TB.** The TB/HIV Working Group will continue to provide coordination of the global response to the TB/HIV epidemic. It will promote the sharing of best practices and lessons learned, and help to define evidence-based strategies to achieve the 2015 targets. It will also work to increase the visibility of TB/HIV through advocacy and promotion of collaborative TB/HIV activities.

The rates of scale-up required for major interventions to achieve the targets for 2015 are illustrated in [Figure 22](#) and [Figure 23](#).

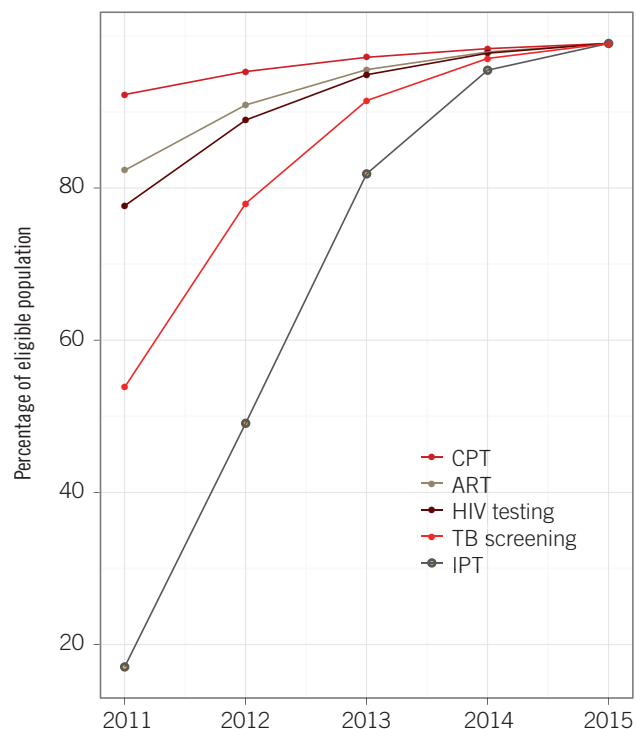
Mobilization of HIV groups and affected communities to advocate for the provision of TB prevention, treatment and care services to all people living with HIV, as well as the strengthening of laboratory and radiology capacity for TB diagnosis, will be crucial to the achievement of all objectives. Technical assistance is also likely to be needed to support the expansion of interventions, and should be harmonized through **TBTEAM**<sup>32</sup> and with other partners and mechanisms wherever feasible.

Further details are shown in the corresponding strategic framework (see pp48–49).

<sup>31</sup> *Three interlinked patient monitoring systems for HIV care/ART, MCH/PMTCT and TB/HIV: standardized minimum dataset and illustrative tools.* Geneva, Switzerland. World Health Organization, 2010. See [www.who.int/hiv/pub/imai/forms\\_booklet.pdf](http://www.who.int/hiv/pub/imai/forms_booklet.pdf)

<sup>32</sup> For more information about **TBTEAM**, see the section of this plan that explains the mechanisms of the Stop TB Partnership.

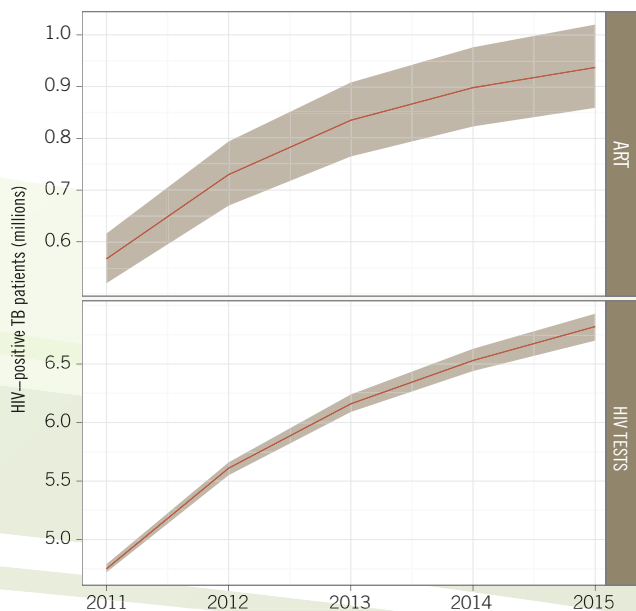
**FIGURE 22** SCALE-UP REQUIRED FOR TB/HIV INTERVENTIONS



**FUNDING REQUIREMENTS**

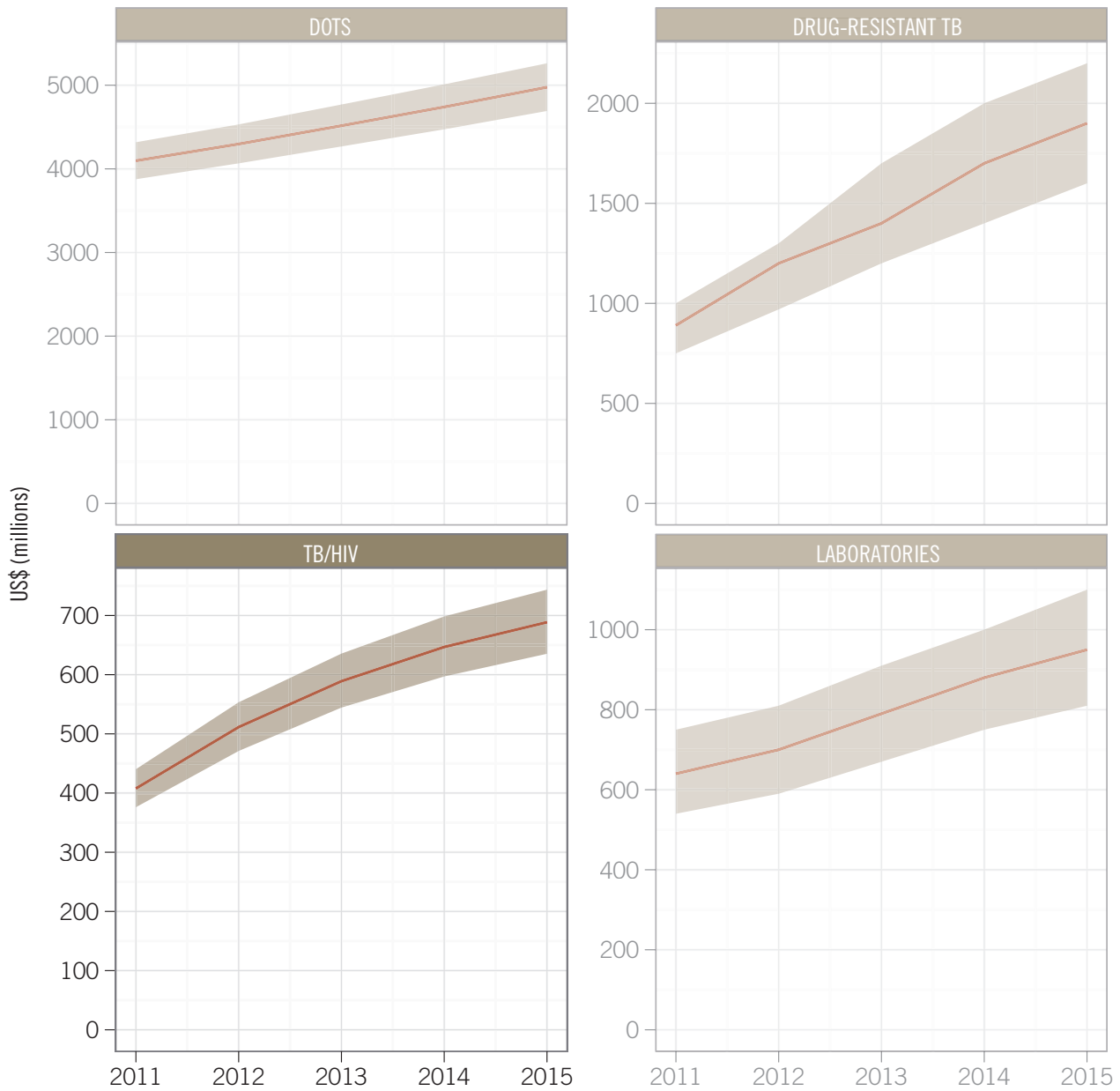
The total funding required for TB/HIV interventions is estimated to be US\$ 2.8 billion for the five years 2011–2015. The annual requirement increases from about US\$ 400 million in 2011 to almost US\$ 700 million in 2015 (Figure 24). Almost all of the funding is needed for the provision of ART (≥85% in all years of the plan); this includes drugs, nutritional support, service delivery (including staff time and the costs of infrastructure and operational costs), training of health workers and other miscellaneous costs. It should be noted that the cost for ART is based on six months of ART only (the period of treatment that overlaps with TB treatment), and not the lifelong costs of ART for people living with HIV. The costs associated with other interventions, including HIV testing, CPT, screening for TB among people living with HIV, and IPT, are relatively low.

**FIGURE 23** NUMBERS OF PATIENTS TESTED FOR HIV AND ENROLLED ON ART, 2011–2015<sup>a</sup>



<sup>a</sup> Shaded areas represent uncertainty bands.

**FIGURE 24** FUNDING REQUIRED FOR TB/HIV, IN THE CONTEXT OF THE OTHER “IMPLEMENTATION” COMPONENTS OF THE PLAN <sup>a</sup>



<sup>a</sup> Shaded areas represent uncertainty bands.



**TB/HIV: STRATEGIC FRAMEWORK, 2011–2015**  
**VISION: NO DEATHS FROM TB AMONG PEOPLE LIVING WITH HIV**

GOAL AND OBJECTIVES	MAJOR ACTIVITIES	INDICATOR(S)	BASELINE (2009)	TARGET FOR 2015
<p><b>Goal:</b> To reduce the global burden of HIV-associated TB</p>		<p>Percentage reduction in TB deaths among HIV-positive people by 2015 compared with baseline of 2004.</p>	<p>~10%</p>	<p>50%</p>
<p><b>Objective 1:</b> Scale up access to HIV testing among TB patients</p>	<p>Update national policy for HIV testing in TB patients and TB suspects as appropriate; train counsellors and health care workers on HIV testing and counselling; procure and distribute commodities; conduct rapid testing for HIV.</p>	<p>Percentage of TB patients who know their HIV status.</p>	<p>26%</p>	<p>100%</p>
<p><b>Objective 2:</b> Scale up access to CPT* for HIV-positive TB patients, according to international guidelines</p>	<p>Train health care workers on collaborative TB/HIV activities and management of HIV-associated TB; provide CPT.</p>	<p>Percentage of TB patients diagnosed as HIV-positive started on (or continuing on previously initiated) CPT during TB treatment.</p>	<p>75%</p>	<p>100%</p>
<p><b>Objective 3:</b> Scale up access to ART for HIV-positive TB patients, according to international guidelines</p>	<p>Update national policy such that all HIV-positive TB patients are eligible for ART; train health care workers on collaborative TB/HIV activities and management of HIV-associated TB; address stigma and discrimination to promote access to TB and HIV services among the most at-risk populations; strengthen laboratory capacity needed to monitor ART; provide ART.</p>	<p>Percentage of TB patients diagnosed as HIV-positive started on (or continuing on previously initiated) ART.</p>	<p>37%</p>	<p>100%</p>
<p><b>Objective 4:</b> Scale up TB screening among people living with HIV, according to international guidelines</p>	<p>Update national policy on ICF; mobilize HIV stakeholders to provide TB prevention, treatment and care services to all people living with HIV; train health care workers (including community health workers) providing HIV services on collaborative TB/HIV activities and the management of HIV-associated TB; strengthen laboratory capacity needed for TB diagnosis (culture, DST, histopathology); strengthen radiology capacity for TB diagnosis (chest X-ray, ultrasound).</p>	<p>Percentage of all people living with HIV enrolled in HIV and PMTCT care assessed for TB, during their previous visit to HIV care services.</p>	<p>~33%</p>	<p>100%</p>

\* Abbreviations and notes: IPT - isoniazid preventive therapy; ICF - intensified case-finding (of TB among people living with HIV); CPT - cotrimoxazole preventive therapy; ART - antiretroviral therapy; PMTCT - prevention of mother-to-child transmission (of HIV). Health care workers includes community health workers.

OBJECTIVES (CONTINUED)	MAJOR ACTIVITIES	INDICATOR(S)	BASELINE (2009)	TARGET FOR 2015
<p><b>Objective 5:</b> Scale up access to IPT among people living with HIV and who do not have active TB, according to international guidelines</p>	<p>Update national policy on IPT; mobilize HIV stakeholders to provide TB prevention, treatment and care services to all people living with HIV; train health care workers (including community health workers) on collaborative TB/HIV activities and the management of HIV-associated TB; provide isoniazid and pyridoxine drugs.</p>	<p>Percentage of people living with HIV enrolled in care started on IPT, among those who are eligible for IPT <i>(NB. It is anticipated that about 50% of people living with HIV will be eligible for IPT)</i></p>	0.2%	100%
<p><b>Objective 6:</b> Scale up the implementation of measures for TB infection control in health care facilities providing services to people living with HIV</p>	<p>Conduct annual surveillance for TB disease among health care workers (including community health workers); develop an infection control plan for facility-level managerial activities, administrative controls, environmental controls and personal protection measures, and implement these measures; train health care workers providing care for people living with HIV on TB infection control.</p>	<p>Ratio of TB notification rate among health care workers to notification rate among general population</p> <p>Number of TB/HIV HBCs with a plan for infection control in health facilities providing services to people living with HIV</p>	n/a*	~1
<p><b>Objective 7:</b> Scale up implementation of interlinked patient monitoring systems for TB/HIV and recording of TB deaths among people living with HIV</p>	<p>Train health care workers on collaborative TB/HIV activities and monitoring and evaluation; provide interlinked patient monitoring recording and reporting formats; strengthen programme capacity in the monitoring and evaluation of collaborative TB/HIV activities (including supervision).</p>	<p>Number of TB/HIV HBCs reporting on TB deaths among people living with HIV</p>	n/a	63**
<p><b>Objective 8:</b> Coordinate global-level efforts to reduce the burden of HIV-related TB</p>	<p>Organize meetings of the TB/HIV Working Group; disseminate global policy guidance on TB/HIV, with particular attention to ICF, IPT and infection control.</p>	<p>Number of international partners participating in meetings of the TB/HIV Working Group</p> <p>Number of countries in which national policy on ICF and IPT has been updated according to international guidelines</p>	10	10

\* Abbreviations and notes: n/a - not available. Health care workers includes community health workers.

\*\* All of the 63 countries that have been defined as global priorities for implementation of TB/HIV collaborative activities.

## 4. LABORATORY STRENGTHENING

### INTRODUCTION: DEFINITIONS, TARGETS AND PROGRESS TO DATE

Laboratory diagnosis of TB through microscopic examination of sputum for the presence of acid-fast bacilli (AFB) has been the cornerstone of the diagnostic process for people suspected of having TB. Ensuring the availability of laboratories in which a reliable diagnosis of TB can be made through quality-assured AFB microscopy is essential for effective TB control. This requires strengthening of basic laboratory services in many countries – which will benefit not only TB control, but will also help to strengthen health systems as a whole.

The use of AFB microscopy for the diagnosis of TB was the initial focus of the DOTS strategy (see also the **DOTS** component of this plan), which emphasized the detection and treatment of sputum-smear positive cases of pulmonary TB (i.e. the most infectious cases and those most likely to transmit TB within the community).

AFB microscopy alone, however, is insufficient for the diagnosis of all people with TB, as is well-recognized in the *Stop TB Strategy* (see also the **Overview**). AFB microscopy will not identify people who have smear-negative forms of TB and it cannot be used to detect drug-resistant forms of TB. Smear-negative pulmonary TB is especially common among people who are HIV-positive. To diagnose these cases, sputum specimens can be cultured (grown) in laboratories, after which it is possible to diagnose or rule-out TB. In the past, cultures were grown on solid media and it took 4–6 weeks to obtain a result. More recently, liquid culture and molecular technologies have been recommended to enable a substantial reduction in diagnostic delays. Diagnosis of drug-resistant TB involves identifying *Mycobacterium tuberculosis* from clinical specimens and conducting drug susceptibility testing (DST) to confirm or exclude resistance. Recently, rapid tests for drug resistance have become available. However, due to a lack of laboratory capacity worldwide, only about 12% of TB patients with MDR-TB and

an even smaller fraction of people with XDR-TB are being diagnosed. The majority of existing culture and DST laboratories in resource-limited settings do not meet minimum standards for laboratory biosafety or technical proficiency.

Achieving the 2015 targets for TB control will require a revolution in which laboratory strengthening is given high and urgent priority at global and country level, with the latest WHO laboratory guidance and policies on new diagnostic tests and biosafety translated into the development, financing and implementation of concrete plans for expanding and upgrading laboratory services. A vigorous campaign to make accurate TB diagnosis available to all people who need it will require new approaches to setting laboratory norms and standards, implementation of new diagnostics, competent and well coordinated technical assistance (harmonized through **TBTEAM**<sup>33</sup> and other partners), resource mobilization and accelerated knowledge transfer.

Recognizing the urgent need to scale up laboratory quality and services worldwide, the Stop TB Partnership Coordinating Board established **GLI**<sup>34</sup> as a new Working Group in October 2008. GLI provides policy guidance on appropriate laboratory technology and best practices and oversees global initiatives aimed at helping countries to build, scale up and upgrade laboratories.

### OVERVIEW OF PLAN GOALS, OBJECTIVES, TARGETS AND ACTIVITIES, 2011–2015

The plan for laboratory strengthening has been defined such that it relates very clearly to the other elements of the Global Plan. The overall goal is to substantially improve the availability and quality of laboratory services to diagnose TB, and monitor the treatment of TB, especially in countries with a high burden of TB.

The first three objectives are directly related to the diagnosis of sputum and culture-positive TB, including

<sup>33</sup> For more information about **TBTEAM**, see the section of this plan that explains the mechanisms of the Stop TB Partnership.

<sup>34</sup> For more information about **GLI**, see the section of this plan that explains the mechanisms of the Stop TB Partnership.

particular attention to the diagnosis of smear-negative TB in people living with HIV (see also the **DOTS** and **TB/HIV** components of this plan), and to the rapid diagnosis of MDR and XDR-TB (see the **Drug-resistant TB** component of this plan). Indicators and targets have been harmonized with those included in related components of the plan wherever relevant (for example, targets for testing for drug resistance appear in the plans for Drug-resistant TB and Laboratory strengthening in this component). The fourth and fifth objectives cover the cross-cutting issue of quality management and the global coordination of efforts to strengthen laboratories worldwide through GLI.

The objectives, and associated targets and activities, are as follows:

**Objective 1: Increase access to quality-assured AFB microscopy with effective external quality assurance (EQA).** By the end of 2015, all of the 149 countries<sup>35</sup> considered in the Global Plan should have at least one laboratory per 100 000 population able to perform AFB microscopy with effective EQA. More than 90% of AFB laboratories assessed for quality assurance should meet international standards. In recognition of the new technologies now available, 20% of AFB laboratories should have replaced conventional bright field microscopes with light-emitting diode (LED) microscopes. These LED microscopes enable enhanced diagnostic accuracy (and increased detection of smear-positive cases of TB) by allowing laboratory staff to visualize TB bacilli much more easily.

