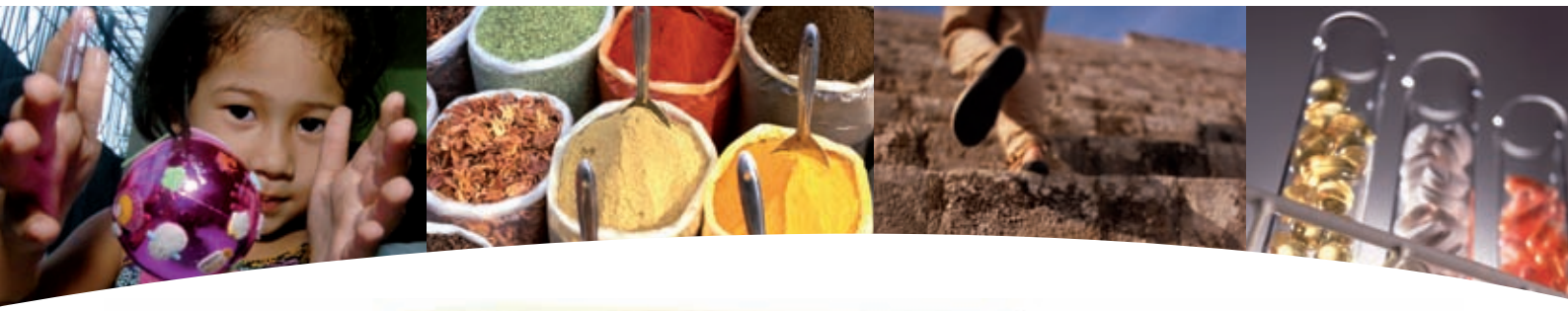
World Health Organization

Stop TB Partnership

THE GLOBAL PLAN TO STOP TB 2006-2015: PROGRESS REPORT 2006-2008

ACTIONS FOR LIFE: BUILDING A SUCCESSFUL FUTURE TOGETHER



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Abbreviations

ACSM	advocacy, communication and social mobilization
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
BCG	Bacille Calmette-Guérin
CPT	co-trimoxazole preventive therapy
CTBC	community-based TB care
DEWG	DOTS Expansion Working Group
DOT	directly observed treatment
DOTS	the basic package that underpins the Stop TB Strategy
DST	drug susceptibility testing
EQA	external quality assurance
FIND	Foundation for Innovative New Diagnostics
G8	Group of eight countries (Canada, France, Germany, Italy, Japan, Russian Federation, United Kingdom, United States of America)
GDF	Global TB Drug Facility
GLC	Green Light Committee
GLI	Global Laboratory Initiative
Global Fund	The Global Fund to fight AIDS, Tuberculosis and Malaria
Global Plan	Global Plan to Stop TB, 2006–2015
HBC	high-burden country of which there are 22 that account for approximately 80% of all new TB cases arising each year
HIV	human immunodeficiency virus
HRD	human resource development
IPT	isoniazid preventive therapy
IUATLD	International Union Against TB and Lung Disease
MDG	Millennium Development Goal
MDR	multidrug resistance (resistance to, at least, isoniazid and rifampicin)
NAAT	nucleic acid amplification test
NGO	nongovernmental organization
NRL	national reference laboratory
NTP	national tuberculosis control programme or equivalent
PAL	Practical Approach to Lung Health
PPM	Public–Private Mix
TB	tuberculosis
TBTEAM	TB Technical Assistance Mechanism
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNITAID	international facility for the purchase of drugs and diagnostics for HIV/AIDS, malaria and TB
WHO	World Health Organization
XDR-TB	TB caused by MDR strains that are also resistant to a fluoroquinolone and, at least, one second-line injectable agent (amikacin, kanamycin and/or capreomycin)

Executive summary

The Global Plan to Stop TB, 2006-2015[1] sets out the strategic directions of the Stop TB Partnership for the decade 2006–2015. It also summarizes the actions, expected impacts and costs of the activities that are needed to achieve global targets set for 2015 and accelerate the development of new tools (diagnostics, drugs and vaccines) for global control of tuberculosis (TB). This document assesses the progress made in 2006–2008 towards implementing the Global Plan, highlighting achievements, challenges and areas requiring new or more intensified effort.

Important progress was made in implementing basic TB control. DOTS, the cornerstone of the World Health Organization's (WHO) Stop TB Strategy,[2] is available for 97% of the world's population. The number of new smear-positive cases notified to WHO under DOTS programmes in 2007 (2.5 million) exceeds the Global Plan benchmark (2.2 million). Some 155 countries have adopted national strategic plans for TB control, including all 22 high-burden countries. Political commitment has contributed to securing the treatment success target (85%) beyond the Global Plan milestone (83%). The Global Drug Facility (GDF) has provided substantial assistance by channeling more than 13 million treatments to countries since its creation in 2001.

The detection rate of new smear-positive cases increased from 58% in 2005 to 63% in 2007 but fell short of the 2007 milestone (68%). The rate of increase in the case detection has slowed considerably, suggesting that the 2010 Global Plan milestone (78%) will not be achieved unless countries take rapid and innovative actions. Although rates of TB incidence, prevalence and mortality (per 100,000 population) are in decline, population growth is forcing the absolute number of new TB cases upwards.

Drug susceptibility testing of TB cases increased almost three-fold at the country level [from 64,000 in 2005 to 172,000 in 2007]. The Green Light Committee (GLC) more than tripled its approval rate for multidrug-resistant TB (MDR-TB) treatment following internationally recommended guidelines. Despite these encouraging signs, the great majority of MDR-TB cases did not receive treatment in GLC-approved programmes showing that countries and partners must enhance efforts to ensure access to high-quality management of MDR-TB. The serious challenges to overcome includes lack of qualified human resources, poor infection control, unavailability of new drugs, insufficient laboratory capacity and weak surveillance systems. The limitations of available treatment options – including non-prequalified drugs and suppliers, high drug costs, and barriers to registering and procuring quality-assured drugs – hamper universal access to health services for the prevention, management and control of MDR-TB. The emergence of extensively drug-resistant TB (XDR-TB) is another significant challenge to the already complex field of drug-resistant TB.

The implementation of national collaborative activities to address TB/HIV and its impact on patients' lives is progressing. From 2005 to 2007, the number of countries with a national policy to test people living with HIV for TB increased from 27 to 118. By 2007, 49 countries reported testing more than half of their notified TB patients for HIV, a remarkable achievement in such a short period of time. Likewise, the estimated number of TB patients tested for HIV more than doubled, from 0.3 million in 2005 to 0.9 million in 2007. African countries with a high prevalence of HIV (accounting for approximately 75% of HIV-positive TB cases) tested 41% of their notified TB cases for HIV in 2007, signaling important progress from the 14% tested in 2005. Globally, however, only 27% of all notified TB patients were tested for HIV in 2007, far behind the Global Plan milestone (56%).

For the plan period 2006–2008, countries made much less progress in screening HIV-positive people for TB, increasing the numbers of people on isoniazid preventive therapy and providing antiretroviral therapy and co-trimoxazole preventive therapy, although improvements occurred throughout the reporting

[1] *The Global Plan to Stop TB, 2006–2015: actions for life towards a world free of tuberculosis.* Geneva, World Health Organization and Stop TB Partnership, 2006 (WHO/HTM/STB/2006.35); hereafter referred to as "the Global Plan".

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

period. Progress in these areas will need to advance rapidly, and pressing challenges addressed, in order to achieve the Global Plan 2010 milestones for TB/HIV. Such challenges include, but are not limited to, weak integration of TB and HIV service delivery, lack of recognition of the importance of integrating TB in HIV services and limitations in current technologies.

Advances in research and development include expansion of the pipeline for new tools to prevent, diagnose and treat TB. A major step forward is the introduction to referral laboratories of diagnostic technologies capable of providing results in a few hours or days instead of weeks. A new diagnostic technology (molecular line-probe assay) for referral laboratories, endorsed by WHO in 2008, marked another key innovation. Rolling out this and other new diagnostic tools in the next few years should be a priority for countries. Of seven promising tools currently in late-stage development and evaluation, four require only laboratories equipped with basic resources and limited training. Much more progress is needed to develop and evaluate tests to detect active TB at the first point of care.

Phase III clinical trials conducted by Stop TB partners on gatifloxacin and moxifloxacin will shed light on the possibility of shortening the current regimen for TB. Other promising compounds have entered Phase II trials. Despite these gains, the pipeline of new drugs is insufficient to expect entirely new regimens by the dates outlined in the Global Plan; thus, a robust and sustained pipeline of new candidates and backup discovery programmes are essential to success.