**Objective 2: Improve the diagnosis of TB among AFB smear-negative TB cases, especially among people living with HIV.** A key target is to improve diagnosis of smear-negative cases by using culture and/or molecular-based tests. By 2015, the 36 countries that are in one or both lists of the 22 high-burden and the 27 high MDR-TB burden countries should have at least one culture laboratory per 5 million population, or equivalent capacity to diagnose smear-negative TB using rapid molecular tests.<sup>36</sup>

**Objective 3: Increase access to rapid laboratory diagnosis of drug-resistant TB among TB patients considered at risk of M/XDR-TB.** By 2015, all patients that have been previously treated for TB should be tested for MDR-TB. Furthermore, any new TB cases (i.e. that have not had TB in the past) should also be tested for MDR-TB, if they are considered at high risk (for example, they are a contact of a known case of MDR-TB, or they were diagnosed in a setting where the prevalence of MDR-TB is known to be high). In recognition of the availability of rapid tests, more than 50% of tests for drug resistance among new TB patients and more than 90% of tests among previously treated patients should be done using rapid tests by 2015. Among confirmed cases of MDR-TB, at least 90% should have a DST test result for a fluoroquinolone and a second-line injectable drug.

**Objective 4: Establish laboratory quality management systems.** By 2015, more than half of all national reference laboratories (NRLs) should be implementing a quality management system that meets international standards, at least 95% should have appropriate biosafety measures in place and ideally half should have an accredited quality management system in place.

<sup>35</sup> All countries excluding high-income countries.

<sup>36</sup> The 22 HBCs are, in alphabetical order: Afghanistan, Bangladesh, Brazil, Cambodia, China, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, the Philippines, the Russian Federation, South Africa, Thailand, Uganda, the United Republic of Tanzania, Viet Nam and Zimbabwe (see also the DOTS component of this plan). The 27 high MDR-TB burden countries are, in alphabetical order: Armenia, Azerbaijan, Bangladesh, Belarus, Bulgaria, China, the Democratic Republic of the Congo, Estonia, Ethiopia, Georgia, India, Indonesia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Myanmar, Nigeria, Pakistan, the Philippines, the Republic of Moldova, the Russian Federation, South Africa, Tajikistan, Ukraine, Uzbekistan and Viet Nam. These lists of countries account for about 80% and 85% respectively of the global total of drug-susceptible and drug-resistant cases of TB. Countries with populations of less than 5 million need at least one laboratory.

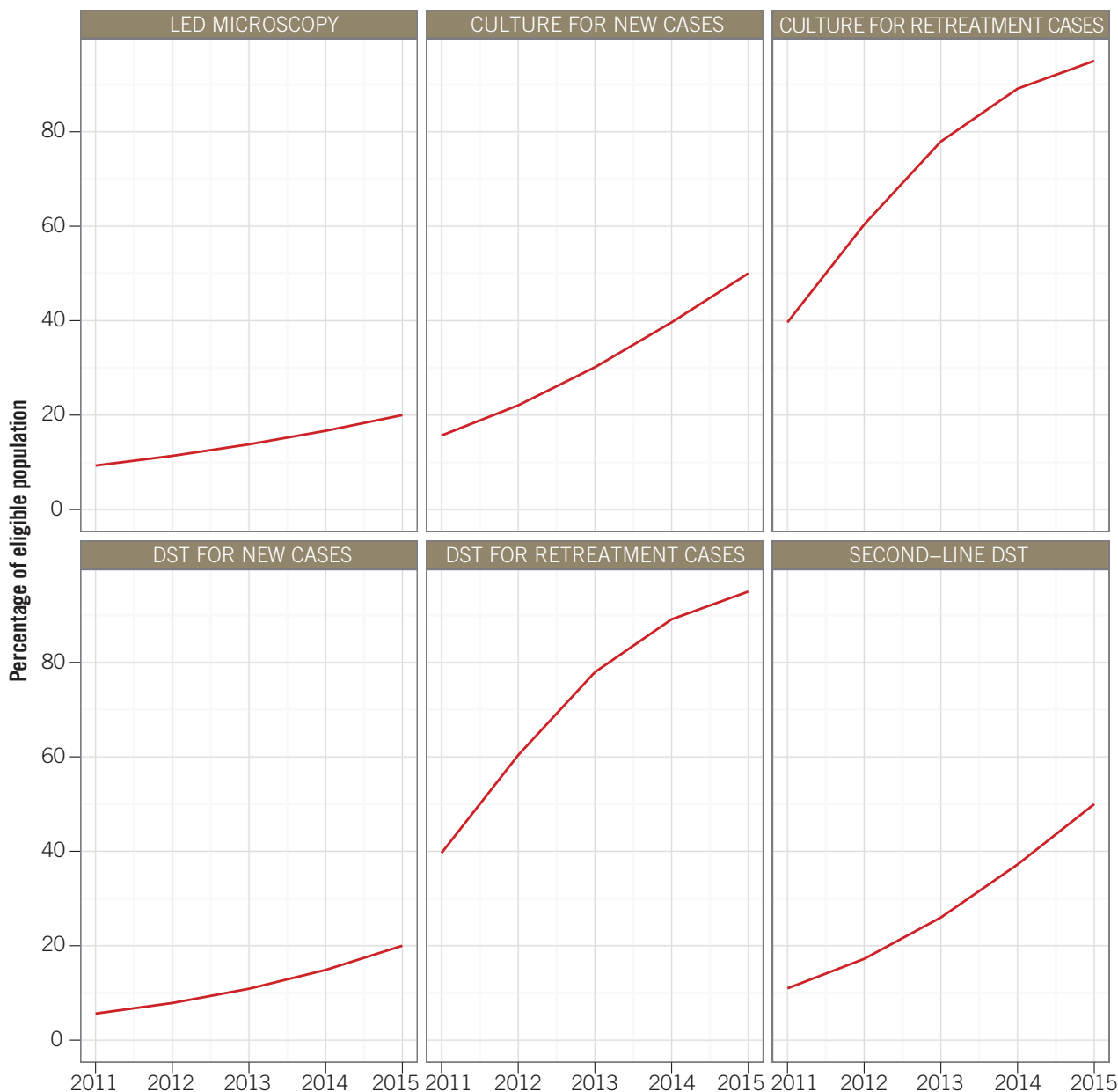
**Objective 5: Coordinate global level efforts to strengthen laboratory capacity to diagnose all forms of TB through GLI.** The rates of scale-up required for the main elements of the plan are illustrated in **Figure 25**.

To ensure that laboratory capacity is adequate, several essential elements must be addressed simultaneously within comprehensive strategies and national laboratory strengthening plans. Fundamental to this work is collaboration between TB control programmes and public health laboratory systems at country level, in the following areas:

- infrastructure, biosafety and utilities;
- human resource development (including training and retention);
- specimen referral, supply chain management and logistics;
- equipment and maintenance;
- technical procedures (disease-specific);
- quality assurance; and
- data management.

Further details are shown in the corresponding strategic framework (see pp54–55).

**FIGURE 25** SCALE-UP REQUIRED FOR LABORATORY SERVICES

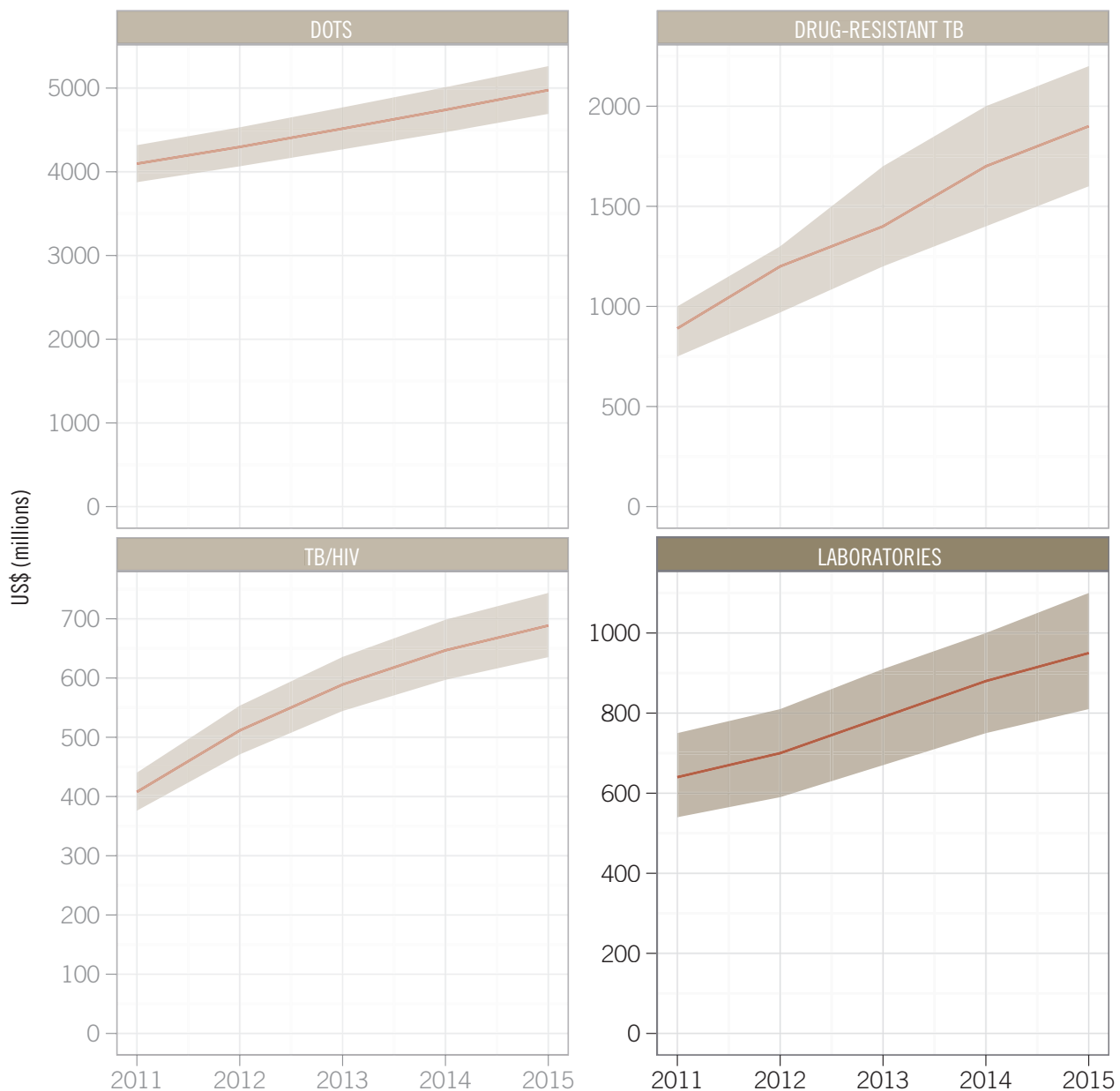


## FUNDING REQUIREMENTS

In 2015, an estimated 900 million sputum smears, 13 million culture (or equivalent) investigations and seven million tests for drug resistance (including use of rapid tests based on molecular technologies) will be needed to meet the targets defined above. To make this possible, at least 2000 new culture and DST laboratories (or equivalent) need to be established and more than 20 000 new laboratory technicians trained and deployed. The total funding required is

estimated to be US\$ 4 billion for the five years 2011–2015, increasing annually from US\$ 0.6 billion in 2011 to US\$ 1 billion in 2015 (Figure 26). In addition, it is anticipated that a further 10% of the total funding required for laboratory strengthening will be needed for technical assistance.

**FIGURE 26** FUNDING REQUIRED FOR LABORATORY STRENGTHENING, IN THE CONTEXT OF THE OTHER “IMPLEMENTATION” COMPONENTS OF THE PLAN <sup>a</sup>



<sup>a</sup> Shaded areas represent uncertainty bands.

## LABORATORY STRENGTHENING: STRATEGIC FRAMEWORK, 2011–2015

VISION: INTEGRATED TB DIAGNOSTIC SERVICES DELIVERING RAPID, QUALITY-ASSURED TESTS TO ALL WHO NEED THEM THROUGH A NETWORK OF ACCREDITED LABORATORIES

GOAL AND OBJECTIVES	MAJOR ACTIVITIES	INDICATOR(S)	BASELINE (2009)	TARGET FOR 2015
<p><b>Goal:</b> To substantially improve the availability and quality of laboratory services to diagnose TB and monitor the treatment of TB, especially in countries with a high burden of TB</p> <p><b>Objective 1:</b> Increase access to quality-assured AFB microscopy with effective EQA*</p>	<p>Maintain and operate the existing laboratory network; strengthen existing laboratory networks with more laboratories (where needed), external quality assurance and the introduction of LED microscopy.</p>	Number of TB cases diagnosed and notified	5.8 million	6.9 million
		Number of cases of MDR-TB diagnosed	30 000	270 000
<p><b>Objective 2:</b> Improve the diagnosis of TB among AFB smear-negative TB cases, especially among people living with HIV</p>	<p>Scale up laboratory capacity to diagnose smear-negative TB; introduce new molecular-based technologies; conduct tests.</p>	Number of countries with ≥ 1 AFB microscopy laboratory per 100 000 population	≥75**	149
		Percentage of AFB microscopy laboratories that are quality-assured	n/a	≥90%
		Percentage of AFB microscopy laboratories using LED microscopes	<1%	20%
		Number of countries among the 22 HBCs and 27 high MDR-TB burden countries with ≥1 culture laboratory per 5 million population	18–21**	36
		Percentage of AFB smear-negative, newly notified TB cases screened using a culture and/or molecular-based test	<1%	≥50%
		Percentage of AFB smear-negative, previously treated TB cases screened using a culture and/or molecular-based diagnosis	<1%	≥90%

\* Abbreviations: EQA - external quality assurance; LED - light-emitting diode; n/a - not available.

\*\* Among the 149 countries included in the Global Plan that reported data to WHO, 75 countries had at least one AFB laboratory per 100 000 population while 26 did not report data and 48 had less than one AFB laboratory per 100 000 population. (See also strategic framework for DOTS). Among the 36 countries that are one of the 27 high MDR-TB burden countries, three countries did not report data to WHO (Tajikistan, Azerbaijan, Lithuania).

OBJECTIVES (CONTINUED)	MAJOR ACTIVITIES	INDICATOR(S)	BASELINE (2009)	TARGET FOR 2015
<p><b>Objective 3:</b> Increase access to rapid laboratory diagnosis of drug-resistant TB among TB patients considered at risk of M/XDR-TB*</p>	<p>Expansion of laboratory capacity to test for first- and second-line drug resistance; phasing in of rapid tests for resistance to first- and second-line drugs for all new cases considered at high-risk of MDR-TB and previously treated TB cases.</p>	<p>Percentage of new TB cases tested for drug resistance</p>	7%	20%
		<p>Percentage of previously treated TB cases tested for drug resistance</p>	7%	100%
		<p>Percentage of tests for drug resistance performed on new cases done using rapid tests</p>	<5%	≥50%
		<p>Percentage of tests for drug resistance performed on previously treated cases done using rapid tests</p>	5%	≥90%
<p><b>Objective 4:</b> Establish laboratory quality management systems</p>	<p>Introduce laboratory accreditation schemes; disseminate biosafety guidance; strengthen quality assurance and quality control activities.</p>	<p>Percentage of confirmed cases of MDR-TB with a DST result for fluoroquinolones and a second-line injectable drug</p>	15%	≥90%
		<p>Percentage of NRLs implementing a quality management system according to international standards</p>	<5%	≥50%
		<p>Percentage of NRLs in which appropriate biosafety measures are in place</p>	<5%	≥95%
		<p>Percentage of NRLs in which an accredited quality management system is in place</p>	<5%	≥50%
<p><b>Objective 5:</b> Coordinate global level efforts to strengthen laboratory capacity to diagnose all forms of TB via the GLI</p>	<p>Meetings of the GLI Working Group; development of policy guidance and oversight of the implementation of global initiatives; advocacy and resource mobilization; global-level workshops; expansion of the TB SRNL network.</p>	<p>Number of partners actively involved in GLI laboratory strengthening efforts</p>	30	100
		<p>Number of GLI Core Group meetings held per year</p>	12	12
		<p>Total number of functional SNRLs</p>	29	≥50

\* Abbreviations: XDR-TB - extensively drug-resistant TB; NRL - national reference laboratory; GLI - Global Laboratory Initiative; SNRL - supranational reference laboratory.



## PART II

# RESEARCH AND DEVELOPMENT

### A QUANTUM LEAP IN TB RESEARCH

TB elimination – the reduction of disease incidence to one per million population – is more than an aspiration. We know it could become a reality by 2050. But this will only happen if we achieve radical transformation in the way TB is diagnosed, treated and prevented. This goal can be realized only if TB research is both intensified and envisioned in an entirely new way. It must be viewed as a continuum from basic research (to enhance fundamental understanding) to operational research (to achieve optimal implementation).

New technologies are needed for optimal prevention, diagnosis and treatment of all forms of TB in people of all ages, including those living with HIV. Such tools must deliver quicker results, be affordable to the poor and applied in combination to secure a cumulative epidemiological impact and simplified management of TB control. These advances will require a quantum leap in our understanding of fundamental TB science, which underpins discovery and development of new diagnostics, drugs and vaccines.

Clinical trials for evaluating new tools and demonstrating their impact in national TB control programmes are essential, as are creative intellectual property mechanisms that protect public health and enhance access to new technologies. Further, we will need novel health system designs that advance the adoption and diffusion of new technologies.

Recent breakthroughs will bring new TB tools to the market over the next five years. In diagnostics, the

recently introduced molecular line probe assays can detect MDR-TB in a few days instead of weeks. Four new or improved TB diagnostic technologies and approaches were recently endorsed by WHO and are currently being introduced. New diagnostics that offer shorter response times for sputum culture and sensitivity testing will soon be available. The pipeline of new TB drugs has expanded, with 38 compounds in preclinical and clinical development, including nine TB drug candidates in late-phase clinical trials. We can now hope for a shortened treatment time of three to four months for drug-susceptible TB. Shorter treatments for drug-resistant TB using novel combinations of new chemical entities with both existing and repurposed drugs will also soon be available. Currently nine TB vaccine candidates are in clinical trials, and by 2020 it is expected that new generation TB vaccines will be available.

Looking beyond 2015, we have good evidence for the dramatic impact that new tools, used in combination, could have on the overall TB burden. Recent research in the WHO South-East Asia Region has suggested that a combination of a neonatal pre-exposure TB vaccine, a two-month treatment regimen effective against drug-susceptible and -resistant strains of TB and a novel DNA amplification-based diagnostic test could potentially reduce the incidence of TB by 71%<sup>37</sup>. To reach elimination, however, such a combination would need to be supplemented by new delivery strategies (such as mass vaccination campaigns) and effective new treatments for latent TB infection.

<sup>37</sup> Abu-Raddad LJ et al. Epidemiological benefits of more effective tuberculosis vaccines, drugs and diagnostics. *Proceedings of the National Academy of Science (USA)*, 2009.106(33):13980–5.

The Global Plan to Stop TB 2011–2015 has a more detailed roadmap for meeting the 2015 research goals. Unlike the original plan launched in 2006, it includes blueprints for fundamental and operational research, in addition to the key areas of new diagnostics, drugs and vaccines. This invigorated roadmap reflects the Stop TB Partnership's more fully developed – and ambitious – research agenda.