The Global Plan calls for at least 20 vaccine candidates to have entered Phase I clinical trials by 2015. To date, nine vaccine candidates have entered clinical trials, some moving beyond Phase I. Several others are in preclinical development and are expected to enter clinical trials in the coming years. By the end of 2008, three vaccine candidates had entered Phase II clinical trials, exceeding the milestone of at least two vaccines, and one candidate is due to enter Phase IIb in 2009. Such impressive progress in vaccine development is encouraging, but much more needs to be done to address several challenges and accomplish the goal of introducing a new vaccine by, or before, 2015.

Funding is among the greatest challenges to achieving the goals of the Global Plan. In 2006–2008, donor agencies and governments of endemic countries substantially increased their contributions to implement Global Plan activities at the country level, but the funding gap was still over US$1 billion per year. For research and development, this gap was approximately US$ 0.5 billion for 2007. Clearly, meeting Global Plan expectations for new diagnostics, drugs and vaccines will be possible only if sustainable funding is secured.

These funding gaps highlight the importance of strengthening advocacy to mobilize resources and harness implementation and research and development efforts. Powerful advocates in 2006–2008 included the United Nations Secretary-General's Special Envoy to Stop TB, celebrities and goodwill ambassadors. Partners also made great strides in ensuring that TB was on the agenda at key events such as G8 summits, international AIDS conferences and the annual World Economic Forum.

Partnership building was enhanced substantially; strategic alliances were forged with the Global Fund to Fight AIDS, TB and Malaria, UNITAID, key bilateral donors, multilateral agencies, nongovernmental organizations, think-tanks, civil society and the private sector. WHO, the hosting agency of the Partnership, renewed its full commitment to the Partnership following the second external evaluation of the Stop TB Partnership in 2008 (see Annex 1). During the reporting period, the Partnership grew from 463 partners in 2005 to 967 at the end of 2008. In addition, national partnerships flourished in several endemic and donor countries; and advocacy, communication and social mobilization activities at country level increasingly caught the attention of country and local leaders.

Progress made during the first three years of the Global Plan has stimulated greater hope for the future. On the implementation side, addressing access (especially by the poor and vulnerable) to first line treatment, as well as MDR-TB and TB/HIV remain the most challenging tasks. Progress in TB/HIV collaborative activities has accelerated in the past two years; however, progress on MDR-TB remains very low and in need of major efforts. For the research and development field, there is an urgent to fill the pipeline with novel candidates. Increasing the funding for both implementation and research and development must be a top priority to achieve the Global Plan objectives.

New guidance and tools, tested and endorsed by partners, are becoming available for many aspects of TB programme management and control. Such new approaches bring additional challenges: partners and countries must continue to work together under the umbrella of the Stop TB Partnership and WHO respectively to ensure full implementation of the Global Plan to Stop TB.

Background

Tuberculosis (TB) is an airborne infectious disease that is preventable and curable. In most cases, if detected early and fully treated, people with the disease quickly become non-infectious and eventually cured. Yet in 2007, there were an estimated 9.27 million new cases of TB[1,2]. There were also 1.3 million deaths from TB HIV-negative people and an additional 456,000 deaths among HIV-positive people. Multidrug-resistant TB (MDR-TB), extensively drug-resistant TB (XDR-TB), TB/HIV are stifling attempts to control TB and causing suffering, death and impoverishment worldwide.

The first Global Plan to Stop TB (2001–2005)

In 2001, a five-year consensus-based Global Plan to Stop TB was launched at the First Global Partners' Forum. This first Global Plan identified DOTS expansion and adaptation as critical in confronting the emerging challenges of HIV and anti-TB drug resistance and the importance of boosting research and development for new diagnostics, drugs and vaccines. Implementation of this Plan demonstrated that TB control is succeeding globally and that scaling up interventions to serve millions of people is possible. Despite the advances made during the plan period, however, serious challenges remained.

The second Global Plan to Stop TB (2006–2015)

The second Global Plan to Stop TB, introduced by the Stop TB Partnership in 2006, describes the actions and funding needed over the decade 2006 to 2015 to accelerate progress in TB control, develop and introduce new tools and address the above challenges. For each technical area and region of the world, the Plan identifies explicit targets, actions and benchmarks that – if met individually – will achieve international targets to Stop TB. These targets are:

- detecting at least 70% of new sputum smear-positive TB cases and curing at least 85% of these cases.
- halting and reversing the incidence of TB by 2015 (Millennium Development Goal 6 Target 6c);
- halving prevalence and death rates by 2015 compared with their levels in 1990;

Implementation of this plan will mark an important step in achieving the ultimate goal: elimination of TB by 2050[3].

Clearly, the success of the Global Plan depends on the collaborative efforts of interested parties in eliminating TB as a public health problem, including endemic countries, international organizations, donors from the public and private sectors, governmental and nongovernmental organizations (NGOs) and individuals.

The Stop TB Partnership seeks to promote and coordinate the contributions of this broad range of stakeholders to catalyse action at global and country levels. Its primary mode of operation is through the Partnership structure – including the Coordinating Board, the Partners Forum and the working groups, subgroups and task forces – through joint planning, information-sharing and collaboration.

The Stop TB Strategy

The Stop TB Strategy is a framework to guide national strategies for effective TB control and underpin all efforts made to implement the second Global Plan. The six-point strategy, developed by the World Health Organization (WHO) over a two-year period, builds on the success of DOTS while also addressing the key challenges to comprehensive TB treatment and care, including MDR-TB and TB/HIV. The strategy seeks to strengthen health systems, engage all care providers, empower people with TB and communities, and promote research.

About this document

This interim report on the implementation of the second Global Plan summarizes the progress made during the plan period 2006–2008. It describes the actions taken by countries and the international community of partners and the extent to which

[1] Countries in the regions comprising the Established Market Economies and Central Europe have high per capita income levels and low TB incidence rates, and for those reasons were not included in the Global Plan. Data presented in this progress report include only those countries in the Global Plan, i.e. countries in Central Europe and Established Market Economies are excluded.

[2] Includes sputum smear-positive, sputum smear-negative and extrapulmonary cases.

[3] Elimination is defined as the occurrence of 1 case per million people.

Global Plan benchmarks and targets have, or have not, been met. Where targets have not been met, this document attempts to describe the reasons why progress has been slow – and how Stop TB partners are planning to help addressing these challenges.

All 2006-2008 data related to DOTS, TB/HIV and MDR-TB have been reported through the WHO annual TB data collection form. All the results and methods have been published in the annual Global TB Control report[1]. Data on progress made in the development of new tools have been provided by the R & D working groups. Most of the 2006-2007 funding data on research and development are drawn from the Treatment Action Group (TAG) report[2].

Following publication of this report, the epidemiological and financial scenarios contained in the Global Plan will be revised to allow for progress achieved, recommendations made and challenges discussed in this document.

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

[2] *Tuberculosis Research and Development: A Critical Analysis of Funding Trends, 2005–2007: An Update.* Treatment Action Group, 2009

Chapter 1:
Addressing TB control

A. Overview

An overview of progress in implementation and financing of TB control at country level compared with the milestones defined in the Global Plan is provided in Table 1 and Figure 1 (a and b).

Table 1: Global Plan Milestones for DOTS Expansion and Enhancement, TB/HIV, MDR-TB and ACSM

INDICATOR	2006	2007	2008
DOTS EXPANSION New ss+ cases notified under DOTS (millions)			
Global Plan target	2.1	2.2	2.2
Actual	2.5	2.5	n/a
New ss+ case detection rate under DOTS (%)			
Global Plan target	65%	68%	71%
Actual	62%	63%	n/a
New ss+ treatment success rate (%)			
Global Plan target	83%	84%	84%
Actual	85%	n/a	n/a
MDR-TB Laboratory-confirmed MDR-TB cases treated by GLC-approved programmes (thousands)			
Global Plan target	20	69	116
Actual	1.6	2.8	12
TB/HIV TB patients tested for HIV129 (millions)			
Global Plan target	1.6	2.0	2.3
Actual	0.6	0.9	n/a
Diagnosed HIV-positive TB cases enrolled on CPT (millions)			
Global Plan target	0.5	0.6	0.7
Actual	0.1	0.2	n/a
Diagnosed HIV-positive TB cases enrolled on ART (millions)			
Global Plan target	0.2	0.3	0.3
Actual	0.1	0.1	n/a
ACSM Number of HBCs in which communication and social mobilization activities are being carried out			
Global Plan target	2	7	12
Actual	11	15	19

The key messages are:

- The number of TB patients treated in DOTS programmes has increased, as has the case detection rate. However, progress in case detection of new smear-positive cases lags behind Global Plan expectations, and the gap is widening;
- The treatment success rate achieved in DOTS programmes has surpassed the targets set in the Global Plan, reaching 85% in 2006;
- There has been progress in scaling up diagnosis and treatment of MDR-TB, but this has been slow. The number of patients diagnosed and treated in GLC-approved projects or programmes reached only 12,000 in 2008, about one-tenth of the target set in the Global Plan and less than 3% of the estimated 500,000 cases of MDR-TB that occurred in 2008;
- There has been impressive progress in scaling up collaborative TB/HIV activities, particularly provision of HIV testing for TB patients in African countries. Nonetheless, the number of HIV-positive TB patients started on CPT and ART is about one-third of the milestones set in the Global Plan, and provision of IPT for HIV-positive people without TB remains extremely limited;
- The number of high-burden countries implementing ACSM has grown, but many countries are seeking further technical guidance to support implementation of this component of TB control;
- Based on data provided for 101 countries with 93% of the world's TB cases, the funding gap for implementation of TB control (excluding the Eastern European region) has been at least US$ 1 billion in each year 2006–2008. In the Eastern European region, available funding exceeded the milestones set in the Global Plan;
- Funding for DOTS implementation came closest to matching Global Plan milestones, especially in 2008. Funding for MDR-TB and TB/HIV fell far short of the requirements estimated in the Global Plan. To accelerate progress in scaling up diagnosis and treatment for MDR-TB and collaborative TB/HIV activities while also increasing case detection rates in DOTS programmes, funding for TB control will need to increase substantially.

Further details are provided in the next four chapters, which in turn provide an assessment of progress in implementation of DOTS, collaborative TB/HIV activities, diagnosis and treatment of MDR-TB and ACSM.

Figure 1a: Global Plan estimates of funding requirements compared with available funding, 2006-2008 (all regions excluding the Eastern European Region).

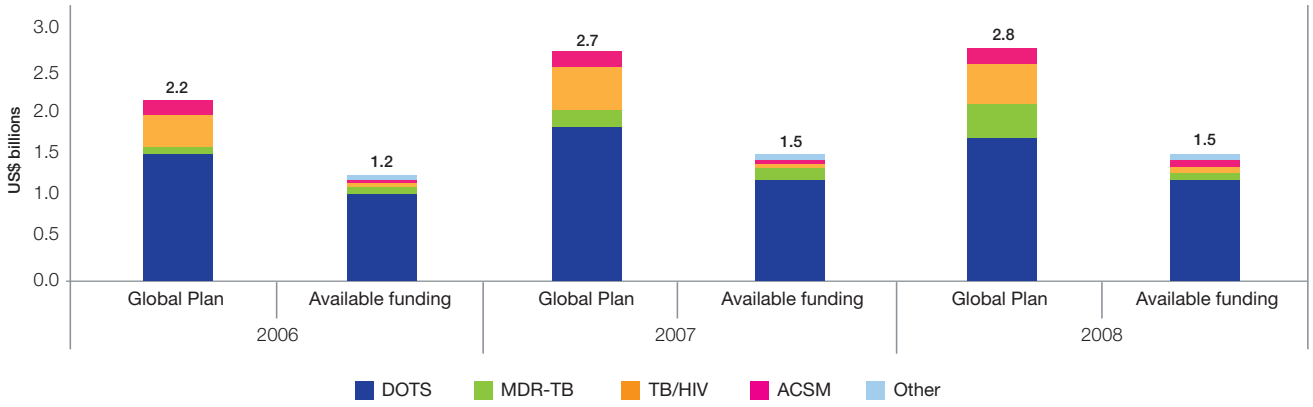
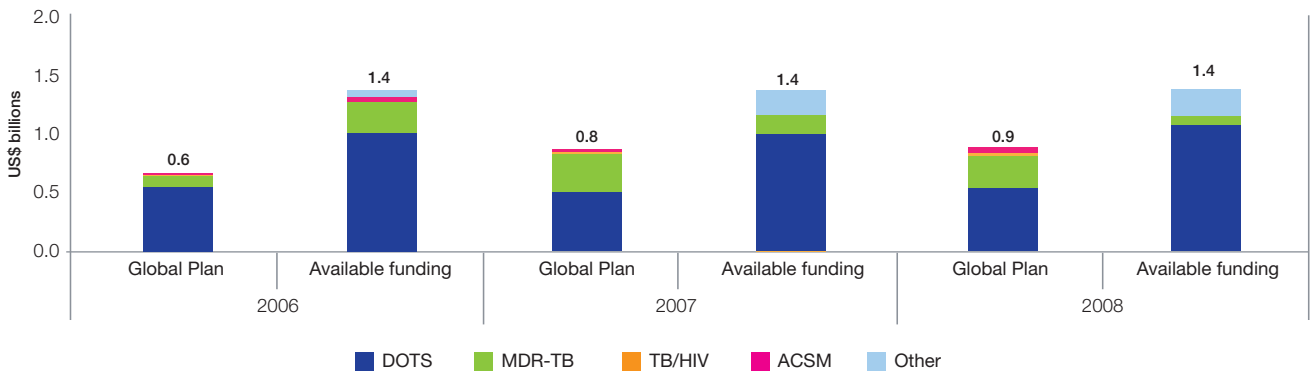


Figure 1b: Global Plan estimates of funding requirements compared with available funding, 2006-2008 (only Eastern European Region).



B. DOTS expansion and enhancement

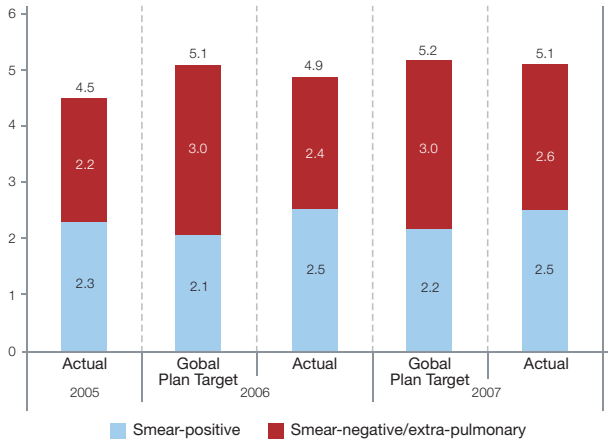
DOTS, the basic package that underpins the Stop TB Strategy, was launched by WHO in 1995. By 2005, nearly 27 million people had been treated in DOTS-based programmes, and 97% of the world's population lived in areas where DOTS was being implemented by public health services.

The Global Plan requires that DOTS be expanded to ensure that all TB patients, regardless of age, gender or socioeconomic status, have access to optimal TB diagnosis and care. DOTS services must also be enhanced through better and earlier case detection, quality-assured bacteriology, standardized treatment with supervision and patient support, an effective drug supply and management system, and improved monitoring, evaluation and impact measurement. Both expansion and enhancement require a sustained increase in financing.

I. Global progress

Countries and partners made great progress in DOTS expansion and enhancement during the first three years of the Global Plan. Several critical targets and benchmarks for the reporting period were met or exceeded. This progress is also reflected in the increased funding seen during the first three years of the Global Plan (see Budget requirements and financial investment). Such achievements clearly show the strong commitment of endemic countries and donors, as well as partners – including civil society, people affected by the disease, and multilateral and technical agencies.

Figure 2: TB case notifications under DOTS (millions)



DOTS coverage increased during the reporting period. By the end of 2007, 97% of the world's population lived in countries that had adopted DOTS (up from 93% in 2005), and population coverage exceeded 90% in all regions except African countries with low HIV prevalence, and the Latin American Region.

Case notifications

One of the success stories of the reporting period was the striking increase in the number of new cases of smear-positive TB notified under DOTS programmes. New smear-positive case notifications exceeded Global Plan expectations (Figure 2[1], Table 2). The number of new cases (of all forms[2]) notified under DOTS also increased during the reporting period, from 4.5 million (2005) to 5.1 million (2007).

The greatest increases in such case notifications were seen in the South-East Asian Region (207 000 more notifications in 2007 than in 2005, an increase of 12%), the Western Pacific Region (90 000 more, about 8%) and the Eastern Mediterranean Region (89 000, 32%). African countries with high HIV prevalence reported a greater increase in notifications (74 000) than other African countries (14 000) but had a slightly lower percentage increase (8% compared with an increase of 9% in other African countries from 2005 to 2007). While the Latin American Region reported a substantial two-year increase (15%), the bulk of this occurred from 2005 to 2006: very little increase (1.1%) occurred from 2006 to 2007 (see Progress by region).

Notifications of new smear-negative and extrapulmonary cases gained ground on Global Plan targets during the period.

Case detection rates

The global case detection rate for new smear-positive cases in DOTS-based programmes increased from 58% in 2005 to 63% in 2007, but lags behind the milestone of 68% in the Global Plan[3]; the rate of increase must accelerate if the Global Plan target of 78% by 2010 is to be met (Figure 3[4]).

Some regions that had made great strides continued to advance and, in some cases, exceed expectations. The Western Pacific Region (77%) surpassed its 2007 Global Plan milestone for detection of smear-positive cases (75%). Other regions also exceeded their Global Plan milestones for 2007, including the Eastern Mediterranean Region (60% rate compared with a 56% milestone) and the Eastern European Region (54% compared with 53%). The Latin American Region (72%) and the South-East Asia Region (69%) fell just short of their 2007 milestones (75% and 70% respectively).