Recognizing the urgent need for stepped up funding and commitment for TB research, the Stop TB Partnership launched the Research Movement in 2006. This initiative has three overarching goals: to lead on efforts to increase resources for TB research; to provide a forum for TB researchers and funders of TB research to coordinate their priorities and actions; and to encourage a coherent and comprehensive global TB research roadmap. It further seeks to strengthen the wide community of researchers engaged in development of new drugs, diagnostic methods and vaccines; operational researchers, who investigate how to make TB services more accessible and efficient; and basic researchers.

Together with the Research Movement, the Working Groups on New Diagnostics, New Drugs and New Vaccines will continue drawing together TB patients and their advocates, doctors and other health workers, research scientists, donors, governments, national TB programmes, pharmaceutical companies and commercial manufacturers in a common effort.

Global investment in TB research and development has decelerated in the three years since the *Global Plan to Stop TB 2006–2015* was issued. Between 2006 and 2007 investment rose by US\$ 56 million, to a total US\$ 474 million. However between 2007 and 2008 investment rose by just US\$ 36 million, to US\$ 510 million.<sup>38</sup>

The Global Plan to Stop TB 2011–2015 calls for a total investment of US\$ 9.8 billion to reach the Partnership's 2015 research and development targets. With adequate funding for research and development, we will be well on our way towards TB elimination. Without it, we will fail the next generation and perhaps even their children.

**Michel Greco**

*Chair, Working Group on New Vaccines*

**Giorgio Roscigno**

*Chair, Working Group on New Diagnostics*

**Mel Spigelman**

*Chair, Working Group on New Drugs*

**Christian Lienhardt**

*Senior Scientific Adviser,  
Stop TB Partnership Research Movement*

<sup>38</sup> *Tuberculosis research and development: a critical analysis*. New York, Treatment Action Group (TAG), 2009.

# 1. FUNDAMENTAL RESEARCH

## INTRODUCTION

Development of new TB new diagnostics, drugs and vaccines is an inherently slow and uncertain process, with potential technologies eliminated at every step. To increase the chance of effective products passing each hurdle to become available for TB care and control, the number of high quality product candidates entering the pipeline must be sufficiently large. Engineering new technologies to identify, treat and ultimately prevent the disease requires a solid knowledge base about the pathogen that causes TB (*Mycobacterium tuberculosis*, or *M. tuberculosis*), as well as the natural history and pathology of TB in humans. Continued and adequate attention to fundamental science is needed to maintain the flow of new technologies into the product pipeline, and to ensure that a sufficient number of new product candidates and strategies enter clinical development, and thus will ultimately contribute to the elimination of TB.

Within the *Global Plan to Stop TB 2006–2015*, fundamental research efforts were considered as an integral part of new diagnostic, drug and vaccine development. To address the importance of fundamental science as the driver of product development and TB control innovation, a global consultation among scientists and other key stakeholders was conducted in 2010 by the Stop TB Partnership Research Movement, in collaboration with the National Institute of Allergy and Infectious Diseases (NIAID), a component of the US National Institutes of Health (NIH) and the Treatment Action Group (TAG), to further advance the integration of biomedical science into TB care and control. The consultation identified a set of key research questions and gaps in TB science that are critical to driving essential innovation as well as directing the attention of relevant funders and other partners.

The resulting TB research goal and objectives outlined below are intended to communicate the broad research areas that will benefit from closer collaboration among disciplines – including basic research, translational research, product development science, clinical research and epidemiology – and

that are likely to yield significant advances by 2015. They indicate initial research directions that most urgently require additional attention. Many aspects are already being addressed by scientific disciplines, institutions and individual scientists, and important data are already emerging that will be integrated into the larger TB research road map between now and 2015.

## OVERVIEW OF OBJECTIVES

Fundamental science is an integral part of an aggressive, transformational research response to TB that underpins the development of new diagnostics, drugs and vaccines. This approach is central to achieving the goals of the *Global Plan to Stop TB 2006–2015* and the MDGs by 2015.

The three major objectives for fundamental research in the next five years are defined and explained below.

**Objective 1: Improve the characterization of human TB using modern biomedical, epidemiological and clinical approaches.** Although many studies have been conducted in humans and with animal models, our understanding of the natural history and pathological mechanisms of TB in humans remains incomplete. To achieve this objective, researchers from many scientific disciplines must collaborate to better understand the nature of *M. tuberculosis*, how humans respond to it, how disease develops and how it eventually spreads to others. Since TB is a chronic infection and not every infected person develops active TB in the same manner, it is critical to closely characterize the steps that lead from exposure to infection and from infection to active disease, and how both the infected person and the pathogen contribute to these processes. This will facilitate greater understanding of the occurrence and transmission of TB, including among those who are also affected by HIV and other co-epidemics. Elucidating the overall spectrum of TB, and the transitions between the main stages of human disease, are key to understanding and predicting disease progress and identifying opportunities for intervention.

Although we know that *M. tuberculosis* causes TB, we do not yet understand where precisely in the body the bacteria are located or whether and how their location and numbers dictate how TB develops. This knowledge is central to the purposeful design of more effective TB drugs. There is increasing evidence that *M. tuberculosis* utilizes nutrients in specific ways to affect its growth in human cells and lung lesions, influencing how TB disease develops, how the bacteria respond to TB drugs and possibly also to anti-TB vaccines. In addition, we are beginning to understand how the genetic make-up of *M. tuberculosis* influences whether the body can clear the infection, remain infected or develop active disease, but further studies in this area are needed.

In humans, the symptoms and lesions that are a hallmark of TB disease are the result of how the human body reacts to infection by this pathogen. Of particular importance is to understand why, in some patients, lung lesions are able to wall-off bacteria and prevent disease, while in others the same lesions can break open and contribute to the growth and contagious spread of bacteria. Since not all aspects of the role and dynamics of these lesions can be studied in humans, animal models are essential to generate testable hypotheses for human studies.

Lastly, at a population level, it is important to define the key epidemiological characteristics of TB, through the assessment of variations in TB dynamics in endemic settings, and identification of the smallest epidemiological unit we need to study in order to capture the most relevant differences (local communities, regions, countries).

Thus, to drive critical innovation by 2015, TB science would benefit significantly from increased efforts in the following areas:

- define the most critical phases of human TB that mark the transition from latent infection to active disease;
- elucidate the correlation between *M. tuberculosis* growth characteristics and immune system reactions to it during the different phases of TB disease;
- develop highly sensitive methods to determine the location of bacilli in patient tissues, in order to define whether and how bacterial numbers correlate with disease stages and outcome;
- characterize how TB lesions develop over time and how they impact the dynamics of TB disease;
- collect and evaluate existing information about the epidemiology of TB to identify critical areas to be addressed through collaborative research involving all relevant scientific disciplines.

**Objective 2: Address key molecular features of host/pathogen interactions.**

Given the dynamic nature of TB, detailed understanding of host-pathogen interactions at the molecular level first requires definition of the respective contribution of the *bacillus* and the *host*, and then of their *interaction*.

It has been suggested, but as yet unconfirmed, that different sub-populations of *M. tuberculosis* exist in humans at various stages of the disease and that these populations differ in how they respond to drug treatment, affecting the ultimate disease outcome. It is not known whether the bacteria that remain after an initial two months of drug treatment are vitally different from those that are eliminated during the initial intensive phase of therapy. Such knowledge would enable us to intentionally develop drug regimens that are optimized for elimination of bacteria, potentially at all stages of disease. Highly sensitive methods are required to determine when all viable bacteria have been eliminated from a patient, or when bacterial numbers are low enough that patients can be considered essentially cured.

To fully understand TB from the patient perspective, we need to further define how the immune system is able to eliminate *M. tuberculosis* in most latently-infected individuals, and why in others this mechanism fails and active TB develops. It is likely that a combination of human and bacterial genetics, specific location of bacteria and overall immune and health status play major roles.

Thus, to drive critical innovation by 2015, increased efforts are needed in the following areas:

- identify whether bacterial populations with different growth characteristics can be identified in TB lesions;
- confirm whether TB transmission and/or disease development correlate with specific genetic strains of *M. tuberculosis* in different parts of the world;
- define and agree upon common methods and data sets to be used by researchers to describe and categorize the disease-causing potential of *M. tuberculosis* found in high-burden countries;
- conduct studies in communities in high-burden countries to determine how human genetics are related to development and eventual outcomes of TB infection and active disease;
- more closely define, characterise and locate immune responses that are most critical/fail at each stage of TB;
- identify the immune system and bacterial components that affect *M. tuberculosis* elimination from the body.

**Objective 3: Define critical questions that must be addressed to expedite development of new tools for TB control.** Answering the fundamental questions raised as part of objectives 1 and 2 (above) enables the development of novel tools for TB control, and also helps to highlight specific gaps in understanding that will further aid new product development.

A key requirement for **new diagnostic tools** and strategies is to identify at-risk patients at the earliest possible stage, in order to provide the most appropriate care for prevention or treatment of TB. To identify people who are infected with *M. tuberculosis* but without active TB, it is essential to identify either components of the *M. tuberculosis* bacterium or characteristics of the host immune response that reliably indicate the presence of live *M. tuberculosis*, irrespective of where the infection occurs or immune system status.

Thus, to drive critical innovation by 2015, increased efforts are needed in the following areas:

- identify bacterial and/or host molecules that differentiate between people with active TB, those with latent infection and individuals not affected by TB;
- determine how to measure growth characteristics of *M. tuberculosis* bacteria within TB lesions;
- develop highly-sensitive methods for detecting low-abundance bacterial components that indicate the presence of live *M. tuberculosis* in patient samples.

A key requirement for **new drugs and treatment strategies** is to better understand the natural history of *M. tuberculosis* infection in individual patients. This requires piecing together the details of the bacterial life-cycle from individual data sets, combining the results of studies from all areas of microbiology in a systematic way. This comprehensive view (designated as ‘system biology’) will allow identification of vulnerability points of *M. tuberculosis*, to which novel drugs can be purposefully directed. In addition, it will also provide a better understanding of how current therapies eliminate the bacterium and whether they can be combined in new ways to improve their effectiveness.

Thus, to drive critical innovation by 2015, increased efforts are needed in the following areas:

- identify and confirm the presence of *M. tuberculosis* populations with different growth characteristics in patients and determine how they influence the effectiveness of current drug therapies;
- identify the most vulnerable points in the life-cycle of *M. tuberculosis* that can be potentially targeted by drug compounds;
- study how existing and new TB drugs can be optimally combined to affect maximum elimination of *M. tuberculosis*.

Lastly, for **vaccines**, the key goal is to understand how to prepare the host immune system against *M. tuberculosis* infection and disease. Although the majority of individuals exposed to *M. tuberculosis* do not develop active TB, those with disease can develop TB more than once, suggesting that the immune system does not recognize *M. tuberculosis* sufficiently well to protect the body against re-infection or a second course of disease. This

makes the development of an effective vaccine very challenging. Why prior infection and disease do not protect against recurrent TB must be fully understood, and components of the host immune system that are critical for the elimination of the bacteria must be identified. To guide the development of new vaccines, we also need to understand the advantages and limitations of the current vaccine, bacille Calmette-Guérin (BCG), and whether its effectiveness can be improved.

Thus, to drive critical innovation by 2015, increased efforts are needed in the following areas:

- determine the characteristics, type and differences of immune responses to TB among people who are naturally protected, those who are immune compromised, and those who are receiving TB drugs;
- determine the immune changes that cause and/or signal recurrence of active TB in patients who have already experienced the disease;
- determine what components of *M. tuberculosis* are typically recognized by the immune system, even though the pathogen may not be eliminated.

## FUNDING REQUIREMENTS

According to the latest TAG report<sup>39</sup> basic research accounted for US\$ 170 million (28%) of the US\$ 614 million total invested in TB research and development in 2009. That year, 43% of the overall research investment can be attributed to the US NIH, with its NIAID leading TB research globally. According to official reports, NIH invested US\$ 188 million in research for TB in 2008, US\$ 216 million in 2009 and an estimated US\$ 199 million in 2010. The Bill and Melinda Gates Foundation disbursed US\$ 124 million for TB research and development in 2007 and US\$ 165 million in 2008, which included annual basic TB research investments of US\$ 5 million and US\$ 2.4 million respectively.

It is now widely recognized that more attention and investment must be assigned to fundamental and translational TB research in order to drive essential innovation. Investments in recent years should be

considered as minimal requirements. To estimate and project the actual funding requirements for basic TB research, its underlying importance to the development of new diagnostics, drugs and vaccines, and current research investments were given due consideration. Fundamental research as part of the Global Plan to Stop TB 2011–2015 defines and examines overarching questions in human TB to which the disciplines of basic, translational, clinical and epidemiological science contribute – a new way of looking at fundamental research.

Given the difficulty of pricing activities in biomedical science that are focused on knowledge generation rather than product development, and given that NIH/NIAID is a major global leader and supporter of integrated fundamental TB research (comprised of basic, translational and clinical research), its average annual investment in TB research was used as a proxy indicator of funding requirements, and also of what other major stakeholders might be expected to invest in basic TB research. While TAG defined basic research as “undirected, investigator-initiated research that aims to uncover fundamental knowledge about *M. tuberculosis* and other closely related organisms”, basic research is only one of the many disciplines that work together to enhance our knowledge about fundamental science in TB. The NIH/NIAID budget was used as the baseline since, in essence, it covers activities in basic, translational, clinical and epidemiological science, but does not necessarily include high-level collaborative studies that will have to be developed to meet the goals of the fundamental research activities proposed here. To accommodate for the uncertainty of how to budget these highly integrative programmes, it was felt appropriate to at least double the NIH/NIAID expenditures on TB biomedical research as a first estimate. In this way, an annual aggregate estimate of US\$ 400 million was generated, representing an overall fundamental TB research investment need of US\$ 2.1 billion during the five years of the Global Plan to Stop TB 2011–2015.

<sup>39</sup> *Tuberculosis research and development: 2010 Report on Tuberculosis Research Funding Trends, 2005–2009*. New York, Treatment Action Group (TAG), 2010.

## 2. NEW DIAGNOSTICS

### INTRODUCTION: TARGETS AND PROGRESS TO DATE

Despite its poor effectiveness in detecting TB bacilli, microscopic examination of sputum remains the only widely available diagnostic tool for identifying TB in most high-burden countries. Drug susceptibility testing (DST), if available, is usually performed only after treatment failure, delaying the diagnosis of drug resistance and removing many opportunities to interrupt transmission. While TB treatment success rates have been shown to be steadily improving, case detection rates are levelling off in many places. In African countries, for example, less than half of the estimated cases are being detected in DOTS programmes. Compounded by the spread of drug resistance and TB/HIV co-infection, the lack of effective, quality controlled diagnostic tools jeopardizes recent gains in TB control. The *Global Plan to Stop TB 2006–2015* called for the development and use of new, more sensitive, simpler and cost-effective diagnostic tools that will improve TB control as well as improve quality of patient care.

Since the initiation of the Global Plan, substantial progress has been made in research and development of new diagnostic tools, and the last three years have seen the creation of a rich pipeline of potentially useful new technologies. For some new diagnostic tools, an impressive body of evidence already supports their use. Based on this evidence, WHO (through its Strategic and Technical Advisory Group on TB [STAG-TB]) has endorsed the use of at least ten new diagnostic technologies and approaches since 2007. This included liquid culture for rapid drug susceptibility testing, combined with rapid speciation methods, endorsed by WHO in 2007. Molecular line probe assay (LPA) for rapid screening for multidrug-resistance was similarly endorsed in 2008 and deployed in an increasing number of countries. Non-commercial culture methods for rapid drug susceptibility testing were also endorsed by WHO in 2009. A more sensitive definition of ‘positive smear’ and ‘smear-positive case’, and a reduced number of smear examinations required to improve smear

microscopy were recommended by the organization in 2007. Coupled with the recommended use of light-emitting diode (LED) fluorescence microscopy for more sensitive smear microscopy (endorsed in 2009) and the use of same-day sputum collection and examination to reduce initial default (also called ‘front-loaded’ microscopy, also endorsed in 2009), this approach significantly increases the likelihood of better case detection at the most peripheral levels of health systems. The recent development of a fully automated, real-time Nucleic Acid Amplification Test that allows a diagnosis of TB and assessment of rifampicin resistance in less than two hours could have a profound impact on the detection of TB and MDR-TB cases, at least at district and referral level. The technology was endorsed by WHO in late 2010 and plans for its operationalization in endemic countries were immediately initialized. The publication of a ‘blueprint’<sup>40</sup> outlining the steps and procedures for development and evaluation of new TB diagnostics provides a coherent and up-to-date description of the TB diagnostic technologies under development. This has also enabled the development of an Impact Assessment Framework to assess the influence of new diagnostics on TB control.

Nevertheless, TB case detection remains markedly less than optimal, and was estimated by WHO in 2009 to be 63% globally. Tools to detect active TB at the point-of-care level, predict disease progression, screen for multi- and extensive- drug resistance (MDR and XDR respectively), TB/HIV co-infection and paediatric TB, are still conspicuously lacking. Moreover, while much progress has been made in developing and introducing new diagnostic tools, many new technologies require elaborate and expensive biosafety infrastructure, limiting their use to district facilities and national reference laboratories. Lastly, availability of new diagnostic tools does not necessarily ensure their adoption and use, so translation of policy into practice requires a better understanding of barriers to implementation as well as tried and tested approaches to overcoming such barriers.

<sup>40</sup> Stop TB Partnership’s New Diagnostics Working Group and World Health Organization. *Pathways to better diagnostics for tuberculosis: a blueprint for the development of TB diagnostics*. Geneva, World Health Organization, 2009.

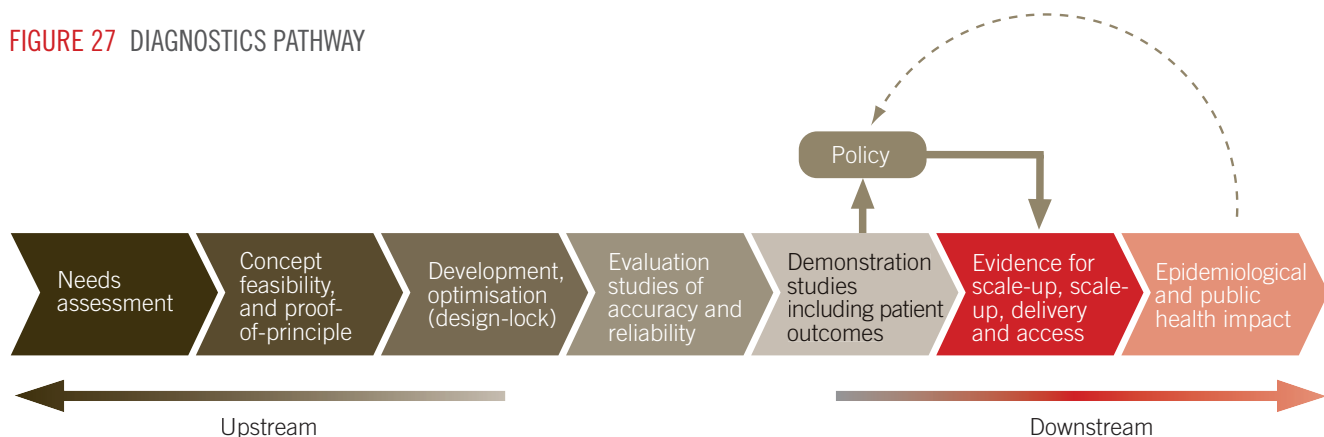
## OVERVIEW OF PLAN GOAL, OBJECTIVES, TARGETS AND ACTIVITIES

The goal of the new diagnostics component of the Global Plan 2011–2015 is to increase detection of active TB at point-of-care level, diagnose latent TB infection, predict disease progression, and screen for multi- and extensively drug-resistant TB, HIV-associated TB and paediatric TB.