[1] Includes new sputum smear-positive, sputum smear-negative and extrapulmonary cases.

[2] Includes new cases notified under DOTS for all countries in the Global Plan, i.e. countries in Central Europe and Established Market Economies are excluded here.

[3] The case detection rate is calculated as the number of cases notified divided by the number of incident cases estimated for that year, expressed as a percentage. While the number of notified cases exceeded the Global Plan target, the estimated number of incident cases in the subsequent years after the launch of the Global Plan (2006 and 2007) was higher than anticipated in the Global Plan.

[4] Global rate among all countries in the Global Plan, i.e. countries in Central Europe and Established Market Economies are excluded here.

Table 2: Global Plan Milestones for DOTS Expansion and Enhancement

INDICATOR	2006	2007	2008
New ss+ cases notified under DOTS (millions)			
Global Plan target	2.1	2.2	2.2
Actual	2.5	2.5	n/a
New ss+ case detection rate under DOTS (%)			
Global Plan target	65%	68%	71%
Actual	62%	63%	n/a
New ss+ patients successfully treated under DOTS (millions)			
Global Plan target	1.8	1.8	1.8
Actual	2.1	n/a	n/a
New ss+ treatment success rate (%)			
Global Plan target	83%	84%	84%
Actual	85%	n/a	n/a
New ss-/extrapulmonary cases notified under DOTS (millions)			
Global Plan target	3.0	3.0	3.1
Actual	2.4	2.6	n/a
New ss-/extrapulmonary case detection rate under DOTS (%)			
Global Plan target	66%	69%	72%
Actual	48%	51%	n/a

The case detection rate was lowest in the African Region: countries with high HIV prevalence (48%) and low HIV prevalence (46%) were significantly behind 2007 milestones (69% and 63% respectively), suggesting that intensified efforts to increase case detection are needed in the African Region.

The detection of smear-negative and extrapulmonary cases also lags behind Global Plan expectations, and by a larger amount (51% worldwide for 2007 compared with the milestone of 69%). Only the Eastern European (91%) and the Eastern Mediterranean (65%) regions met their Global Plan milestones for 2007.

Treatment success rates

The increase in the global smear-positive treatment success rate (Figure 3) during the reporting period led to an important accomplishment: the rate of 85% in 2006 surpassed the Global Plan milestone for that year (83%) and one of the two outcome targets of the Stop TB Partnership, to cure at least 85% of TB cases, was achieved.

This global success can be attributed in large part to the high treatment success rates reported from the South-East Asia and Western Pacific regions (87% and 92%, respectively). Eastern Mediterranean countries (86%) and African countries with a high HIV prevalence (78%) also achieved their 2007 milestones. The Latin American Region fell short of its 2006 milestone (–9%), as did Eastern European countries (–10%) and African countries with a low HIV prevalence (–14%). In Latin America, the treatment success rate declined during the reporting period, probably because DOTS expanded to parts of countries where health services are not yet available/well developed.

In addition, the number of smear-positive patients treated in DOTS-based programmes globally in 2006 (2.1 million) was higher than the number forecast in the Global Plan (1.8 million). The full impact expected from an 85% treatment success rate in terms of reductions in incidence, prevalence and mortality, however, requires a higher case detection rate than is often found. Until the number of cases undetected and actively transmitting TB disease is reduced, regions achieving high treatment success rates will not reduce incidence as rapidly as possible.

Achievement of the 85% target is multifactorial; prime credit belongs to countries, but also to key initiatives such as the Global Drug Facility[1] (GDF) – which has delivered more than 13 million treatments to over 80 countries worldwide since 2001 – and its donors.

Incidence, prevalence and mortality

The incidence of TB in terms of rates per capita peaked in 2004 and is now in decline, as estimated by WHO, suggesting that

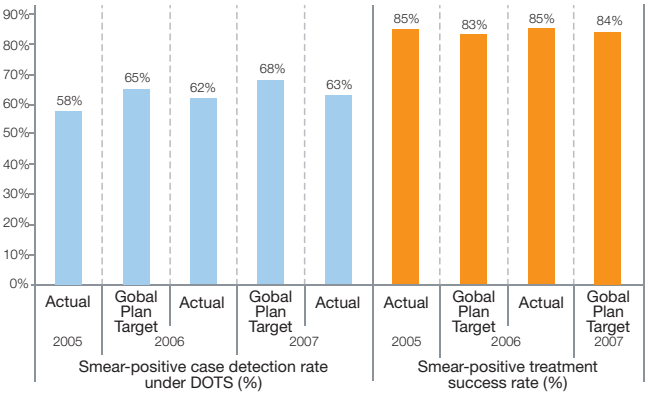
GUIDING GLOBAL DOTS EXPANSION AND ENHANCEMENT

The Stop TB Partnership established the DOTS Expansion Working Group (DEWG) in 2000. The DEWG is an inter-institutional arrangement between financial and technical partners, NTPs and community representatives to expand access to diagnosis and treatment in line with the Stop TB Strategy. To ensure that each component of DOTS expansion receives the attention it requires, the DEWG has established a number of specialized collaborations:

- A subgroup on Public–Private Mix (PPM) to develop global policy on PPM and assist countries to implement national policies and guidelines that engage all care providers.
- A subgroup on Childhood TB to develop and assist countries to implement guidelines that include the coverage of childhood TB as part of routine NTP activities.
- A subgroup on TB and Poverty to develop and advocate for approaches and interventions that enhance the way in which the general needs of the poor and the specific needs of vulnerable populations are addressed in the delivery of TB services.
- A Global Laboratory Initiative (GLI) to coordinate worldwide efforts to develop and implement standardized, harmonized approaches to laboratory strengthening.
- A TB Technical Assistance Mechanism (TBTEAM) to ensure that sufficient access to rational, high-quality technical assistance allows countries to implement international standards for TB control and to achieve global targets for TB control.
- A TB and Health Systems Task Force to develop guiding principles for NTPs on how to contribute to health systems strengthening.

More: http://www.stoptb.org/wg/dots_expansion

Figure 3: Smear-positive case detection and treatment sucess rates



[1] http://www.stoptb.org/gdf/

the epidemic has been halted in line with MDG (Millennium Development Goal) 6 Target 6c, well ahead of the target date of 2015. While this is reassuring, the rate of decline in incidence rates is slow at less than –1% per year. This is far short of the 5–10% decline annually that is theoretically feasible.

On the other hand, the total number of new TB cases is increasing as a result of population growth in several regions of the world. There were 9.27 million new cases in 2007, compared with 8.8 million new cases in 2005. An estimated 1.37 million of the new cases of TB in 2007 were among HIV-positive people (about 15% of all new cases).

Global TB prevalence declined during the reporting period (from 14 million cases in 2005 to 13.6 million in 2007), continuing a trend that began in 1990. Among regions, the Eastern Mediterranean, Latin American, South-East Asia and Western Pacific regions are all on track to at least halve prevalence rates by 2015. In the African and European regions, these rates are above or close to the same level as in 1990. Without significant acceleration in these regions, it is unlikely that the target of halving prevalence by 2015 will be met.

As with prevalence rates, TB mortality rates are declining globally, although faster in some regions than others. The Eastern Mediterranean, Latin American, and South-East Asia regions are on track to halve mortality rates by 2015. If the mortality in the Western Pacific Region does not decline faster than the rate 2005-2007, however, it will narrowly miss the 2015 target. WHO projections indicate that neither the African Region nor the European Region will reduce mortality rates to 1990 levels by 2015 and, as a result, it is unlikely that the 1990 global TB mortality rate will be halved by 2015.

An estimated 1.3 million HIV-negative people died from TB in 2007, and an additional 456 000 TB deaths occurred among HIV-positive people.

Political commitment

The Global Plan refers to increased political commitment as a key foundation for success in many areas (e.g. MDR-TB, new tool development, TB/HIV) and describes several ways in which it will manifest (e.g. as greater domestic funding, creation and implementation of national policies, increased human resources).

Such varying expectations and measurements make it difficult to comprehensively assess the global change in political commitment. One indicator of change in political commitment that can be measured, however, is financing for TB control from governments.

During the first three years of the Global Plan (2006–2008), Stop TB partners invested substantial resources to generate international advocacy and media attention with the aim of increasing financing for TB control. As described later in this document, these efforts led to greatly increased domestic and international financing.

A second, alternate measure of political commitment is the creation and adoption of national strategic plans for TB control. Such efforts were highly successful: at the end of 2007, a strategic plan was reported to exist in 155 countries, including all 22 high-burden countries (HBCs).

Technical assistance

In addition to increased funding, another concrete and significant improvement in technical assistance during the period was the launch of the Stop TB Partnership's TB Technical Assistance Mechanism[1] (TBTEAM) in 2007. The TBTEAM is part of the DOTS Expansion Working Group and coordinated by WHO.

Since its creation in 2007, TBTEAM made progress in setting up operations, building partnerships and providing access to donor funding for technical assistance. Its partners were able to access funds for technical assistance that could not be provided by the Global Fund to fight AIDS, Tuberculosis and Malaria[2] (the Global Fund). TBTEAM catalysed much needed technical assistance to over 100 countries that were applying for grants from the Global Fund or that required help in overcoming bottlenecks in implementing grants from the Global Fund. During those two years, countries that received TBTEAM assistance were approved by the Global Fund for TB grants of approximately US$ 1.2 billion.

Childhood TB

The Global Plan calls for improved "registration of children with TB and reporting of their treatment outcomes by NTPs, and to use this information to ensure they receive a high standard of care." It also calls for universal access to child-friendly drug formulations and isoniazid preventive treatment.

During the reporting period, WHO and partners developed and published guidance for national TB programmes on the management of childhood TB,[3] where no such formal, comprehensive guidance had formally existed before. The International standards for tuberculosis care[4] (which describes a widely endorsed level of care that all practitioners, public and private, should seek to achieve) now includes policies for diagnosing and caring for children. In addition, WHO revised the standard TB recording and reporting system – accounting for two age groups (0–4 and 5–14 years) rather than one – to support better reporting (and, as a necessary precursor, registration) of TB in children. Such formal changes reinforce the importance of TB care for children.

[1] http://www.stoptb.org/wg/tbteam
[2] http://www.theglobalfund.org
[3] Guidance for national TB programmes on the management of childhood TB. Geneva, World Health Organization, 2006 (WHO/HTM/TB/2006.371).
[4] International standards for tuberculosis care. The Hague, Tuberculosis Coalition for Technical Assistance, 2006.

Scientific evidence and policies for the future treatment of childhood TB,[1,2] were also developed during the reporting period. Such treatment became more accessible through high-quality, child-friendly formulations offered to countries by the GDF.

Laboratory strengthening

Substandard laboratory services are described in the Global Plan as a constraint to the delivery of high-quality care, contributing to low case detection rates worldwide and preventing an effective response to the challenges of TB/HIV and drug-resistant TB. For example, although it is estimated that approximately 511 000 new MDR-TB cases occurred in 2007, fewer than 30 000 cases (approximately 6%) were successfully diagnosed and notified.

The priority for laboratory strengthening in the Global Plan is to improve the performance of sputum smear microscopy to allow more rapid initiation of treatment and ensure external quality assurance (EQA). Targets in this area are to create capacity for culture of *Mycobacterium tuberculosis* and for drug susceptibility testing (DST) in all countries (by 2015) and to introduce more accurate and inexpensive diagnostic tools into routine NTP operations.

EQA was conducted for a high proportion of laboratories in South-East Asia and the Western Pacific (91% and 85% respectively), with much lower figures in other regions. Among the HBCs, coverage of EQA was reported as 100% (in 2007) in seven countries: Bangladesh, China, Indonesia, the Philippines, Uganda, Mozambique and Thailand. Details of DST and creation of capacity for culture are described in later sections of this document, particularly MDR-TB and New Diagnostics.

During the reporting period, the international community recognized the urgent need for greater commitment from technical agencies and donors to develop and fund standardized, harmonized approaches to laboratory strengthening. In 2007, partners established a Global Laboratory Initiative[3] (as defined in the sidebar on page 14) to guide and coordinate efforts to strengthen laboratories, and optimize the network of partners involved in laboratory strengthening.

In addition, several important new WHO policies[4] were established to improve the quality of services provided by national laboratory networks, including:

- revising the definition of a new sputum smear-positive pulmonary TB case such that a case is defined as presence of at least one acid fast bacilli in at least one sputum sample in countries with a well-functioning EQA system;
- reducing from three to two the number of specimens to be examined for screening of TB cases in countries where a well-functioning EQA system exists, where the workload is very high and where human resources are limited, simultaneously reducing costs and delays (particularly for the poor) and relieving the burden on over-stretched health systems;
- using a liquid medium for culture and DST in middle-income and low-income countries, followed by its use for rapid species identification to address the needs for culture and DST (liquid culture systems are the standard of care for TB diagnosis and patient management in industrialized countries);
- recommending molecular line probe assays as a tool for rapid screening of patients at risk of MDR-TB.

Public–private mix

Patients with symptoms of TB seek and receive care from a variety of health-care providers within and outside NTPs. These include private clinics operated by formal or informal practitioners; prison, military and railway health services; private, academic or even public hospitals; pharmacies and drug shops; businesses (such as garment factories, mining companies and tea estates); health-insurance organizations; professional associations; NGOs; and faith-based organizations (FBOs). The public–private mix (as defined in the sidebar on page 14) approach seeks to ensure that all health care providers collaborate with the NTP to make TB care available in line with international standards.

The Global Plan envisages that countries will develop and implement national policies and operational guidelines to engage all providers of TB care and control, including those who are used by the poor and vulnerable.

Since the launch of the Global Plan in 2006, there has been a shift increasing recognition of the importance of engaging and enhancing collaboration among diverse health-care providers, evidenced by the increasing number of countries that have begun implementing PPM-related activities. The number of HBCs scaling up PPM interventions more than tripled between 2005 and 2007, from four to 14 countries.[5] More than 16 countries have PPM components in their approved Global Fund grant applications.

[1] Ethambutol efficacy and toxicity: literature review and recommendations for daily and intermittent dosage in children. Geneva, World Health Organization, 2006 (WHO/HTM/TB/2006.365).

[2] A research agenda for childhood TB. Geneva, World Health Organization, 2007 (WHO/HTM/TB/2007.381).

[3] http://www.who.int/tb/dots/laboratory/gli/

[4] http://www.who.int/tb/dots/laboratory/policy

[5] Global tuberculosis control: surveillance, planning, financing: WHO report 2008. Geneva, World Health Organization, 2008 (WHO/HTM/TB/2008.393).

PUBLIC–PRIVATE PARTNERSHIP IN PAKISTAN

While many countries have embarked on engaging all care providers in TB control using public-private mix approaches, the example of Pakistan demonstrates how the country has benefitted from the NTPs systematic approach and sustained commitment to developing viable grassroots partnerships for TB control.

Pakistan's large and diverse private health sector (both profit and not-for-profit) is extensively used by TB patients. In recent years, successive NTP managers have given high priority to developing viable partnerships with health-care providers in this sector by using a systematic approach that is consistent with the steps recommended in WHO guidelines. The introduction of PPM began with a situational analysis used to design a range of PPM models suitable for a variety of providers, including those who provide first points of contact for the poorest. Developing national operational guidelines as a foundation for countrywide implementation was followed by establishing and funding staff positions specifically for PPM at national, provincial and district levels. The government also made a strong financial commitment, with 39% of the domestic funding available for TB control allocated to PPM in its 2005–2010 development plan.

The operational guidelines address practical considerations for implementation including, for example, establishing agreements with district level decision makers to engage in public-private partnership DOTS; creating coordination committees at provincial and district levels modelled upon the national steering committee; identifying, selecting and approaching private partners; establishing memoranda of understanding; training and certifying providers and providing them with the needed resources; mechanisms for recording, reporting, monitoring and supervision and ensuring that the general public is adequately informed.

Many partners are now contributing to TB control through PPM approaches, and evidence of their contribution to case detection in Pakistan is emerging. A WHO-assisted mission conducted in 2008 found that in 2007, PPM initiatives accounted for almost 20% of total notifications (39,635) and just over 20% of notifications of new smear-positive cases (20,129).

Several studies have demonstrated that PPM can make a positive contribution to case detection and cure rates, while reducing the financial burden on poor patients. A review of evidence indicates that PPM initiatives can help increase (by 10–40%) case detection rates.[1] Experience from evaluations of small- to medium-sized programmes, and a few scaled up initiatives (see box "Public-private partnership in Pakistan"), shows that PPM can make a major contribution to national notifications.

TB and poverty

TB infection is transmitted more readily in the environmental conditions associated with poverty: overcrowding, inadequate ventilation and malnutrition. The poor are at higher risk not only for disease but also for not being able to access high-quality TB care, as a result of financial and other access barriers.

Between 2005 and 2008, partners worked together to stimulate actions to reduce such barriers for the poor.[2] A key theme in the TB and Poverty guide is the need to strengthen TB case detection and treatment efforts as close to the point of care as possible in order to provide maximum benefits to the poor. Collaboration between partners has already delivered positive results, for example with those partners working in laboratory strengthening and research on new diagnostics. This work has ensured that costs to patients are included in the evidence base when considering new policies, such as the reduction in the number of specimens to be examined for screening of TB cases from three to two. Innovative ways of engaging with patients' first points of contact in care seeking are also being researched and documented, such as the use of local shopkeepers for referral of chronic coughers, home based care providers and community based healthworkers for the transportation of sputum. Further work is also being conducted on poverty and MDR TB, reviewing, through intervention, the process required to establish a referral laboratory in a resource poor setting and the costs that patients face in accessing an MDR TB diagnosis. In addition, research on the economic impact of access to diagnosis and treatment is being carried out in several countries, including Kenya and Viet Nam. Studies are also being conducted in Western China to identify means of making the Chinese TB programme more pro-poor. This includes exploring the possibility of insurance companies paying user fees direct to providers rather than patients being required to pay in advance and then having to apply for reimbursement.