Accurate detection of all forms of TB cases for appropriate treatment, and detection of latent TB infection (for active disease prevention) are key to reaching the Global Plan targets and are essential components of eliminating TB by 2050. The Partnership Working Group on New Diagnostics is committed to ensuring that diagnostic research is carried out across the research spectrum – from discovery to demonstration and impact evaluation – to ensure appropriate and affordable diagnosis is available at all levels of health care (Figure 27). It is expected that full implementation of diagnostic research and development activities will mean that by 2015:

- new markers for determination of latent TB infection, disease progression, active disease, and first- and second-line drug resistance are identified and validated (around 75 validated markers in total);
- improved and new technical platforms to meet required target specifications are developed (around nine single or multiplex platforms in total);
- a portfolio of new and improved diagnostics tests meeting the disease target specifications up to validated design-locked products is developed (around 17 validated tests);
- evaluation and demonstration studies, specifically in paediatric and TB/HIV co-infection patient groups, are conducted (around four successfully demonstrated tests);
- the impact of new and improved diagnostics on TB detection rate, access to treatment, patient benefit, cost-effectiveness, equity and poverty (including mathematical modelling studies), will have been evaluated (around 20 studies);
- operational research studies will have been carried out to evaluate how to optimally deliver diagnostic services in routine TB programmatic settings, and to estimate related costs and other resources used by national TB programmes (NTPs) (around 20 studies);
- registration and regulation of validated tools for TB diagnostics will be enhanced and harmonized (in at least 25 countries).

FIGURE 27 DIAGNOSTICS PATHWAY



Source: Stop TB Partnership's New Diagnostic's Working Group. *Pathways to better diagnostics for tuberculosis: a blueprint for the development of TB diagnostics (2009)*. Geneva, World Health Organization, 2010.



The four major objectives for new diagnostics are defined and explained below.

**Objective 1: Address existing knowledge gaps obstructing development of new diagnostic tools**

The development of new diagnostics poses great challenges to the scientific community, since our understanding of many of the underlying processes remains incomplete, and suitable biomarkers have yet to be identified. It is increasingly recognized that future progress in TB diagnostic development is dependent upon an expanded programme of ‘upstream’ fundamental and discovery research aimed at appropriate biomarker identification and characterisation.

**Objective 2: Develop a portfolio of new diagnostic tests**

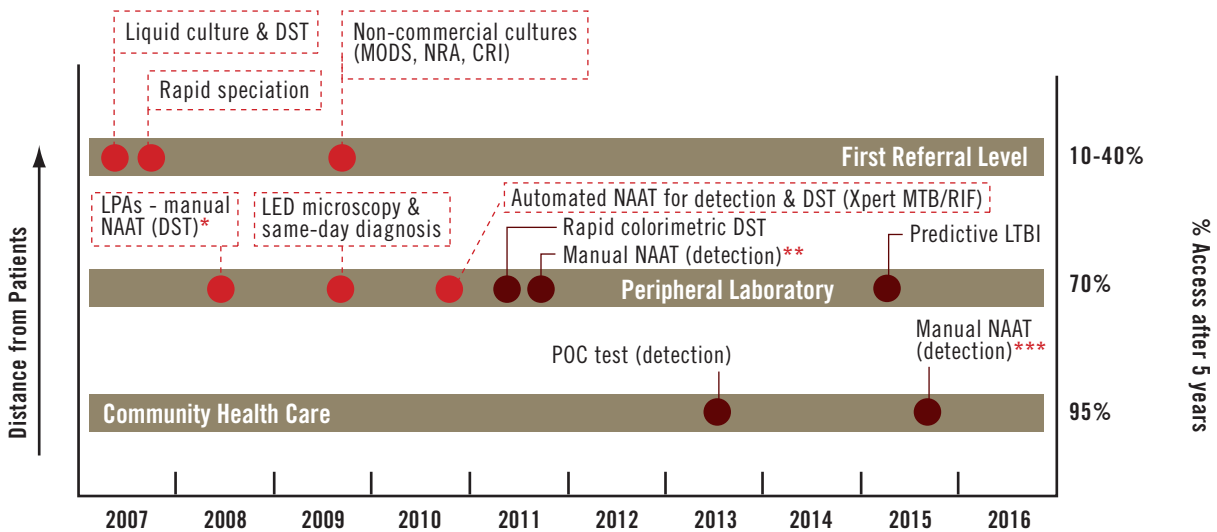
A portfolio of projects focusing on detection of all forms of TB in all age groups, as well as MDR-TB and latent TB infection, will be established, founded on the biomarkers identified and platforms developed in Objective 1. The projects will be purposefully

identified and/or designed to be responsive to the specific diagnostic needs at various levels of public health systems in high-burden countries (e.g., first referral level or district laboratory, peripheral laboratory or microscopy site, and point-of-care or rural health post). The essential targets for product introduction at the various levels are outlined in Figure 28.

**Objective 3: Evaluate the portfolio of new diagnostic tools, demonstrate patient benefit and predict likely impact**

Once technical evaluation is completed with relevant accuracy and validity studies, the effectiveness of any new diagnostic tool, and its capacity to serve at the required level of health service, need to be properly evaluated. This requires evaluation studies in high-burden countries, including studies on active, latent, TB/HIV and drug-resistance testing, especially in paediatric patients and in high-HIV settings. Demonstration projects must assess the incremental value of new tools, examine potential algorithms, and evaluate patient outcomes. Studies are needed

FIGURE 28 TARGETS FOR INTRODUCTION OF TESTS, LEADING TO SUSTAINABLE ADOPTION, 2006–2015



**Abbreviations**

- CRI: Colorimetric redox indicator assay
- DST: Drug Susceptibility Test
- LED: Light-emitting diode
- LPA: Line probe assay
- LTBI: Latent TB Infection
- MODS: Microscopic observation drug-susceptibility
- NAAT: Nucleic Acid Amplification Test
- NRA: Nitrate reductase assay
- POC: Point of Care

- \* Manual NAAT: technology for MTB Drug Susceptibility Testing
- \*\* Manual NAAT: technology for MTB detection at the Peripheral Lab
- \*\*\* Manual NAAT: technology for MTB detection at the Community Health Care Level

Technologies in boxes: endorsed by WHO

to predict the impact of new diagnostics on TB detection rate and access to appropriate treatment, including equity- and poverty-related analyses.

**Objective 4: Ensure that fully validated new diagnostic tools are widely available and appropriately used in endemic countries**

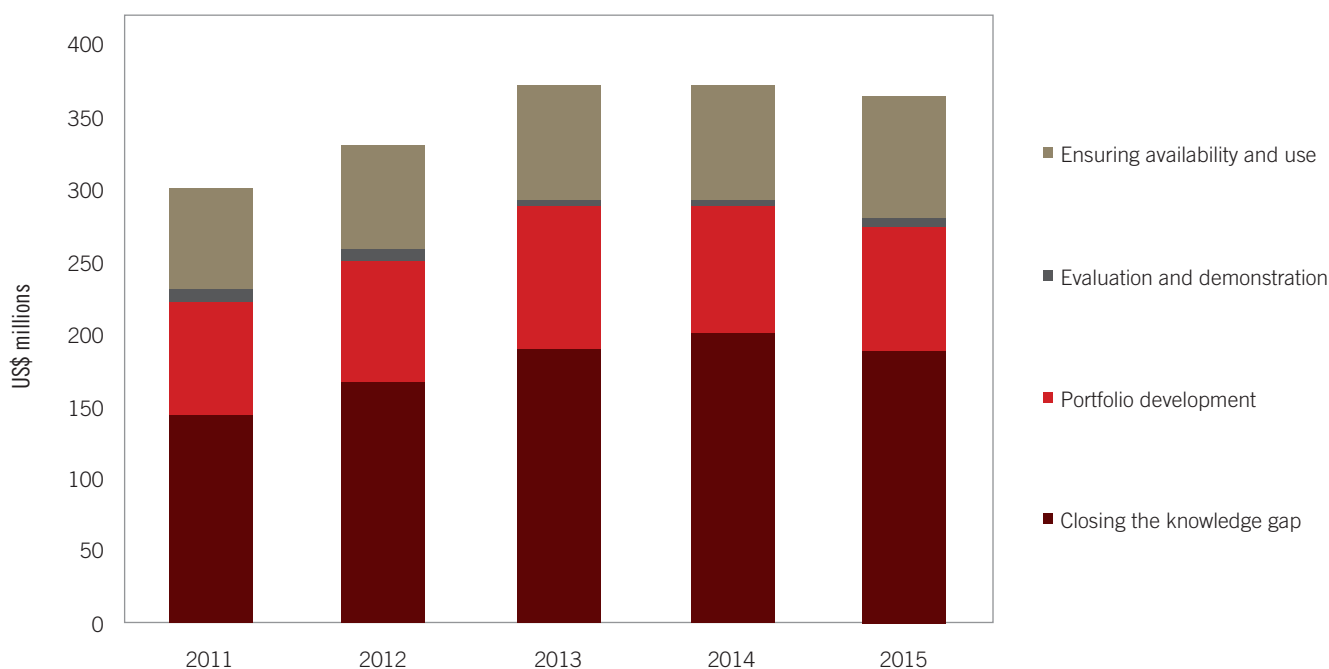
There is often a significant delay between the emergence of new tools, related policy development and their uptake at country level. Operational and impact assessments studies must be performed to reduce this delay and to inform on the benefits for the patient and health systems. Registration of fully validated tools needs to be accelerated in low-resource countries and laboratory capacity enhanced so as to allow implementation of new tests as appropriate. This demands harmonization of regulatory requirements for TB diagnosis through wide consultation of stakeholders (regulatory bodies, manufacturers and public health agencies) and supporting studies that create confidence in such a harmonized approach.

Further details are shown in the corresponding strategic framework 2011–2015 (pp66–67).

## FUNDING REQUIREMENTS

The search for the new diagnostics that are essential to boost TB control worldwide requires increased funding. It is estimated that in the five years 2011–2015 a total of US\$ 1.7 billion is required, increasing from US\$ 300 million in 2011 to just over US\$ 364 million in 2015 (Figure 29). Experience to date indicates that much more upstream fundamental and discovery research is needed to keep the development pipeline filled with candidate diagnostics ('omics' and biomarker identification). Due to attrition during the selection and assessment processes, substantially more candidates must be identified to deliver the required number of validated, and later fully evaluated, tests. This requires a wider resource of good quality bio-banks, which are very expensive to maintain. Policy and guideline formulation also now requires a more substantial evidence base to support change, such as evaluation of patient outcomes, health service needs and impact assessment.

FIGURE 29 FUNDING REQUIRED FOR NEW DIAGNOSTICS



## NEW DIAGNOSTICS: STRATEGIC FRAMEWORK, 2011–2015

VISION: COST-EFFECTIVE AND APPROPRIATE NEW DIAGNOSTIC TOOLS MAKING A MAJOR CONTRIBUTION TOWARDS BETTER CONTROL OF THE GLOBAL TB EPIDEMIC AND HIGHER QUALITY PATIENT CARE

GOAL AND OBJECTIVES	MAJOR ACTIVITIES	INDICATOR(S)	BASELINE (2010)	TARGET FOR 2015
<p><b>Goal:</b> To increase detection of active TB at point-of-care level, diagnose latent TB infection, predict disease progression, and screen for multidrug- and extensively drug-resistant TB, HIV-associated TB and paediatric TB.</p>	<p>Discovery science to identify new markers with improved discriminative power for active disease, future progression to active disease and new markers of drug resistance for first and second-line drugs; build/improve capacity for discovery research; development of specific technical platforms meeting required test target specifications.</p>	Percentage of eligible cases diagnosed with active TB using tests with accuracy similar to culture but that provide results in less than a week, and which can be used in district and (to some extent) peripheral laboratories	0%	10%
		Percentage of eligible cases of active TB diagnosed using point-of-care tests that are more sensitive and simpler than smear microscopy, and as affordable	0%	1%
		Percentage of suspected new cases of drug-resistant-TB tested for drug resistance using rapid tests with accuracy similar to culture	<5%	50%
		Percentage of previously treated cases suspected to have drug-resistant-TB tested for drug resistance using rapid tests with accuracy similar to culture	<5%	90%
		Percentage of high-risk populations at risk of progressing from latent TB infection to active TB (young children, household contacts and HIV co-infected persons) diagnosed with TB infection	<1%	5%
		Number of new diagnostic markers identified	~100	325
		Number of new diagnostic markers identified and validated for	0 each	25 each
		<ul style="list-style-type: none"> <li>• active disease;</li> <li>• risk of progression to disease; and</li> <li>• drug resistance.</li> </ul>		
		Number of specimen and bio-banks established for discovery/basic research	~2	6
		Number of existing technical platforms (with chemical labels)* with improved technical and clinical performance	0	3
Number of label-free technical platforms** with improved technical and clinical performance	0	2		
Number of breakthrough point-of-care technology platforms with improved technical and clinical performance	0	2		
Number of multiplex platforms or sets of markers that can simultaneously detect TB and HIV	0	2		
<p><b>Objective 2:</b> Develop a portfolio of new diagnostic tests</p>	<p>Development of: improved tests for diagnosis of active TB, based on sputum smear microscopy and culture; new tests for diagnosis of active TB; tests for improved detection of latent TB infection; tests for prediction of disease progression risk; and tests for TB drug resistance.</p>	Number of improved tests for diagnosis of active TB that can be used in district laboratories	1	2
		Number of improved tests for diagnosis of active TB that can be used in peripheral laboratories	1	2
		Number of new tests for diagnosis of active TB that can be used in district laboratories	1	2
		Number of new tests for diagnosis of active TB that can be used in peripheral laboratories	1	2

\* diagnostic platforms with indicator systems (eg. enzyme or gold labels)

\*\* platforms that do not require indicator systems (eg. sensors)

OBJECTIVES (CONTINUED)	MAJOR ACTIVITIES	INDICATOR(S)	BASELINE (2010)	TARGET FOR 2015
		<p>Number of point-of care tests for diagnosis of active TB that can be used in health centers</p> <p>Number of new tests developed for detection of latent TB infection</p> <p>Number of new point-of-care tests (sputum- and non-sputum-based) to predict the risk of disease progression</p> <p>Number of new tests for drug resistance that can be used in district laboratories</p> <p>Number of new tests for drug resistance that can be used in peripheral laboratories</p> <p>Number of new point-of-care tests for drug resistance that can be used in health centres</p>	<p>0</p> <p>2</p> <p>0</p> <p>0</p> <p>0</p> <p>0</p>	<p>2</p> <p>2</p> <p>1</p> <p>2</p> <p>1</p> <p>1</p>
<p><b>Objective 3:</b> Evaluate the portfolio of new diagnostic tools, demonstrate patient benefit and predict likely impact</p>	<p>Improvement in capacity for evaluation trials; evaluation in clinical trials (in synergy with drug and vaccine groups); evaluations specifically in paediatric populations and TB/HIV co-infected populations; demonstration projects, including assessment of the incremental value of tests, algorithms, and patient outcomes; prediction of the impact of improved diagnostics on the TB detection rate and access to appropriate treatment, including equity and poverty analysis; and update of relevant market analyses and needs assessments.</p>	<p>Number of evaluations in clinical trial settings conducted in high-burden countries, including studies on active and latent TB, TB/HIV and drug-resistance testing</p> <p>Number of clinical trial sites established or maintained for evaluation trials</p> <p>Number of evaluations conducted in paediatric and TB/HIV co-infected populations</p> <p>Number of demonstration projects in clinical trials settings conducted in high burden countries</p> <p>Number of demonstration projects including children</p> <p>Number of clinical trial sites established or maintained for demonstration projects</p> <p>Number of publications demonstrating patient benefit and cost-effectiveness of TB diagnostics (including modeling studies)</p> <p>Number of high-burden settings in which patient benefit and cost-effectiveness studies have been conducted</p> <p>Number of market analyses and needs assessments conducted</p>	<p>~7</p> <p>30</p> <p>3</p> <p>8</p> <p>0</p> <p>20</p> <p>16</p> <p>10</p> <p>3</p> <p>~5</p> <p>10</p> <p>7</p> <p>4</p> <p>1</p> <p>10</p>	<p>10</p> <p>60</p> <p>6</p> <p>12</p> <p>2</p> <p>80</p> <p>&gt;36</p> <p>36</p> <p>6</p> <p>25</p> <p>25</p> <p>25</p> <p>8</p> <p>30</p> <p>20</p>
<p><b>Objective 4:</b> Ensure that fully validated new diagnostic tools are widely available and appropriately used in endemic countries</p>	<p>Accelerated registration of fully validated tools, enhanced population coverage and support for lab capacity through deployment of new tests; catalysis of national and international policy changes reflecting impact evidence on new diagnostics and strengthen dissemination of information on new tests and recommendations through communication to stakeholders (e.g., NTPs, Ministries of Health, technical, procurement and funding agencies); sensitization of stakeholders to new diagnostic tools through advocacy communication and social mobilization; operational research on how best to deliver diagnostic services in routine programmatic settings, and estimation of costs and resources used by NTPs; and scale-up of manufacturing for demonstration and implementation.</p>	<p>Number of countries with streamlined (harmonized) regulatory procedures for new diagnostics</p> <p>Number of countries in which national TB programmes (NTPs) have adopted recommended policy changes on new diagnostics at district and peripheral levels</p> <p>Number of countries where relevant quality-assurance procedures for new diagnostics are being implemented</p> <p>Number of new WHO policies on TB diagnostics implemented by NTPs in high-burden countries</p> <p>Number of procurement mechanisms that include new, fully-validated diagnostic tools</p> <p>Number of operational research studies related to delivery and implementation in country-specific programmatic settings</p>	<p>~5</p> <p>10</p> <p>7</p> <p>4</p> <p>1</p> <p>10</p>	<p>25</p> <p>25</p> <p>25</p> <p>8</p> <p>30</p> <p>20</p>

### 3. NEW DRUGS

#### INTRODUCTION: TARGETS AND PROGRESS TO DATE

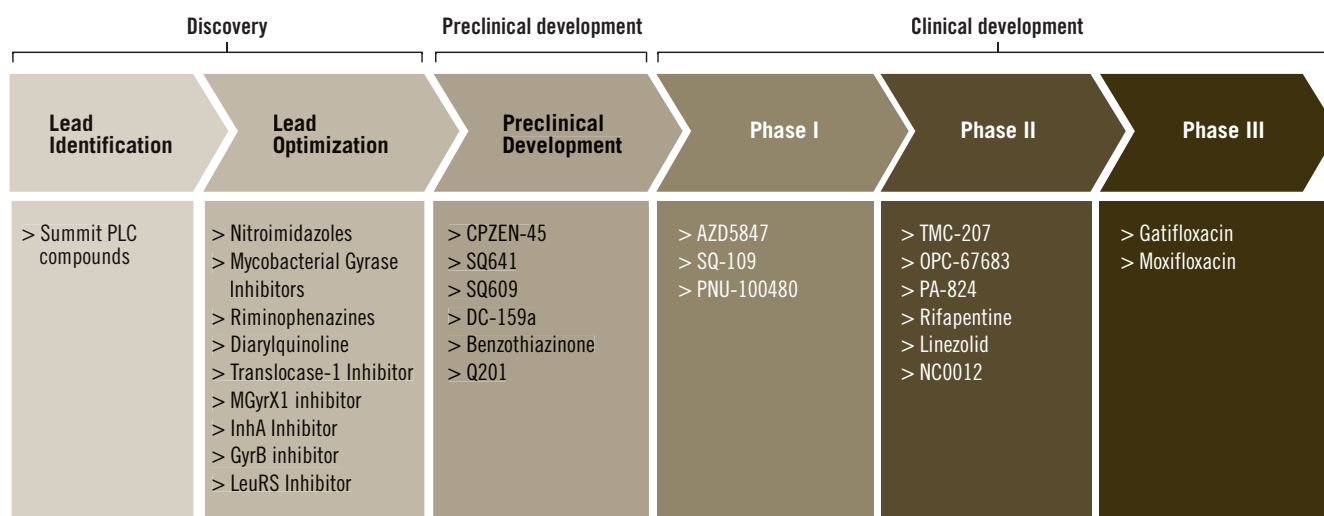
Current treatment of TB is based on drugs that are over 40 years old. Despite its demonstrated efficacy in clinical trials, standardized 6-month chemotherapy of active drug-susceptible TB requires direct supervision in order to ensure adequate treatment adherence and prevent drug resistance. In addition, despite TB remaining the leading cause of death in HIV-infected people in the developing world, treatment of co-infected people is difficult, due to potentially severe drug-drug interactions between rifampicin and some antiretroviral therapy drugs (ART), particularly the protease inhibitors used to treat HIV infection. Drugs that are active against drug-resistant forms of TB are less potent, more toxic, and need to be taken for a long time (at least 18 months). Shorter and simpler regimens that are safe, well tolerated, effective against drug-susceptible and drug-resistant TB, appropriate for joint treatment with ART, children-friendly and amenable to routine programmatic conditions, are all needed urgently. The Global Plan calls for more concerted action to develop and introduce new drugs, preferably with novel mechanisms of action. This would allow the development of shorter TB regimens for both drug-susceptible and drug-resistant disease that are

affordable and easier to manage in the field than the current treatment regimens.

The main targets for development of new drugs in the *Global Plan to Stop TB 2006–2015* were that a novel TB drug would be introduced by 2010, and that the duration of treatment for drug-susceptible TB would be reduced to 3–4 months by 2010 and to 1–2 months by 2015.

While these targets were not met, significant progress has been made over the last five years, and for the first time in 40 years there is a coordinated portfolio of promising new compounds on the horizon, some of which have the potential to become the cornerstone drugs of TB control and possibly to help eliminate TB. Currently there are at least eleven new or repurposed TB drugs under clinical investigation (Figure 30). Of these three are in Phase I (safety) trials, six are in Phase II (early bactericidal activity and sputum culture conversion) trials, and two are in Phase III (efficacy) trials. Progress is also being made ‘upstream’. At least six TB drug candidates are in preclinical development and at least 10 additional candidates and/or screening campaigns to identify new targets/compounds are in the discovery phases.

FIGURE 30 THE DEVELOPMENT PIPELINE FOR NEW DRUGS, 2010



Note: 1) This table only includes projects that have identified a promising molecule (known as a "lead" compound).

2) When this plan went to press, NC001 (which combines PA-824, moxifloxacin, and pyrazinamide) was the first novel TB drug combination regimen being tested at the Phase II stage.

Source: *Stop TB Partnership Working Group on New Drugs - 2010*

To ensure that large-scale multi-centre clinical trials can be carried out according to international requirements, parallel efforts are underway for capacity building and infrastructure development in several endemic countries. These include many African countries (e.g. Benin, Cameroon, Guinea, Kenya, Mozambique, Senegal, South Africa, the United Republic of Tanzania and Zambia), and also China, India, Mexico, Peru, South Korea and Vietnam among others.

On the access and delivery side, in August 2009 the TB Alliance published an analysis entitled *New TB regimens: what countries want* that explores how decision-makers prioritize various factors when evaluating the adoption of new TB regimens.<sup>41</sup> Work is also being carried out by the newly-created Introducing New Approaches and Tools (INAT) subgroup of the Partnership's DOTS Expansion Working Group. This group provides support to countries to ensure that they receive relevant and timely information, as well as technical assistance, to enable the rapid introduction of new tools and approaches for TB prevention and control.

The recent formation of the Critical Path to New TB Drug Regimens (CPTR) Initiative is also a significant step forward in TB drug development. This broad coalition of stakeholders, spearheaded by the Bill and Melinda Gates Foundation, the TB Alliance and the Critical Path Initiative – and including virtually all pharmaceutical companies with compounds for TB treatment in clinical trials – is dedicated to speeding up the development of novel regimens that have a significant impact on shortening the treatment of both drug-sensitive and drug-resistant TB.

## OVERVIEW OF PLAN GOAL, OBJECTIVES, TARGETS AND ACTIVITIES

The goal of the new drugs component of the Global Plan to Stop TB 2011–2015 is to develop and introduce new TB drugs and drug combinations that will result in shorter, safer, more effective and

accessible treatment regimens that cure all forms of TB, are compatible with ART, suitable for children, effective against latent TB infection (LTBI), affordable and easily managed in the field.

If research and development in new TB treatments is significantly enhanced and amplified according to the strategic framework on pp74–75, the following achievements are expected by 2015:

- a new four-month TB treatment regimen – including one new or repurposed drug approved by regulatory authorities for drug-sensitive TB – will be recommended by WHO and available for use;
- two new drugs will be approved by regulatory authorities for drug-sensitive TB;
- at least one new drug for the treatment of drug-resistant TB will be introduced into the market;
- a nine-month regimen for the treatment of drug-resistant TB – including at least one new drug – will be in a Phase III trial;
- a safer, higher-efficacy regimen will be available for treatment of latent TB infection;
- fixed-dose combinations (FDCs) for first-line drugs (including new drugs) will be available and in use;
- child-friendly first-line TB drug formulations will be under development.

In addition, it is expected that activities will be well underway towards the following achievements by 2020:

- at least one 1–3 month regimen – including one or more new or repurposed approved drugs – in clinical development;
- clinical trials for three new TB drug regimens for drug-susceptible TB – including one or more new or repurposed drugs – in progress;
- clinical trials for two new drug regimens for drug-resistant TB – including one new or repurposed drug – in progress;
- TB regimens compatible with ART in late-stage clinical trials.

<sup>41</sup> *New TB regimens: what countries want: The Value Proposition of Existing and New First-Line Regimens for Drug-Susceptible Tuberculosis*. New York, Global Alliance for TB Drug Development, 2009. ([http://www.tb Alliance.org/downloads/publications/TBA\\_VPSreport\\_final\\_flat.pdf](http://www.tb Alliance.org/downloads/publications/TBA_VPSreport_final_flat.pdf), accessed 6 September 2010)

The eight major objectives for new drugs are defined and explained below.

**Objective 1: Increase discovery research in order to substantially expand the pipeline of new TB drug candidates.**

It is estimated that, at best, only one in ten drug candidate that enters clinical trials eventually advances to registration, and there is no assurance that current TB drug candidates and regimens will prove effective enough to be used in novel combinations. A robust and sustained pipeline of new candidates, and back-up discovery programmes, are therefore essential to deliver entirely new regimens based on sound and innovative molecular research. A solid knowledge base on *M. tuberculosis*, as well as the natural history and pathology of TB in humans, are critical for the discovery of new drug candidates. To achieve the objective of radical treatment shortening, validated drug targets relevant to persistent *M. tuberculosis* are required. The identification of surrogate markers of treatment activities will also contribute to shortening the duration of clinical trials.

**Objective 2: Build and maintain the trial site capacity necessary to support trials for drug-sensitive and drug-resistant TB, as well as latent TB infection.**

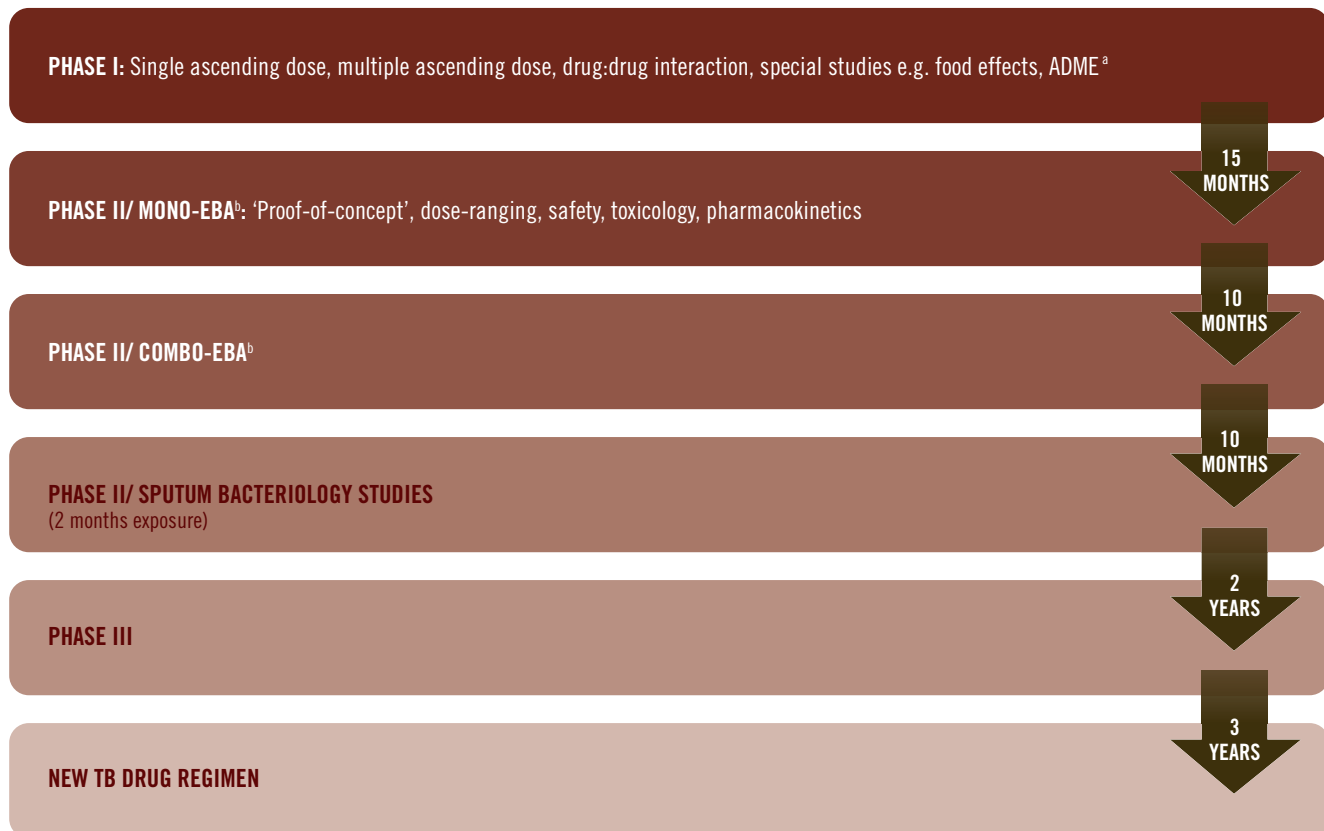
One of the main challenges in TB drug development is the lack of global clinical trial capacity to conduct late-stage controlled trials. These are needed to support the registration of compounds in clinical development. Multiple trial sites are necessary to ensure sufficient enrolment in drug trials and to take into account regional variations. As more drug candidates enter clinical trials as a result of intensified TB drug discovery, it is essential to invest broadly in knowledge transfer, structural upgrading and capacity building to expand the number of sites in endemic countries that are capable of conducting trials that are compliant with international good clinical and good laboratory practice standards. It is also critical to build and maintain existing clinical trial capacity, as many sites are situated in low- and middle-income countries that often lack adequate institutional support. Since the efficacy and safety

of a wide variety of drug regimens/combinations will have to be tested in different populations (including HIV-infected people on ART and MDR-TB patients), a large number of highly-performing clinical trial sites is urgently needed in various countries. This includes the possibility of evaluating and including currently HIV-focused trial sites in order to determine if TB drug trials can be conducted with minimal adjustments. Lastly, it is essential that the communities in which clinical trials will be conducted are fully informed and involved in the preparation and running of trials through specifically set-up Community Advisory Boards.

**Objective 3: Develop a shorter drug regimen for drug-sensitive TB that can be used in combination with HIV treatment.**

In mid-2010, eleven new drugs were in clinical development, which will likely lead to two newly-approved drugs by 2015. Given both the high attrition rate and the inherent lag from pre-clinical phases to ultimate approval, generating five new or repurposed drugs and at least one 1–3 month regimen by 2020 will require an estimated 21 additional new drugs to be in clinical development by 2015. As treatment of TB is based on combinations of drugs, it is essential to start investigating the safety and efficacy of new regimens including new or repurposed drugs early enough in the clinical development pathway, so as to decrease the duration of drug development and hasten the introduction of new drug regimens. Preclinical and early clinical data on novel drugs help to determine whether they display the necessary characteristics of safety and effectiveness in humans. Early bactericidal activity (EBA) studies of single drugs and combinations of drugs, in association with Phase II sputum microbiology studies, will inform the advancement of potential drug combinations to further clinical development phases (Figure 31). In parallel, studies of drug-drug interactions between new TB drugs and ARVs must also be started early in the drug development pathway.

FIGURE 31 REVISED CONCEPT OF DRUG DEVELOPMENT INTEGRATING IDENTIFICATION OF DRUG COMBINATION REGIMENS



<sup>a</sup>ADME - Absorption, Distribution, Metabolism, and Excretion

<sup>b</sup>EBA - Early Bactericidal Activity

Source: Global Alliance for TB Drug Development

**Objective 4: Develop a safer, higher-efficacy and shorter regimen for drug-resistant TB, that is compatible with HIV treatment.** New drugs, especially those with novel mechanisms of action, can form the core of novel shortened regimens for the treatment of drug-resistant TB. While new drug candidates are being tested in superiority trials in MDR-TB patients, Phase II trials of drug combinations have to be carried out early to identify suitable combinations of drugs that offer significant advantages over the present regimen, and that should go on to be tested in Phase III trials. These large-scale trials need to be conducted in a series of sites in high MDR-TB burden areas to ensure sufficient and timely enrolment. Determination of appropriate combination regimens also requires various pharmacokinetic (PK) and drug-drug interaction studies.

**Objective 5: Develop safe, reliable and user-friendly drug regimens that are suitable for treating all forms of TB in children and compatible with HIV treatment.** All drugs that are used in adults should also be tested in children. Because children frequently metabolize drugs in different ways from adults, PK studies are required to examine the distribution of various drugs and formulations in children, in order to ensure that treatment can be fully adapted to them and, if possible, made available in fixed-dose combination formulations. Drug-drug interaction studies with current first- and second-line TB drugs, as well as potential new drugs and ART drugs are also necessary.



**Objective 6: Develop safer, higher-efficacy regimens for latent TB infection that are compatible with HIV treatment and suitable for children.**

The central target for TB control is to cut disease transmission from person-to-person through early and efficient treatment of infectious TB cases. An additional target, however, is to prevent active TB in people who are infected with *M. tuberculosis* and who have a high risk of progression to active disease such as children or people living with HIV. Clinical guidelines currently recommend the preventive use of isoniazid for at least six months, although this presents a number of practical and operational challenges, especially in high-burden countries. Clinical trials are needed to evaluate the safety and efficacy of novel drugs or drug regimens for the prevention of active TB among people who are latently infected.

**Objective 7: Ensure the availability of clear and efficient regulatory guidelines for approval of new TB drugs and regimens, from development to registration of drugs.**

Many TB-endemic countries lack adequate regulatory capacities for reviewing and approving the testing of new drugs in clinical trials, or for approval of new drugs or regimens. This presents a serious challenge to essential demonstration trials in high-burden countries. New strategies are needed for establishing efficient regulatory processes for testing and approving new TB drug regimens, through adequate forums and technical assistance to national regulatory agencies.

**Objective 8: Ensure adoption of new TB drugs and regimens at the country level.**

End-user demand for new TB drugs and regimens is critical to efforts to increase global support and investment. Global, country and community support for new TB drug development is essential to increase investment in TB research and to gain support in clinical trial settings, so that new drugs and regimens are integrated into national policies and guidelines, and used. This requires research on what influences national decision-making on adoption of new drugs or regimens, distribution channels, market structure, community involvement, etc. Drug marketing analyses are also required to advocate for acceptability of new TB drugs and regimens, as well

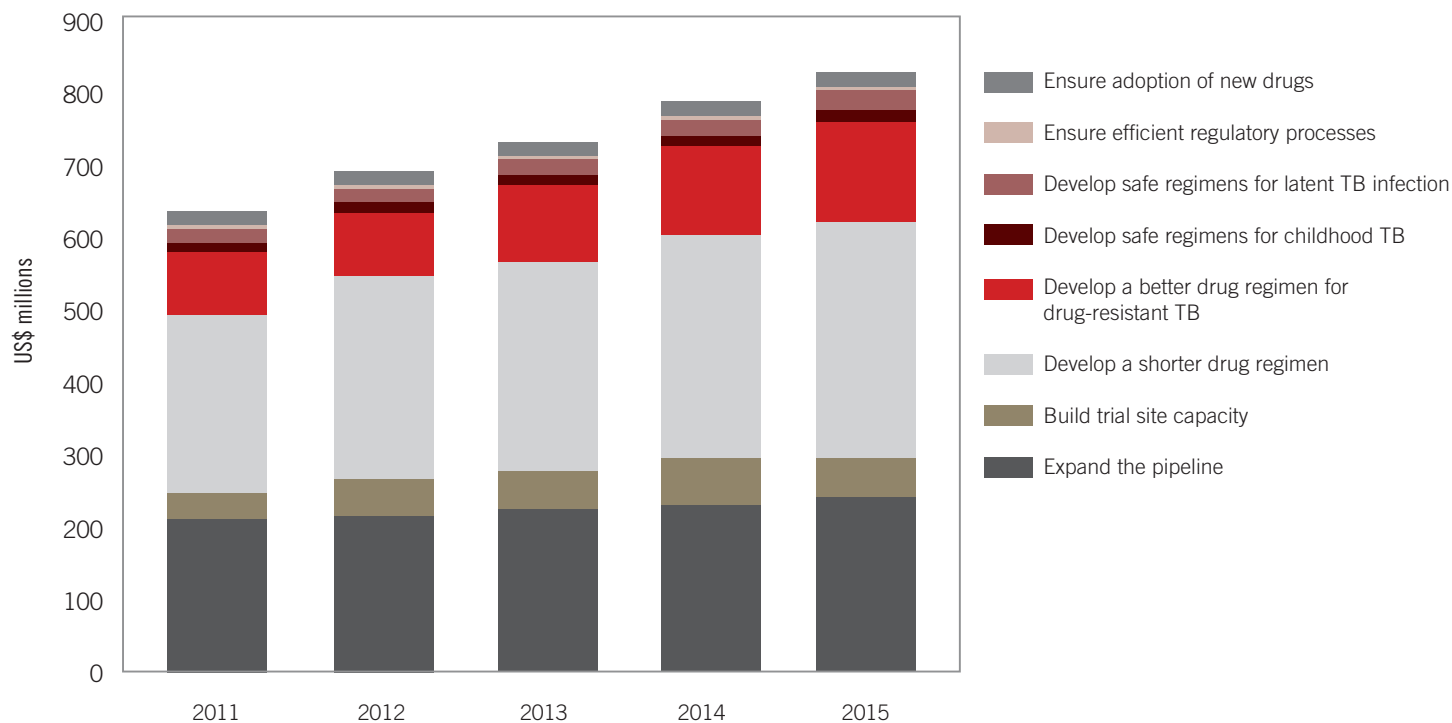
as to ensure that drugs are affordable. In this respect, global policy advocacy efforts are critical to ensuring equitable access and assured quality of TB drugs in high-burden countries.