[1] Lönnroth K, Uplekar M, Blanc L. Hard gains through soft contracts – productive engagement of private providers in TB control. *Bulletin of the World Health Organization*, 2006, 84: 876–883.
Maung M et al. Private general practitioners contribute to TB control in Myanmar – evaluation of a public–private mix initiative in Mandalay Division *International Journal of Tuberculosis and Lung Disease*, 2006, 10:982–987.
Lönnroth K et al. Social franchising of TB care through private general practitioners in Myanmar – an assessment of access, quality of care, equity and financial protection. *Health Policy and Planning*, 2007, 22:156–166.

[2] *Addressing poverty in TB control: options for national TB control programmes.* Geneva, World Health Organization, 2005 (WHO/HTM/TB/2005.352).

Improvements in socioeconomic conditions typically lead to reductions in TB incidence. An important part of TB prevention is therefore to improve socioeconomic conditions as well as to address the more direct factors that increase the risk of TB. The role of social determinants and risk factors in global TB control has recently been analysed[1] and a body of work is being carried forward to identify how institutions working on poverty issues outside TB control can be included as partners in the fight against TB.

Community involvement in TB care and prevention and the Practical Approach to Lung health

The Global Plan calls for TB services to be further decentralized beyond health facilities, to increase geographical access and to foster people's participation in health promotion, prevention and curative services. Country experience shows that community and patient involvement can have a positive impact on case detection and treatment outcomes.

Globally, there has been progress in involving communities in TB care and prevention. In 2006, 20 of the 22 HBCs and 65% of countries in the African Region (where community involvement is a key mechanism for expanding access to high-quality TB care) reported involvement. The available data do not shed much light, however, on the specific activities that are being implemented at the community level, or on the contribution of communities to case detection and treatment success. The scarcity of information provided seems to indicate that this component of the Stop TB Strategy is not a priority yet in many countries.

During the reporting period, partners addressed this gap by developing and publishing standardized guidelines for community involvement in TB care and prevention, and organized workshops in regions to train programme staff in these new guidelines. The revised recording and reporting forms do not provide tools to adequately capture the contribution of communities. Further revision of the form is planned, and guidance on how to modify the existing forms is provided in the Global Fund's monitoring and evaluation toolkit.

The Practical Approach to Lung health (PAL) is a primary health-care strategy for the integrated management of respiratory conditions in patients of five years and older. The Global Plan calls for PAL to be introduced in 20% of developing countries (approximately 30 countries[2]) by 2010. At the end of 2008, 45 countries (including nine HBCs) had at least a plan to initiate PAL. Nine countries were piloting PAL and 11 were in the process of expanding it beyond pilot sites (including one HBC, South Africa). National guidelines for PAL were available or in preparation in 21 countries. PAL implementation is totally or partially funded by the Global Fund in 19 countries, including three HBCs.

Health system strengthening and human resource development

WHO published guiding principles on how NTPs can contribute to strengthening health systems in 2008[3]. This guidance stresses the need for NTPs to help identify and address health system bottlenecks that impede TB control. WHO has collaborated with the Global Fund to develop tools that will assit the development of proposals containing health system strengthening components.

These principles also outline how NTPs can effectively contribute to improved coordination and harmonization across disease programmes by avoiding unnecessary parallel structures, and planning and financing channels. Already today, most NTPs are fully integrated into primary health care and the general health system: according to data submitted to WHO by countries in 2007, TB services were delivered through general health-care facilities in 20 HBCs, and 86% of laboratories performing smear sputum microscopy in HBCs were general laboratories. The national strategic plans for TB control in 19 HBCs explicitly seek to strengthen health systems.

Human resource development (HRD) for TB control is urgently needed in many countries, especially in HBCs. In 2008, only 13 HBCs reported having a comprehensive plan for HRD – a decrease from 2005 (15 HBCs). Only seven HBCs have considered training and staffing needs for all the major components of the Stop TB Strategy. Although 19 HBCs reported having a designated person for HRD in the NTP, only five were full-time staff. Routine monitoring of staff availability and training appears weak in all HBCs. Technical support and advocacy for HRD for TB control has increased and has contributed to the now growing recognition at all levels, internally and externally, of the need to address other aspects of HRD than training, such as the need for routine data to monitor staff turnover to ensure timely training of new staff, improved working conditions, motivation and retention strategies. Systematic development of human capacity is now a key strategy for TB control in many countries. Several countries are in their goals and strategies demonstrating a long term comprehensive approach to HRD. The essential place of a systematic long term approach to HRD for comprehensive TB control is recognized, including: strategic planning and designated staff for HRD at central level NTP; permanent working groups on HRD at central level; standardized systems for training of staff at all levels (training material, master trainers, re-training programmes, periodic revision of training programmes, development of new material based on new needs); recruitment of additional staff at mid level and central level; and work with basic training programmes (medical, nursing, laboratory, public health) including those which are the responsibility of the Ministry of Education.

[1] Lönnroth K et al. Expanding the global tuberculosis control paradigm - the role of TB risk factors and social determinants. In: Blas E, Sivasankara Kurup A, eds. Priority public health conditions: from learning to action on social determinants of health. Geneva, World Health Organization, 2008.

[2] The International Monetary Fund's World Economic Outlook Report (April 2008) identified 152 emerging and developing economies.

[3] *WHO Stop TB policy paper: contributing to health system strengthening: guiding principles for national tuberculosis programmes.* Geneva, World Health Organization, 2008 (WHO/HTM/TB/2008.400).

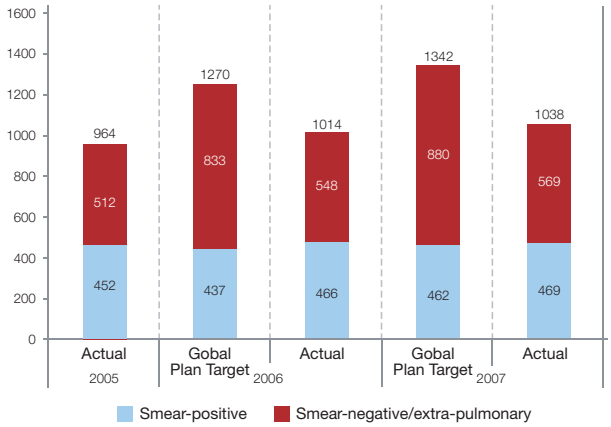
Global strategies and approaches for HRD for the implementation for the Stop TB strategy have been revised and has guided technical support to countries in this area. The Human Resources for Health Action framework has been adapted to the implementation of the Stop TB Strategy and presented in major global events such as the First Global Forum on Human Resources for Health organized in Kampala in 2008 by the Global Health Workforce Alliance.

Development of generic tools for competence development, including competence in the management of human resources and tools for staffing management has continued. Existing generic training modules for competence development for TB control at health facility and district level are being updated and new material, such as training modules for the management of MDR-TB is being developed. Training courses and other learning opportunities on key aspects of Comprehensive TB control have been organized at regional and inter-country level for key staff in NTPs and partners, e.g. training of consultants on PPM, and workshops on health system strengthening and TB control.

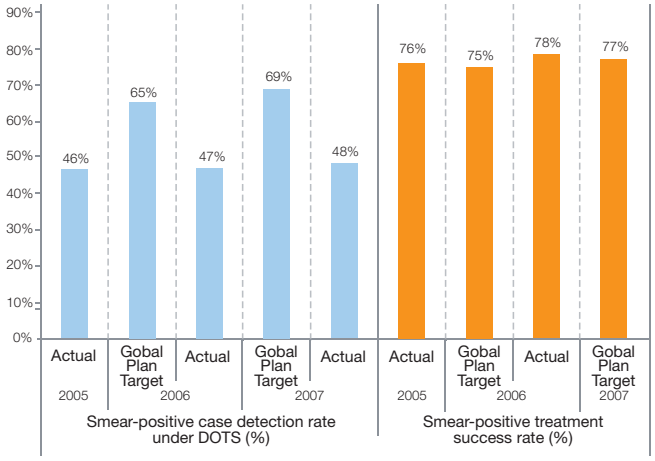
II. Progress by region

African countries with high HIV prevalence

TB case notifications (thousands)