Further details are shown in the corresponding strategic framework for 2011–2015 (pp74–75).

## FUNDING REQUIREMENTS

It is estimated that in the five years 2011–2015 a total of US\$ 3.7 billion is required, increasing from US\$ 0.6 billion in 2011 to US\$ 0.8 billion in 2015 (Figure 32). Although the characteristics and requirements of TB drug development make the cost of bringing new TB drugs and regimens to market significant, the estimation presented here is a conservative one by pharmaceutical industry standards. The lack of good biomarkers for either drug efficacy or cure requires clinical trials to be lengthy and include relatively large patient cohorts. This is especially true in studying treatments for MDR-TB and latent TB infection. Using current drugs and regimens, MDR-TB patients must be treated for at least 18 months and then followed-up for a long period; controlled clinical trials are lengthy and expensive due to high costs of drugs, patient care, follow-up and use of costly mycobacteriology tests. The conduct of clinical trials to internationally acceptable standards requires that trial sites be adequately equipped to recruit and care for patients, as well as to collect, store and analyze large amounts of clinical samples and data. Because TB is a global disease that is present in a wide variety of epidemiological and environmental contexts, clinical trials need to be carried out in a wide range of settings, adding costs and complexity to clinical development programmes.

FIGURE 32 FUNDING REQUIRED FOR NEW DRUGS



## NEW DRUGS: STRATEGIC FRAMEWORK, 2011–2015

VISION: NEW TREATMENTS FOR ALL FORMS OF TB ARE AVAILABLE, WIDELY USED AND MAKING A MAJOR CONTRIBUTION TO THE ELIMINATION OF TB

GOAL AND OBJECTIVES	MAJOR ACTIVITIES	INDICATOR(S)	BASELINE (2010)	TARGET FOR 2015
<p><b>Overall goal:</b> To develop shorter TB regimens that cure all forms of TB, are compatible with antiretroviral therapy (ART), suitable for children, effective against latent TB infection, affordable and easily managed in the field</p> <p><b>Objective 1:</b> Increase discovery research in order to substantially expand the pipeline of new TB drug candidates</p> <p><b>Objective 2:</b> Build and maintain the trial site capacity necessary to support trials for drug-sensitive and drug-resistant TB, as well as latent TB infection</p> <p><b>Objective 3:</b> Develop a shorter drug regimen for drug-sensitive TB that can be used in combination with treatment for HIV</p>	<p>Discovery research to identify new drugs, including new targets; discovery research to improve knowledge of <i>M. Tuberculosis</i>, in particular the mechanism(s) of persistence; discovery research to identify biomarkers of treatment efficacy</p> <p>Maintain existing GCP/GLP** -compliant trial sites and build new ones</p> <p>Phase I trials</p> <p>Phase II EBA** trials for single drugs</p> <p>Phase II Combination (combo) EBA trials</p> <p>Phase II SSSC**</p> <p>Phase III trials</p> <p>Drug-interaction studies on new regimens with standard antiretroviral drugs (ARVs)</p> <p>FDC** formulation development; non-clinical development (PD/PK**, toxicology); regulatory activities; other support activities and potential other costs (business, strategy, project management); safety monitoring and post-launch; chemistry, manufacturing, control (CMC) work</p>	Number of four-month regimens approved, recommended by WHO and available for use	0	1
		Number of new drugs for drug-susceptible TB drugs approved	0	2
		Number of new drugs for drug-resistant TB approved	0	1
		Number of nine-month regimens for drug-resistant TB treatment in late-stage clinical trials	0	1
		Number of safer, higher-efficacy regimens for treatment of latent TB infection	0	1
		Number of fixed-dose combinations (FDCs) of first-line drugs including new drugs available and in-use	0	1
		Number of child-friendly first-line drug formulations in development	0	1
		Number of biomarker(s) identified for treatment efficacy	2	5
		Number of GCP/GLP-compliant sites	~60*	100
		Number of new/repurposed drugs in Phase I trials	3	21
Number of new/repurposed drugs in Phase II EBA trials	6	15		
Number of combinations of drugs in Phase II combo EBA trials	1	10		
Number of Phase II SSSC trials testing new/repurposed drugs	0	8		
Number of new regimens in Phase III trials	2	3		
Number of drug interaction studies on new regimens with standard ARVs	2	12		
Number of drug candidates in Phase I trials	3	21		
Number of drug candidates in Phase II EBA trials	7	25		
Number of drug candidates in Phase II SSSC trials	0	8		
Number of drug candidates in Phase III trials	2	3		
Number of drug candidates post-approval	0	2		

OBJECTIVES (CONTINUED)	MAJOR ACTIVITIES	INDICATOR(S)	BASELINE (2010)	TARGET FOR 2015
<b>Objective 4:</b> Develop a safer, higher-efficacy and shorter regimen for drug-resistant TB, that is compatible with treatment for HIV	Phase II trials of drug combinations Phase II SCCC studies of drug combinations Phase III trials of shorter combined regimens for drug-resistant TB Drug-interaction studies of drugs for treatment of drug-resistant-TB in clinical development with at least 3 other second-line TB drugs	Number of new combinations of drugs in Phase II EBA trials Number of new combinations of drugs in Phase II SCCC trials Number of new shorter regimens for drug-resistant TB in Phase III trials Number of interaction studies of drugs for treatment of drug-resistant-TB	2 0 0 3	10 3 2 12
<b>Objective 5:</b> Develop safe, reliable and user-friendly drug regimens that are suitable for treating all forms of TB in children and are compatible with treatment for HIV	PK studies; drug interaction studies; clinical trials; FDC development	Number of PK studies for first-line, second-line and new drugs Number of drug-interaction studies Number of clinical trials Number of FDCs available and in use	4 4 2 3	13 20 10 4
<b>Objective 6:</b> Develop safer, higher-efficacy regimens for the treatment of latent TB infection (LBTI) that are compatible with treatment for HIV treatment and suitable for children	Phase III clinical trials for drug-susceptible-LBTI**	Duration of regimen for LBTI (in months)	4–6	2–3
<b>Objective 7:</b> Ensure the availability of clear and efficient regulatory guidelines for the approval of new TB drugs and regimens, from development to registration of drugs	Regulatory approval process; technical assistance to national regulatory agencies; produce publications and congressional/country-specific governmental briefings	Number of drug regulatory approvals with endorsement of new regimen(s) by WHO	0	3
<b>Objective 8:</b> Ensure the adoption of new TB drugs and regimens at country level	Research on country-relevant issues that affect decisions on the adoption of new drugs/regimens, distribution channels, market structure, public-private mix approaches, etc.; demonstration projects and locally-relevant operational research; prequalification; global level guidelines and regulation (essential medicines list); advocacy; training of health care staff; branding	Number of new drugs/regimens included in national policy and guidelines Percentage of TB patients treated with new drugs/regimens	0 0	4 >10%

\* Only a proportion of these sites were GCP- and GLP-compliant in 2010.

\*\* Abbreviations: GCP – good clinical practice; GLP – good laboratory practice; FDC – fixed-dose combination; PD – pharmacodynamics; PK – pharmacokinetics; EBA: Early Bactericidal Activity, SCCC : Serial Sputum Colony Counts, LBTI – latent TB infection

## 4. NEW VACCINES

### INTRODUCTION: TARGETS AND PROGRESS TO DATE

Today's TB vaccine, BCG, was developed almost 90 years ago and is routinely given to infants in much of the world. While it provides some protection against severe forms of paediatric TB, it is unreliable against adult forms of pulmonary TB. In addition, BCG is not recommended for use in infants infected with HIV, due to the risk of disseminated BCG disease. There is an urgent need for modern, safe and effective vaccines that prevent all forms of TB, in all age groups and among people with HIV. A great deal of progress has been made in TB vaccine research over the past five years that has strengthened the pipeline of TB vaccine candidates and provided valuable information on TB vaccine development. According to recent modelling studies, the introduction of new effective TB vaccines and vaccination strategies will make a crucial contribution to achieving the Partnership's goal to reduce the global incidence of TB disease to less than one case per million population by 2050, and development of new vaccines to protect against TB is gaining substantial momentum.

Historic opportunities arose in 2000 for development of new TB vaccines, resulting from the availability of techniques for the genetic manipulation of mycobacteria, and completion of the genome sequence of *M. tuberculosis*. These advances have been critical for the construction of new live genetically altered mycobacterial vaccines, viral-vectored vaccines and sub-unit vaccines composed of recombinant antigens. In parallel, advances were being made in understanding the cellular and molecular mechanisms underlying protective immunity in humans, as well as the development of animal models and immunoassays for TB. In the past decade, progress in TB vaccine development has included advancing candidates into clinical trials, maintaining a robust TB vaccine candidate pipeline, developing capacity for large-scale trials and for vaccine production, as well as raising awareness and support for new TB vaccines.

The main target for vaccine development in the *Global Plan to Stop TB 2006–2015* was that two vaccines would be in proof-of-concept trials by 2010 and that one new and safe vaccine would be available by 2015.

As of 2009, 12 TB vaccine candidates had entered clinical trials. Of these, nine are still being tested: five are in Phase I (safety) clinical trials, two are in Phase II trials, and two are in Phase IIb 'proof-of-concept' trials (Figure 33). One vaccine has produced estimates of safety and effectiveness in a targeted HIV-infected population. At least six TB vaccine candidates are in preclinical development,<sup>42</sup> and at least 21 additional next generation candidates are in the vaccine discovery phase.<sup>43</sup> In addition to the development of new TB vaccine candidates, research is also underway to evaluate new delivery platforms that would be affordable and suitable for resource-limited settings, including needle-free delivery.

Next generation candidates are defined as TB vaccine candidates that are in the research and development stage with some preclinical testing performed to show that they may confer protection.

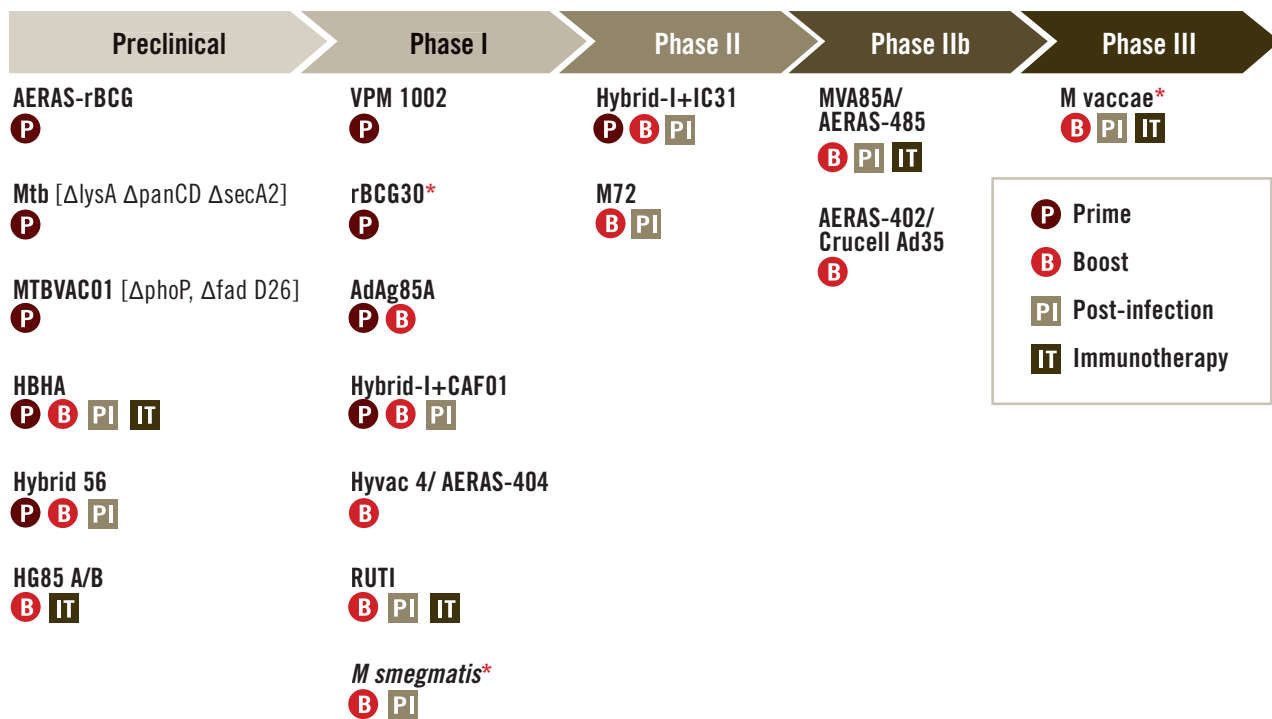
Capacity and infrastructure for large-scale clinical trials are being developed at various sites in several endemic countries. The most advanced of these sites, located in South Africa – and operated by the South African Tuberculosis Vaccine Initiative – is conducting clinical trials of several vaccine candidates, and initiated the first Phase IIb 'proof-of-concept' trial of a preventive vaccine in infants in July 2009. In parallel, epidemiological cohort studies in infants and adolescents are underway in several countries that will provide important baseline TB incidence data and help determine the suitability of sites for large-scale efficacy trials.

In order to ensure an ample supply of quality candidate vaccines for clinical trials and to minimize the lag time between licensure and worldwide distribution, it is imperative to invest in vaccine manufacturing capacity. Currently, some capacity exists in both

<sup>42</sup> Candidates in preclinical development are defined as TB vaccine candidates that are not yet in clinical trials, but have been manufactured under good manufacturing practice (GMP) for clinical use and have undergone some preclinical testing that meets regulatory standards.

<sup>43</sup> Next generation candidates are defined as TB vaccine candidates that are in the research and development stage with some preclinical testing performed to show that they may confer protection.

FIGURE 33 THE DEVELOPMENT PIPELINE FOR NEW VACCINES, 2010



Preclinical vaccine candidates are not yet in clinical trials, but have been manufactured under Good Manufacturing Practice (GMP) for clinical use and have undergone some preclinical testing that meets regulatory standards.

\*indicates candidates that have been in clinical trials in the past, but are not currently being tested in clinical trials

Source: *Tuberculosis Vaccine Candidates – 2010*; Stop TB Partnership Working Group on New Vaccines, Geneva, World Health Organization, 2010.

the private and non-profit sectors, but additional investment will be needed in order to meet future demands for new TB vaccines. Emerging economies will play an important role in vaccine manufacture and delivery, and negotiations are taking place with several manufacturers in countries with emerging economies for production and distribution of new TB vaccines.


Efforts are also underway to implement delivery, regulatory and access strategies for TB vaccines, including the development of effective regulatory pathways that shorten review timelines without compromising the ultimate quality of vaccines. A Task Force on Economics and Product Profiles has been established to support the rapid development and deployment of new TB vaccines once they are licensed, by developing clear guidance on desired product characteristics and the likely economic impact in the context of large-scale TB programmes. A market research project is underway to provide information on potential TB vaccine markets in target countries, as

well as increase understanding of in-country decision-makers' views on procurement and integration of new TB vaccines. Strategies to harmonize regulatory review of TB vaccines in multi-country clinical trials are also under development.

## OVERVIEW OF PLAN GOAL, OBJECTIVES, TARGETS AND ACTIVITIES

The main goal of the new vaccines component of the Global Plan to Stop TB 2011–2015 is to prevent all forms of tuberculosis in all age groups through the development of safe, effective and accessible vaccines that are also safe for people with HIV.

Progress in TB vaccine research over the last five years has informed novel TB vaccine development and strengthened the TB vaccine pipeline. Although development of new TB vaccines has not been as rapid as was anticipated in 2006, due to the inherent complexity in developing biological products, current



development timelines now indicate that three new vaccines will have completed Phase IIb ‘proof of concept’ trials by 2015, and if successful, will enter large Phase III safety and efficacy trials. We can then anticipate that one or more new TB vaccines could be available by 2020. It is therefore expected that with the funding support outlined below, the full implementation of research and development activities presented here will result in a safe and effective TB vaccine that can be distributed at reasonable cost to endemic countries. Towards that end, the Stop TB Partnership Working Group on New Vaccines expects that, by 2015, the following will be achieved:

- four new TB vaccine candidates will have entered Phase III clinical trials for safety and efficacy;
- assays to determine biomarkers and correlates of immune protection will be incorporated into clinical trials;
- sufficient manufacturing capacity and licensing agreements will be in place to ensure ample supply of new TB vaccines for large-scale trials and uptake of new vaccines, once licensed, at reasonable cost;
- appropriate infrastructure and capacity will be in place at multiple sites – in endemic countries with high TB incidence, and in different regions of the world – to conduct large-scale clinical trials that adhere to international standards;
- regulatory pathways and access/delivery strategies will be developed to minimize lag time between licensure and distribution of new vaccines;
- increased public support for and increased investment in TB vaccine development will be ensured.

The seven major objectives for the new vaccines component of the Global Plan are defined and explained below.

**Objective 1: Maintain a robust TB vaccine pipeline by supporting research and discovery.**

Basic research in the fields of immunology and molecular biology is critical for the development of new TB vaccines. Although human clinical trials have begun, the types of immune response that must be induced by a vaccine to prevent TB remain largely undefined. There is no guarantee that TB vaccine

candidates currently in human clinical trials will prove effective, so it is necessary to maintain a full ‘second generation’ pipeline of vaccine candidates that are based on sound and innovative molecular and immunological research.

**Objective 2: Conduct research to identify correlates of protection, and preclinical studies to assess new TB vaccine candidates.**

There is a need to expand discovery and translational research on TB vaccines. Progress with current clinical vaccine candidates does not signal an end of discovery research, but rather provides opportunities to link fundamental research to human studies. It is likely that, as current candidates move through clinical trials, the experience gained will contribute to development of new candidates in an iterative manner. In parallel, further immunological research is needed to develop standardized preclinical and non-clinical assays for new TB vaccines, and to identify correlates of protection to be used in Phase III trials. Since BCG is commonly given at birth in many countries – and will remain the cornerstone of TB vaccination programmes over the period covered by the Global Plan – one possible approach is that new vaccines will complement the immune response induced by the current BCG vaccine. In this prime-boost strategy, new vaccines could be delivered together with BCG at an early age before exposure to *M. tuberculosis* has occurred, or as a separate booster in young adults, or even as an adjunct to chemotherapy. ‘Improved’ BCG and attenuated live *M. tuberculosis* vaccines are being developed and should be studied as replacement vaccines that can also be used in a prime-boost strategy. These new ‘prime’ vaccines are intended to be more effective and safer for use in infants with HIV than BCG. Pre-clinical studies of prime-boost immunization strategies and of new vaccine delivery platforms, as well as preclinical assessments of safety and toxicity, are important prerequisites to preparing for human clinical trials.

**Objective 3: Ensure availability of vaccine production capacity by expanding manufacturing facilities for TB vaccines.**

Adequate manufacturing capacity must exist in order to ensure quality and consistent production of investigational vaccines for large-scale efficacy trials, which can involve tens of thousands of participants. It takes 4–5 years to build a vaccine manufacturing facility and prepare it for commercial production. Some already exists, but investment is necessary to ensure that vaccines are available in areas that need them most, and as quickly as possible after licensure, adequate manufacturing capacity must be developed. Some manufacturing capacity already exists, but investment is needed to ensure that vaccines can be manufactured to meet international regulatory standards and ensure sufficient size for production and worldwide distribution. Manufacturing of live TB vaccines such as a modified BCG or attenuated *M. tuberculosis* presents a particular challenge since it may require dedicated facilities and staff. Activities towards this objective include expanding capacities of existing facilities to produce new TB vaccines, with a particular emphasis on plants in emerging economies. Transfer of vaccine technologies to production units in countries with emerging economies may facilitate vaccine uptake in low- and middle-income regions. In parallel, increasing capacity to produce new vaccine delivery platforms (e.g. aerosol, capsids, airjet, etc) needs to be explored.

**Objective 4: Build capacity for large-scale clinical trials (Phases II and III) of TB vaccine candidates at field sites in TB endemic countries.**

Large-scale vaccine trials need to be conducted in areas with a high burden of disease as incidence of disease must be sufficient to determine efficacy of a vaccine and its safety in large populations. Epidemiologic research is needed in key target groups of interest for new TB vaccines, including infants, adolescents, and people living with HIV. Multiple trial sites are necessary



to ensure sufficient enrolment of individuals for a licensure trial and to address immunological and other responses that may vary by region. Multi-centred trials also improve acceptability by countries once the product is registered. Large-scale efficacy and licensure trials require appropriate capacity and infrastructure to enrol, monitor, diagnose and follow-up such a high level of participation. They also require access to accredited microbiological and immunological laboratories, staff that are trained in good clinical practice (GCP), clinical experience with trials and TB diagnosis, radiological expertise and quality control mechanisms.

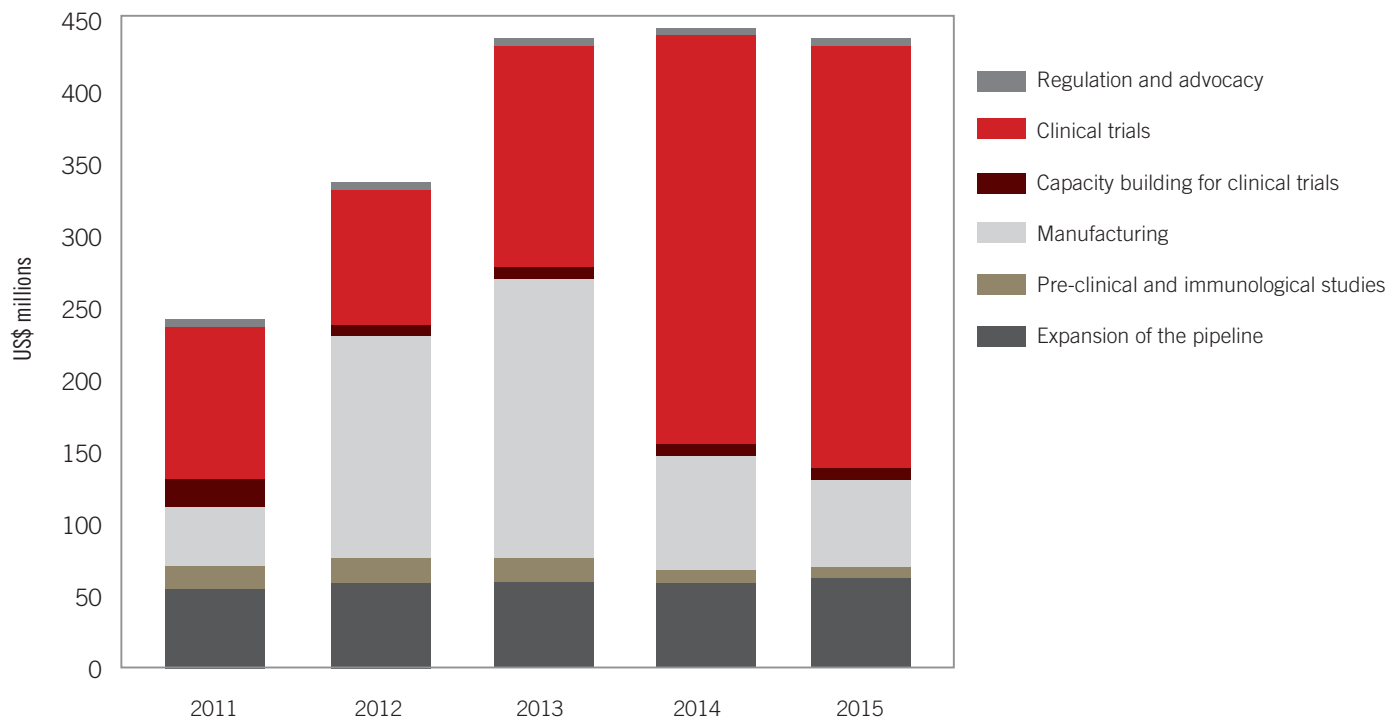
**Objective 5: Conduct Phases I, II and III clinical trials of TB vaccine candidates.** Evaluation of vaccine candidates requires a series of clinical trials of increasing size, complexity and cost, to progressively evaluate safety, immunogenicity and, finally, efficacy. Clinical trials – and particularly large-scale Phase III efficacy trials – are the most costly component of TB vaccine research. Ensuring investments in clinical studies is a major challenge for TB vaccine research. Trials need to be conducted to evaluate safety and efficacy of both prime and boost candidates in infants and children (pre-exposure), as well as in adolescents and adults and in people living with HIV (post-exposure). Trials will also be needed for new vaccine delivery strategies and platforms for TB vaccines (such as aerosol, oral and nasal delivery), as well as new manufacturing technologies (such as spray dried vaccines, currently under development). Vaccines developed with these platforms would be affordable and would also avoid challenges related to vaccine delivery in limited-resource settings. Lastly, the TB vaccine community continues to learn from the BCG vaccine experience in countries that still immunize with BCG. Particularly important are the risks of giving live TB vaccines in communities at risk of HIV/AIDS. It is therefore important to conduct research and testing to better understand BCG, which will be the current prime for many booster vaccines in development.

**Objective 6: Develop delivery, regulatory and access strategies for new TB vaccines.** The lack of adequate regulatory capacities for reviewing and approving the testing of new products in clinical trials in a number of high-burden countries represents a challenge for the timely approval of vaccine trials in developing countries. New strategies are needed for establishing efficient regulatory pathways for new TB vaccines. Studies are also needed to understand the economic and public health impact of new TB vaccines. Vaccine marketing analyses are required to advocate for acceptability of new TB vaccines and to keep vaccines affordable.

**Objective 7: Build support for TB vaccine development and uptake through advocacy, communications and resource mobilization.** Global, country and community support for new TB vaccines development is essential to increase investment in TB research and to gain support in countries where clinical trials are being conducted. End-users' demand for new TB vaccines will be critical to efforts to increase global support and investment. Communities where clinical trials will be conducted should be informed and educated about the trial and there should be opportunity for their involvement, for example through Community Advisory Boards. This support and awareness will be raised through participation in high-level forums and relevant conferences, meetings and events, stakeholder outreach, recognition of the important role of TB vaccines as part of a comprehensive response to the TB epidemic in high-level, international, national and community-led calls to action, increased media attention, and the development of materials that are suitable for the global, national, regional and community level. Lastly, support is needed for the Stop TB Working Group on New TB Vaccines to continue its mission and operations.

Further details are shown in the corresponding strategic framework for 2011–2015 (pp82–83).

FIGURE 34 FUNDING REQUIRED FOR NEW VACCINES



## FUNDING REQUIREMENTS

TB vaccine development is a complex and costly process. It is also a relatively new one, given that current efforts to develop new TB vaccines are the first in over 80 years. Much has been learned over the past decade regarding what will be required to develop new and more effective TB vaccines. Based on this knowledge and experience, it is estimated that the costs to develop new TB vaccines and ensure their availability to those who need them most will be higher than originally anticipated. It is estimated that in the five years 2011–2015 a total of US\$ 1.9 billion is required, increasing from close to US\$ 250 million in 2011 to almost US\$ 440 million in 2015 (Figure 34).

Many factors contribute to this increase in cost. The lack of a suitable correlate of immune protection against TB means that more and lengthier trials with large numbers of participants will be needed in

order to sufficiently test and license new candidates for different target populations, and in various geographical regions. Recent epidemiology studies have provided important baseline incidence data to better determine the necessary size, cost estimates and infrastructure and capacity needs for pivotal Phase III trials. Greater experience with preclinical development, capacity-building in the field for large-scale clinical trials and manufacturing have allowed for better cost estimates to conduct this work. Downstream issues such as vaccine delivery, as well as regulatory, access and advocacy strategies to support development and eventual uptake of new TB vaccines have been identified and for the first time, are now fully accounted for in this plan. It should also be noted that the cost of maintaining BCG programmes as originally included in the Global Plan has been removed from this update, as these programmes are fully funded and do not impact the cost of TB vaccine development.

## NEW VACCINES: STRATEGIC FRAMEWORK, 2011-2015

### VISION: IMPROVED VACCINES AND VACCINATION STRATEGIES MAKING A CRUCIAL CONTRIBUTION TO ACHIEVING TB ELIMINATION BY 2050

GOAL AND OBJECTIVES	MAJOR ACTIVITIES	INDICATOR(S)	BASELINE (2010)	TARGET FOR 2015	
<p><b>Goal:</b> To prevent all forms of tuberculosis in all age groups through the development of safe, effective and accessible vaccines that are also safe for people with HIV</p>		Number of new TB vaccines in Phase III trials	0	4	
		Number of assays to determine correlates of protection in clinical trials	0	3	
<p><b>Objective 1:</b> Maintain a robust TB vaccine pipeline by supporting research and discovery</p>	<p>Research and development related to second-generation TB vaccine candidates; encouragement and coordination of research on new TB vaccines in endemic countries</p>	Number of immune markers for TB disease that can be studied as vaccine correlates of immunity (e.g. cytokines, cellular response, bacteriological assays)	3	4	
		Number of new biomarkers for TB vaccine development	0	2	
		Number of new antigens that can be used in second-generation TB vaccines	0	4	
		Number of standardized assays developed that are transferrable to field settings	0	3	
<p><b>Objective 2:</b> Conduct research to identify correlates of immune protection, and preclinical studies to assess new TB vaccine candidates</p>	<p>Development of standardized immunoassays for use in clinical trials to identify correlates of immunity</p>	Number of assays validated as a surrogate in a clinical trial	0	1	
		Number of assays developed for measuring biological potency	1	3	
	<p>Development of standardized preclinical and nonclinical assays for new TB vaccines</p>	Number of assays developed for measuring toxicity	1	2	
		Number of assays developed for measuring safety (Koch reaction)	1	2	
	<p>Preclinical testing of improved BCG replacement vaccines that can be used as a prime in a prime-boost strategy</p>	<p>Number of prime vaccines tested for safety in immunosuppressed animal models</p>	Number of prime vaccines tested for safety in immunosuppressed animal models	2	5
			Number of prime vaccines tested for protection and immunogenicity in animal models	4	8
<p><b>Objective 3:</b> Ensure availability of vaccine production capacity by expanding manufacturing facilities for TB vaccines</p>	<p>Preclinical testing of booster vaccines for a prime-boost strategy</p>	Number of booster vaccines tested for safety in immunosuppressed animal models and for protection and immunogenicity in animal models	10	13	
		Number of new vaccine delivery platforms appropriate for human testing	0	4	
	<p>Expansion of existing manufacturing facilities producing new TB vaccines when they are ready for distribution, including in emerging economies; development of new facilities capable of manufacturing new TB vaccines, including in emerging economies; development of capacity to produce new vaccine delivery platforms (e.g. aerosol, capsids, patch, etc); manufacturing of trial lots/products</p>	Number of upgraded facilities in high-income countries and in emerging countries	0	2	
		Number of new facilities in high-income countries and in emerging countries	1	2	
		Number of dedicated facilities established for the manufacture of live vaccines	0	1	
<p>Number of processes transferred to facilities in emerging economies</p>	Number of processes transferred to facilities in emerging economies	0	2		
	Number of good manufacturing practices for new vaccine delivery platforms	0	1		

OBJECTIVES (CONTINUED)	MAJOR ACTIVITIES	INDICATOR(S)	BASELINE (2010)	TARGET FOR 2015
<b>Objective 4:</b> Build capacity for large-scale clinical trials (Phases II and III) of TB vaccines at field sites in TB endemic countries	Infrastructure required to support clinical trials in high-burden countries maintained or built, including some in areas with a high prevalence of HIV ; conduct epidemiology studies in infants, adolescents and people living with HIV	Number of sites with the necessary capacity to support clinical trials Number of studies of infant epidemiology conducted Number of studies of adolescent epidemiology conducted Number of studies of epidemiology in HIV-positive adults conducted	5 2 2 0	9 6 4 2
<b>Objective 5:</b> Conduct Phases I, II and III clinical trials of TB vaccine candidates	Clinical trials: including safety and efficacy studies of both prime and boost candidates in people living with HIV, infants and children (pre-exposure); adolescents and adults (post-exposure) vaccinated with BCG, as appropriate	Number of vaccine candidates that have entered Phase I trials Number of vaccine candidates that have entered Phase II trials Number of vaccine candidates that have entered Phase IIb “proof of concept” trials Number of vaccine candidates that have entered Phase III trials	12 3 2 1	20 9 3 4
<b>Objective 6:</b> Develop delivery, regulatory and access strategies for new TB vaccines	Clinical trials of new vaccine delivery platforms (e.g. aerosol, capsids, patch, etc) Research and testing to better understand BCG, which is the prime for many booster vaccines in development	Number of new vaccine delivery platforms that have entered clinical trials (phase 1 or 2) Number of new BCG vaccines for which studies on optimal strain, dose, route, age of administration and efficacy are being conducted	0 2	4 13
<b>Objective 7:</b> Build support for TB vaccine development and uptake through advocacy, communications and resource mobilization	Economic impact studies of new TB vaccines, including the public health impact; development of regulatory pathways; development of implementation strategies for new vaccines; capacity building of regulatory authorities in developing countries Awareness-raising and outreach at the global, country and community levels; development and maintenance of website; development of brochures and other publications; media and communications outreach; community engagement beyond that of clinical trials; participation in conferences and events, briefings and high-level events, stakeholder engagement	Number of marketing studies conducted (cost analysis and economic impact) Number of TB prime and boost vaccines submitted and licensed Number of joint TB vaccine trial reviews by at least 3 African countries as a result of regulatory capacity strengthening (jointly with the African Vaccine Regulators Forum and the Developing Country Vaccine Regulators Network)	2 0 0	4 2 2
<b>Objective 7:</b> Build support for TB vaccine development and uptake through advocacy, communications and resource mobilization	Awareness-raising and outreach at the global, country and community levels; development and maintenance of website; development of brochures and other publications; media and communications outreach; community engagement beyond that of clinical trials; participation in conferences and events, briefings and high-level events, stakeholder engagement	Number of international TB vaccine conferences organized Number of countries that have developed a national new TB vaccine introduction plan Number of TB vaccine acceptance strategies in high burden countries developed for • replacement “Prime” vaccine for BCG • new “Booster” TB vaccine Number of specific TB vaccine community education materials developed	1 0 0 each 1	3 5 1 each 5

## 5. OPERATIONAL RESEARCH

### INTRODUCTION

Programme-based operational research (defined as research specifically aimed at developing interventions that result in improved policy-making, better design and implementation of health systems, as well as more efficient methods of service delivery), is necessary to optimize TB control and determine the best ways of implementing and monitoring interventions. Operational research is crucial to determining how access to accurate diagnosis and effective treatment of TB can be increased, and how to adapt the DOTS strategy to address the challenges posed by drug resistance and HIV infection. Financial and technical support is required to enhance local capacity for operational research, and national plans for TB control should include budgeted activities for operational research as a routine part of programme activities. These include: (a) situation analyses studies to assess the nature and extent of a health or service delivery problem; (b) studies to evaluate ongoing or novel health interventions or programme performance; (c) studies to test the effectiveness of specifically designed service delivery interventions; and (d) descriptive studies to evaluate the impact and cost-effectiveness of new interventions.

In its broad sense, operational research covers a large *spectrum of activities*, from local setting-oriented research to improve TB control programme performance, to international policy-guiding research, including the assessment of new interventions to improve TB control (effective and efficient use of new tools, and determination of the conditions/requirements under which they can be effectively implemented). The type and scale of operational research is largely dependent on the type of questions being addressed, the level of care and users concerned, and the expected (general) relevance of the results. At the *national* level, TB control programmes should develop setting-oriented operational research projects to address local problems and recommend appropriate solutions, involving partners at all steps. At the *international* level, as a robust evidence-base is increasingly recommended for guiding policy-making (including the use of systematic reviews and GRADE evaluation),

multi-centre operational research projects are necessary to address gaps and needs for better TB control worldwide, that would lead to international policy changes.

The Partnership has identified five areas in which gaps presently hamper essential TB control activities or appropriate implementation of innovative technologies and novel service delivery models. These are: (1) access, screening and diagnosis of TB and MDR-TB; (2) sustained collaboration with all health care providers; (3) prevention of TB in HIV patients and combined HIV/TB treatments; (4) access to and delivery of treatment for drug-sensitive TB (including retreatment of cases failing first-line treatment) and drug-resistant TB cases (including infection control); and (5) capacity building. In all these areas, priority questions have been identified that need to be properly addressed to improve TB control worldwide and reach the Global Plan goals by 2015.

### OVERVIEW OF PLAN GOAL, OBJECTIVES, TARGETS AND ACTIVITIES

The overall goal of the Operational Research component of the Global Plan to Stop TB 2011–2015 is to contribute to the elimination of TB by improving the performance of TB control programmes and creating the evidence base necessary to introduce new tools in programmatic settings at local, national and international level.

The seven major objectives for the operational research component of the Global Plan are defined and explained below.