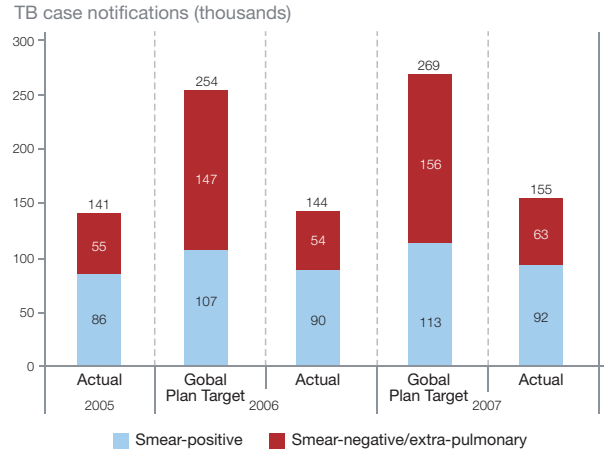


Smear-positive case detection and treatment sucess rates

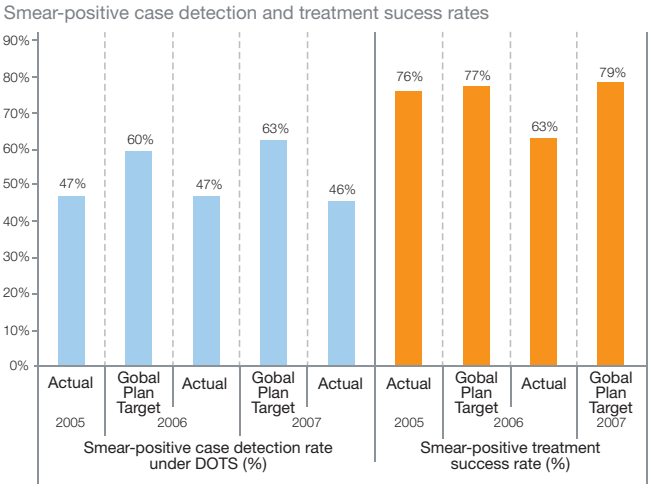


African countries with low HIV prevalence

TB case notifications (thousands)

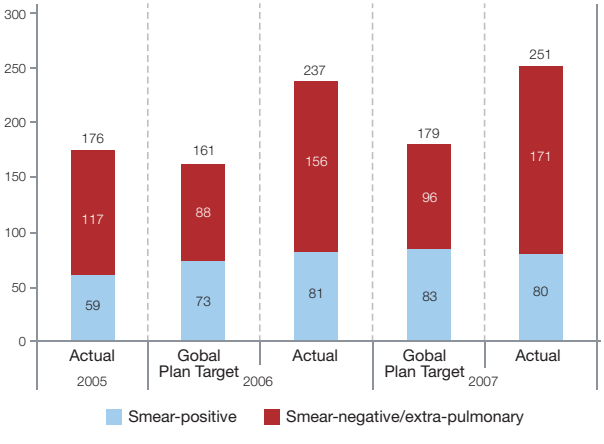


Smear-positive case detection and treatment sucess rates

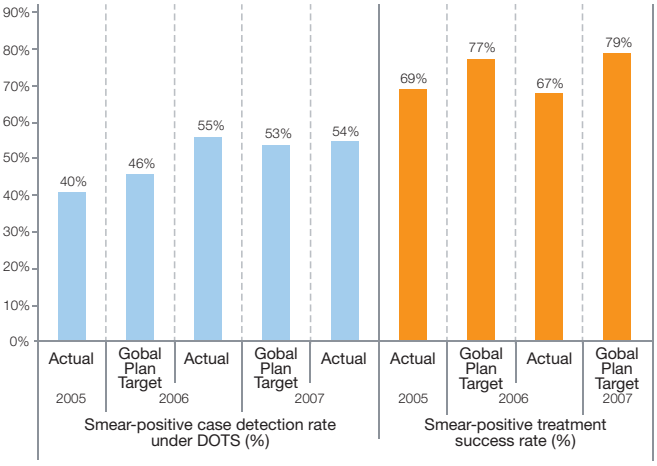


Eastern European countries

TB case notifications (thousands)

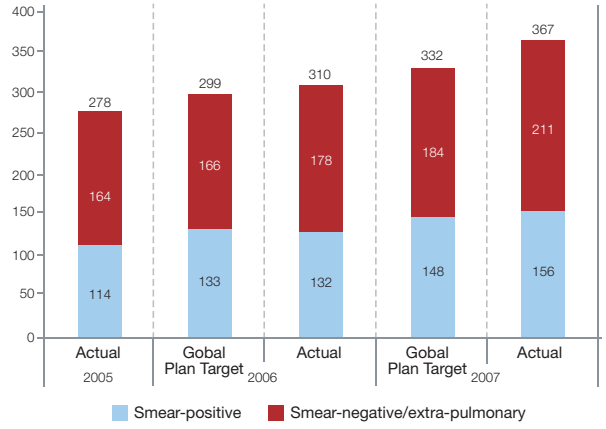


Smear-positive case detection and treatment sucess rates



Eastern Mediterranean countries

TB case notifications (thousands)



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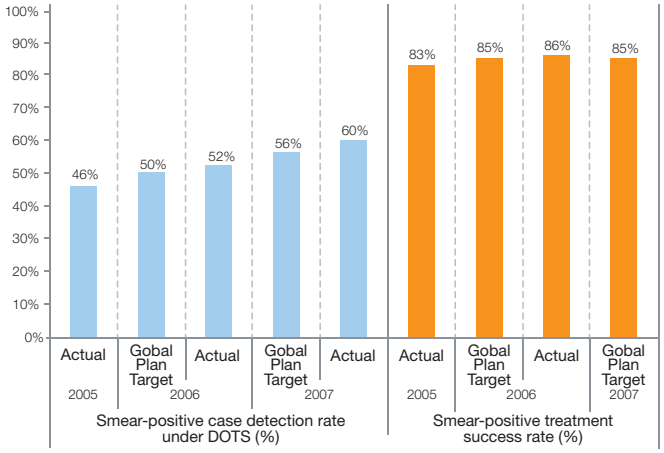
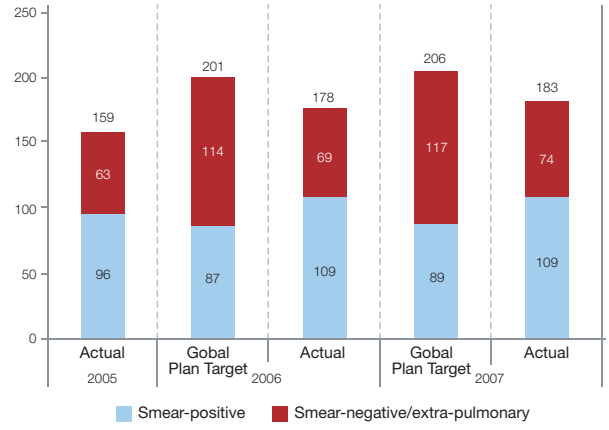


Latin American countries

TB case notifications (thousands)



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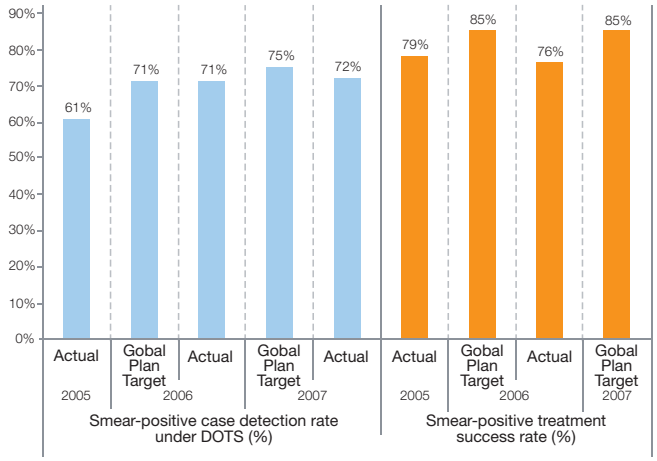
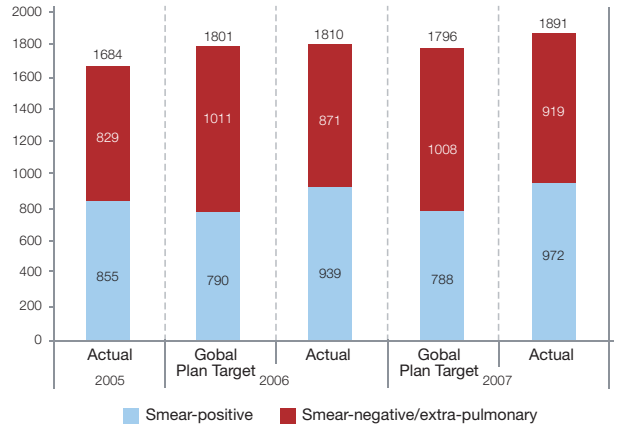
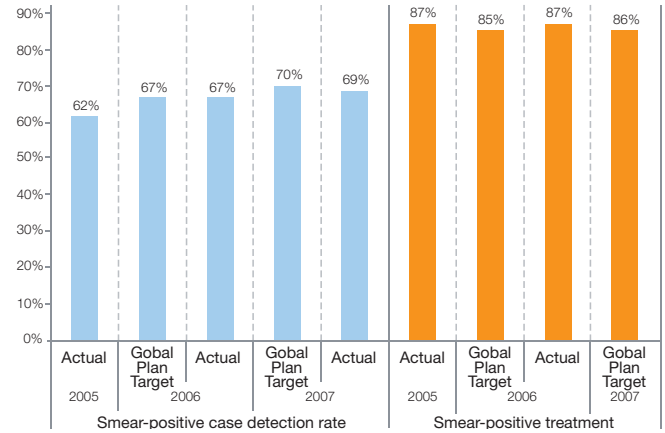