**Objective 1: Improve access to and use of diagnostic services to increase early TB case-detection and improve the diagnosis of drug-sensitive and -resistant TB, and TB/HIV co-infection.** TB control in most endemic countries relies heavily upon passive case-finding that is based on direct sputum smear microscopy. It is estimated that only about 60% of all infectious TB cases are currently detected with this test, and a proportion of

diagnosed patients do not return to the clinic after submitting their first specimen. Among the estimated half a million cases of MDR-TB that occur globally each year, only a very small fraction are identified and treated appropriately. From a programmatic perspective, this is largely due to services not being accessible to patients, for a variety of reasons that need to be investigated and properly addressed. Since 2007, WHO has endorsed the use of new diagnostic technologies or approaches that, if used wisely, should facilitate considerably improved TB control. There is insufficient evidence available, however, at the country level to determine which specific package of diagnostic tests would work best in given settings. This requires conducting operational research around TB diagnostics and related services, based on careful situation analysis. For optimization of TB diagnosis and improved passive case-finding, barriers to diagnosis in communities and at the health provider level (public and private) should be identified. This will help define optimal opportunities for bringing TB diagnostic services closer to the community. Active case-finding activities should be strengthened through definition of appropriate algorithms and test methods, and by targeting screening among high-risk groups (i.e. people living with HIV, prisoners, vulnerable groups, MDR suspects, patient contacts).

The new diagnostic technologies and approaches endorsed by WHO include a variety of optimized smear microscopy approaches, molecular diagnostic tests, and commercial and non-commercial options for culture and drug-susceptibility testing. The delivery of these services depends upon the existence of a functional and interconnected health system. Operational research will help define the optimal use and integration of these methods at all levels of the health services. All the above should concur to building accessible, effective and efficient diagnostic services with new diagnostic tools.

**Objective 2: Foster operational research for sustainable public-private partnerships in TB care and control.** In many countries, a significant proportion of patients with suspected TB present themselves to a range of public and private

care providers that are not linked to national TB programmes. These include informal and formal, commercial and non-profit, individual and institutional private sector care providers, employee health services, general and speciality public hospitals, academic institutions, as well as prison and military health services. Available evidence shows that TB diagnosis and treatment practices of many such ‘non-programme’ care providers are inappropriate and impose unacceptable financial burden on patients. Several examples of Public-Private Mix (PPM) projects have demonstrated the feasibility, effectiveness, cost-effectiveness and scalability of engaging non-programme care providers in TB care and control. As a consequence, WHO advises countries to undertake baseline and periodic national situation assessments to determine the need and scope of implementing and scaling-up PPM options.

While some examples exist of PPM projects that have been taken to a large scale, the knowledge gaps for suitable models or approaches for nationwide PPM scale-up are immense. It is not known, for example, how countries or projects are prioritizing care providers for engagement, so we need to learn more about specific models and approaches for scale-up. These include the use of incentives and enablers, regulatory approaches, as well as social marketing and franchising. More information is needed about the role of PPM in the broader aspects of intensified case-finding and to measure the contribution of PPM to TB care and control, so as to understand the resource requirements of scale-up.

**Objective 3: Improve implementation of joint TB/HIV control activities at the global, regional and national levels.** WHO recommends that all people living with HIV (PLHIV) are screened for TB and that, if TB is ruled-out, isoniazid preventive therapy (IPT) should be provided to prevent the occurrence of the disease. Despite this recommendation, however, it is estimated that less than 1% of PLHIV received IPT in 2008<sup>44</sup>. Among PLHIVs who develop active TB, mortality remains unacceptably high. Early initiation of co-trimoxazole and antiretroviral therapy can reduce this mortality, but linking TB treatment to HIV care and treatment in co-infected patients has

<sup>44</sup> *Global tuberculosis control 2009*. Geneva, World Health Organization, 2009 (WHO/HTM/TB/2009.411).

proven challenging, due to several barriers. For these reasons, operational research is urgently needed in countries hit by both epidemics to optimize prevention and treatment of TB in people living with HIV.

Operational research is also required to determine the best strategies and optimal models to integrate and deliver joint TB and HIV interventions both at community and health facility levels, including IPT for PLHIV and ART for HIV-infected TB patients. Research is necessary as well to define the best models of community participation for enhanced TB case-finding and early HIV detection in order to reduce delay in initiation of TB and HIV care, and to assess the cost-effectiveness of joint TB/HIV interventions delivered through community approaches and health facilities.

The implementation of the WHO-recommended policies on IPT and treatment of TB in PLHIV should be investigated to assess their impact on the proportion of PLHIV who develop TB disease and on the mortality among PLHIV during TB treatment. Specific attention should be given to studying these questions in different contexts of TB and HIV co-epidemics. In PLHIV who are eligible for both IPT and ART, studies should investigate the optimal duration, safety, efficacy and cost-effectiveness of IPT and its role in reducing the risk of active TB, particularly under programme conditions. Best operational models to scale-up IPT in HIV care settings, including frequency of symptom screening, monitoring tools and measures to maintain high adherence among patients and health workers should be identified and tested.

Lastly, optimal infection control measures to reduce TB transmission among PLHIV should be evaluated through research in HIV care settings in health facilities, at home and in the community, aimed at identifying the best operational models (i.e. practical, feasible, effective and easily reproducible).

**Objective 4: Improve access to and delivery of treatment for drug-sensitive, MDR and XDR-TB and encourage community participation.** Access to health care is the cornerstone of TB control programmes that must ensure that all detected patients receive a full course of appropriate treatment.

Limited access and poor adherence to therapy remain major obstacles in the global fight against TB. In 2008, while 86% of new patients with smear-positive pulmonary TB were reported to have been cured or to have completed treatment globally, more than a third of all TB cases were not reported or detected at all, and more than 90% of HIV-infected TB patients were not started on ART. Access to MDR-TB therapy remains extremely low. In 2009, only 30 000 (7%) of the 440 000 estimated MDR-TB cases globally were notified, and of them only 11 000 (3%) were put on treatment known to be consistent with international guidelines. Moreover, success of MDR-TB treatment, where it is available, is not guaranteed. A cohort of 4500 MDR-TB patients treated under programmatic conditions between 2004 and 2006 had a treatment success rate of 60%, and a death rate of 12%.

Operational research must be conducted to identify ways to improve access to care and treatment for all TB patients. Various methods should be investigated, depending on the epidemiological and geographical situation. These should include options such as door-to-door screening for chronic cough, mobile vans to collect and deliver sputum specimens, integrated sputum collection with HIV diagnosis, for example. In relation to TB treatment, predictive factors for treatment default should be identified and various adherence interventions tested. One possibility is to improve 'patient locators' at the time of identification or registration of suspected TB patients, such as mobile phones of patients and relatives, or better geographical addresses. Research should evaluate whether these approaches improve case-holding and reduce treatment default. Similarly, HIV-infected TB patients should have access to decentralized, fully integrated combined treatment. The provision of both TB and ART drugs should be in the same facility or location. Research should identify ways to provide joint treatment at health centres and to engage communities (structures, support and links with traditional social systems).

Lastly, optimal strategies for integration and scale-up of drug-resistant TB management *within* TB control programmes should be defined and evaluated. This should include: development and evaluation of algorithms for selecting patients eligible for drug sensitivity testing and second-line treatment in different settings; development and evaluation of

strategies for provision of second-line treatment; identification of bottlenecks for scaling-up access to MDR-TB treatment in different settings; and development of strategies for the implementation of TB infection control measures at all levels.

**Objective 5: Strengthen capacity to conduct operational research at country level.** Despite international interest in operational research, to date the amount of research published from resource-limited settings has been relatively limited. At the same time, agencies such as the Global Fund explicitly state that up to 10% of country proposal budgets should be for monitoring and evaluation, including operational research. There is wide consensus that operational research is important at national level to improve programme performance and at international level to guide policy recommendations. Questions remain, however, on how to develop appropriate capacity to conduct the research.

National TB control programmes often have limited expertise, infrastructure, staff and funds to undertake operational research. To address this challenge, capacity in operational research needs to be built at national level and collaborations with public research institutes, universities and NGOs need to be forged. Existing approaches to the development of capacity in operational research (including training) should be critically evaluated. Training should provide a theoretical background in research methods (protocol development, data collection, data analysis and writing of papers) and practical experience with fieldwork, and needs to cover both quantitative and qualitative research. Mentorship programmes can also help, and offer the advantage of supporting selected candidates through various levels of training coupled with ‘on-the-job’ training and practical experience. Finally, the resources needed for building efficient capacity in operational research at national level should be carefully estimated, with attention to training models and career development for research trainees, so as to retain staff and ensure the sustainability of research.

Further details are shown in the strategic framework for 2011–2015 on pp88–89.

## FUNDING REQUIREMENTS

According to the 2009 TAG report<sup>45</sup>, operational research was estimated to account for US\$ 47 million (8%) of the US\$ 614 million invested in TB research and development worldwide in 2008. However, in that report, operational research included randomized controlled studies of existing interventions or targeted evaluation of new or existing interventions, considered by many as not part of operational research. In addition, the report did not include estimates from major donors such as the Global Fund to fight AIDS, Tuberculosis and Malaria.

Operational research is crucial to building the evidence base that is essential for introducing new tools in programmatic settings, as well as to improve current strategies and optimize existing tools. Based on financial data reported to WHO by 32 low- and 67 middle-income countries, the proportion of operational research in total national TB programme expenditures (funding received) was about 1% in 2007–2009. The estimated amounts budgeted for operational research in 2009 and 2010 in the same countries was in the same order of magnitude. On this basis, it is estimated that in the five years 2011–2015, a total of US\$ 0.4 billion is required to conduct operational research in TB high-burden countries.

<sup>45</sup> *Tuberculosis research and development: a critical analysis*. New York, Treatment Action Group (TAG), 2009.



**OPERATIONAL RESEARCH: STRATEGIC FRAMEWORK, 2011–2015**  
**THE VISION: EXPAND AND IMPROVE TB CONTROL ACTIVITIES LOCALLY, NATIONALLY AND INTERNATIONALLY IN ORDER TO MOVE TOWARDS TB ELIMINATION BY 2050**

GOAL AND OBJECTIVES	MAJOR ACTIVITIES	INDICATOR(S)*
<p><b>Goal:</b> To conduct research aimed at improving TB control performance and methods of service delivery, and create the evidence base necessary to introduce new tools in programme settings at local, national and international level in order to move towards elimination of TB</p> <p><b>Objective 1:</b> Improve access to and use of diagnostic services to increase early TB case-detection and improve the diagnosis of drug-sensitive and –resistant TB, and TB/HIV co-infection</p>	<p>Identification of the socioeconomic and qualitative barriers that influence TB diagnosis at patient and health provider levels; development of interventions that are most effective in overcoming these barriers; investigation of how to bring TB/HIV diagnostic services closer to the community and how to integrate them in the general health system; identification of which populations/high-risk groups should be screened, what they should be screened for, and how; research on service delivery to find out how to introduce new tools in current health systems; identification of the ideal combination of diagnostic tools to be introduced in health systems and define what determines the appropriateness of particular combinations to given national programmes/health services; evaluation of the scale-up and post-scale-up impact of new diagnostic test(s) and particularly the public health and societal consequences.</p>	<p>Number of Operational Research (OR) studies conducted at programme level that have led to changes in the national programme guidelines so as to increase performance</p> <p>Number of OR studies conducted at programme level that have led to changes in the delivery of programme services</p> <p>Number of OR studies conducted at local/national level that collected reliable data so as provide evidence for the introduction of new tools (diagnostics, drugs, vaccines) in programme conditions</p> <p>Number of OR studies conducted at international level that collected reliable data so as provide evidence for the introduction of new tools (diagnostics, drugs, vaccines) in programme conditions</p> <p>Number of studies** to identify local barriers to TB diagnosis access in order to allow better use of existing systems for diagnosing TB (all forms) in various populations (including difficult-to-reach populations) and specific risk groups</p> <p>Number of studies investigating ways to bring diagnostic services closer to the community and how to integrate them in the general health system</p> <p>Number of studies carried out to identify high risk groups for different forms of TB at which to target intensive case-finding (people living with HIV, prisoners, vulnerable groups, MDR suspects, contacts)</p> <p>Number of studies defining appropriate screening algorithms and test methods</p> <p>Number of newly defined national programme approaches including revised clinical algorithms for TB diagnosis with clarification of the proper use of new diagnostic tool(s) in specific settings and populations so as to maximize their impact</p> <p>Number of studies describing methods for improved technical performance of sputum smear microscopy services for TB, including recently endorsed techniques, and evaluating the impact on TB case notifications and number of patients cured, as well as cost-effectiveness of the approach</p> <p>Number of studies describing presumptive (non-bacteriological) detection of smear-negative tuberculosis (including HIV-associated TB) through smear negative clinical algorithms, and evaluating their application in routine settings to increase the number of TB cases detected and accessing treatment</p> <p>Number of studies describing means to increase detection of smear-negative TB cases using rapid culture-based techniques and/or line probe assays and evaluating the impact on the proportion of newly detected cases and their access to treatment, as well as the cost-effectiveness of the approach in routine settings</p> <p>Number of studies describing means to increase detection of MDR-TB cases using rapid culture-based techniques and/or line probe assays and evaluating the impact on the proportion of newly detected MDR-TB cases and their access to second-line treatment, as well as the cost-effectiveness of the approach in routine settings</p> <p>Number of quantitative and qualitative studies evaluating the post-scale-up impact of new diagnostic test(s)</p> <p>Number of cost-effectiveness studies</p>
<p><b>Objective 2:</b> Foster operational research for sustainable public-private partnerships in TB care and control</p>	<p>Improvement and scale-up of existing approaches to engaging all health care providers; measurement of the contributions of different provider groups to TB care and control; encouragement of involvement of as yet unengaged providers; development and assessment of responses to changing involvement of diverse providers in TB care and control; encouragement of introduction of regulatory approaches such as mandatory TB case notification, certification and accreditation, and restricting access to anti-TB drugs to collaborating care providers.</p>	<p>Number of evidence-based PPM models and approaches to scale-up that include contextualised analyses of reasons for success/failure</p> <p>Number of qualitative studies assessing enablers and incentives for different care providers</p> <p>Number of intervention cohort studies assessing enablers and incentives for different care providers</p> <p>Number of routine cohort reports, observational and qualitative studies with providers and users assessing the quality of TB care and control, using the International Standard for TB Care as the benchmark</p> <p>Number of situation analysis studies assessing the contributions of different care providers to TB control</p> <p>Number of situation analysis studies assessing the abilities of different providers to improve user access, case detection and outcomes for underserved groups, and reduce diagnostic delays and costs of care</p> <p>Number of integrated costing studies and cost modelling studies to understand resource requirements for scale-up</p> <p>Number of situation analysis studies of various models and approaches</p> <p>Number of mapping studies identifying potential new providers that could provide accessible and effective services</p> <p>Number of structured evaluation of existing approaches to better understand providers' practices regarding the use of new diagnostics and drugs in the private sector</p> <p>Number of structured evaluation of existing approaches on which to develop an evidence base of regulatory approaches that include contextualised analyses of reasons for success/failure</p> <p>Number of situation analyses and ethnographic mapping studies carried out to better understand providers' practices and willingness to comply with regulation</p>

OBJECTIVES (CONTINUED)	MAJOR ACTIVITIES	INDICATOR(S)*
<p><b>Objective 3:</b> Improve implementation of joint TB/HIV control activities at the global, regional and national levels</p>	<p>Assessment of: optimization of linkages between TB and HIV programmes; the validity of TB screening algorithms in different settings; how to reduce mortality in TB/HIV co-infected patients; the optimal timing of IPT in relation to antiretroviral therapy (ART) and optimal ways to improve adherence to IPT in context specific models; optimization of infection control to reduce TB transmission.</p>	<p>Number of studies determining the best strategies and optimal models to integrate and deliver joint TB/HIV interventions, including antiretroviral therapy, at community and health sector level to HIV-infected TB patients among adults, children and families</p> <p>Number of studies determining the best models of community participation (i.e. effective, feasible, acceptable, sustainable) for enhanced TB case-finding and early HIV detection to reduce delay in initiation of TB and HIV care, and their impact on reducing TB and HIV transmission</p> <p>Number of cost-effectiveness studies of joint TB/HIV interventions delivered through community approach and through health facilities</p> <p>Number of comparative studies (before/after, stepped-wedge design)</p> <p>Number of descriptive (cross sectional) studies identifying factors and used to plan interventions</p> <p>Number of observational prospective (and retrospective) cohort studies</p> <p>Number of comparative studies</p> <p>Number of intervention studies defining the best operational models (i.e. practical, feasible, easily reproducible and effective) to implement and monitor infection control measures in health facilities</p>
<p><b>Objective 4:</b> Improve access to and delivery of treatment for drug-sensitive, MDR and XDR-TB and encourage community participation</p>	<p>Identification of reporting gaps; investigation of reasons for default and possibilities to reduce default; improvement of decentralized and fully integrated access to TB and ART treatment; testing of re-treatment regimen and amplification of drug resistance; PPM collaboration studies; evaluation of strategies for integration/scale-up of drug-resistant TB management into TB control programmes; identification of risk factors for drug-resistant TB.</p>	<p>Number of studies identifying and reporting gaps through comparison of treatment outcomes of new smear-positive TB at different sources (sputum lab registers, TB patient registers, quarterly reports)</p> <p>Number of studies mapping primary defaulters to understand role of geographic and socioeconomic factors</p> <p>Number of studies investigating relationship between drug stock-outs and default/treatment failure/ death/ acquisition of additional resistance</p> <p>Number of studies investigating methods to improve case-holding and reduce defaults</p> <p>Number of situation analysis studies or comparative studies proposing models for integrated TB and ART treatment</p> <p>Number of trials testing safety and efficacy of re-treatment regimen</p> <p>Number of situation analysis studies describing the number of people treated in the private sector and the treatment outcomes</p> <p>Number of studies investigating how to engage with the private sector to capture realistic data on number's of drug-sensitive and drug-resistant TB cases and outcomes</p> <p>Number of qualitative studies investigating why patients use the private sector rather than the public sector</p> <p>Number of studies investigating algorithms for selecting patients eligible for drug-sensitivity testing and 2nd-line treatment in different settings</p> <p>Number of studies investigating strategies for provision of second-line treatment (including adherence and use of incentives and enablers/community-based ambulatory care and support)</p> <p>Number of studies identifying bottlenecks for scaling up access to MDR-TB treatment in different settings</p> <p>Number of studies investigating the effectiveness of existing infection control measures and strategies to improve infection control measures (communities, households, household, and health facilities)</p> <p>Number of observational studies</p>
<p><b>Objective 5:</b> Strengthen capacity to conduct operational research at country level</p>	<p>Description of: existing models of operational research capacity building and the lessons learnt; the impact of existing training models in terms of products/outputs and outcomes; the possible ways of sustaining and retaining trained research staff within programmes; funding mechanisms that can be efficiently used for OR capacity building at national level, with an international/consortium community of practice of facilitators, mentors, standard curriculum and sustained mentorship.</p>	<p>Number of descriptive studies of various models</p> <p>Number of impact evaluation and questionnaire surveys</p> <p>Number of evaluation and questionnaire surveys</p> <p>Number of evaluation and questionnaire surveys</p>

\*Note: baseline status and expected targets are not being indicated here, since Operational Research was not singled out in the original *Global Plan to Stop TB 2006–2015*, so no reference baseline can be identified.

\*\*Refers to published studies in indexed journals.

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