South-East Asian countries

TB case notifications (thousands)

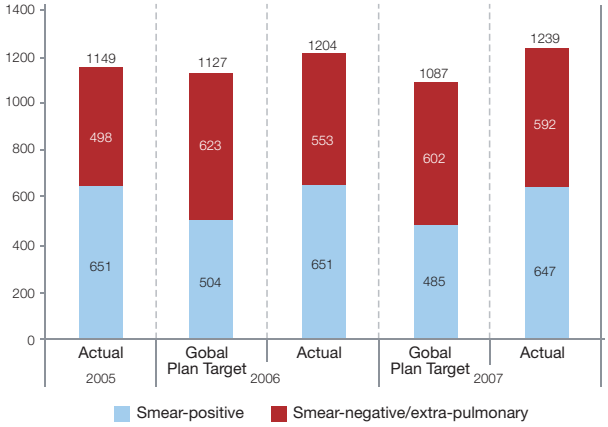


Smear-positive case detection and treatment sucess rates

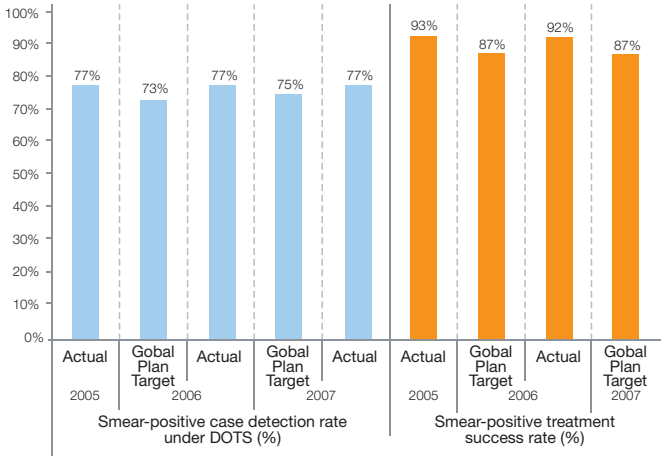


Western Pacific countries

TB case notifications (thousands)



Smear-positive case detection and treatment sucess rates



III. Budget requirements and financial investment

Countries and partners made great progress in DOTS expansion and enhancement during the first three years of the Global Plan. Several critical targets and benchmarks for the reporting period were met or exceeded. This progress is also reflected in the increased funding seen during the first three years of the Global Plan (see Budget requirements and financial investment). Such achievements clearly show the strong commitment of endemic countries and donors, as well as partners – including civil society, people affected by the disease, and multilateral and technical agencies.

DOTS in the Global Plan included the following components: first-line drugs, NTP staff, laboratory supplies and equipment, programme management and supervision, PPM, PAL, and community-based TB care, as well as hospitalization and outpatient visits during treatment.

Data reported through WHO's financial monitoring system allow the funding available and spent on DOTS implementation during the three years 2006–2008 to be compared with funding requirements according to the Global Plan for 101 countries.[1] These 101 countries account for 93% of the world's incident cases of TB.

The funding required for DOTS implementation in these 101 countries for the three years 2006–2008, according to the Global Plan, was US$ 6.6 billion (Figure 4). The funding reported to be available was US$ 7.1 billion.

This shows that, overall, funding available at country level matched the funding needs set out in the Global Plan. At the same time, this overall figure conceals important differences among regions. In particular, funding for DOTS in the African region fell short of the Global Plan, by about US$ 0.2 billion in each year. This is in line with the lower case detection and treatment success rates achieved in this region compared with the Global Plan targets.

Overall, most of the funding for DOTS in these 101 countries was from domestic sources (88%); the other major sources of funding were the Global Fund (6%) followed by grants from other sources (Grants and Loans, both 3%). There was, however, noticeable variation among countries. Further details can be found in WHO's 2009 Global TB Control Report.

IV. Challenges

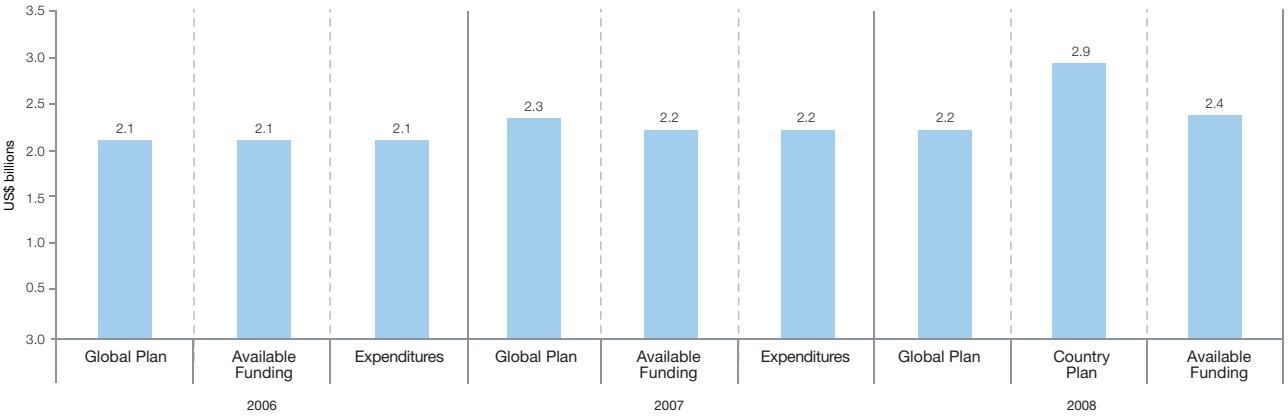
Although remarkable progress has been made in many aspects of DOTS expansion and enhancement and towards achieving the MDG and Partnership targets, progress lags behind Global Plan benchmarks. It is likely that the lack of finances for TB control and human resources (both for national programmes and international technical assistance) play a role in these shortcomings.

The greatest challenge countries face is the need to roll out current Stop TB strategies and innovative approaches to accelerate case detection rate, which has plateaued in the past few years. It is imperative to reach and surpass the 70% case detection rate target in order to ensure declines in incidence at the rate of 6-7% that is considered feasible.

Partners agree that for some aspects of the Stop TB Strategy, particularly for advocacy, communication and social mobilization (ACSM), infection control, laboratory strengthening, MDR-TB and TB/HIV, there are not always enough technical experts to provide the assistance required by countries, when it is needed.

The creation of the GLI holds great promise for the future, especially for efforts to ensure that there are sufficient qualified human resources for laboratories and that necessary investments in equipment are made.

Figure 4: Funding required for DOTS in the Global Plan compared with available funding and expenditures reported by countries, 2006-2008



Note: Since expenditure data for 2008 have not yet been reported to WHO, funding requirements for 2008 in the Global Plan are compared with a) the funding required for DOTS according to country plans and b) the funding available for these plans.

[1] WHO requests information about funding for TB control from all countries on an annual basis, using a system established in 2002. During the period 2006–2008, 101 countries reported complete data.

The foundation management of childhood TB now exists, but meeting Global Plan targets will require that childhood TB is fully integrated or embedded in national TB control plans in all HBCs. In many countries, the necessity of childhood TB is accepted, but strategies to implement child-friendly TB control programmes are lacking.

The precise contribution of PPM implementation to national and global progress in TB control remains unclear owing to the absence of systematic recording of PPM-related data in the routine recording and reporting systems in most countries. By 2007, only nine HBCs were systematically recording the source of referral of patients and where they were receiving treatment, and fewer were extracting data from these records in a systematic way.

The management of HRD needs for the implementation of the Stop TB strategy remains a major challenge for most countries, in particular large countries with decentralized management of heath services. TB High Burden countries are facing similar challenges in maintaining achievements, enhancing quality and introducing and scaling up new interventions such as TB-HIV collaborative activities and the management of MDR-TB. Key challenges, not only for NTPs but for the health system as a whole, include maintaining sufficient and competent staff - when health staff in integrated public health delivery systems are overstretched, there is not enough staff to do the job (too few positions); vacancies are high in some countries; there is a high turn over of staff; and there is insufficient intake into basic training programmes. Training specific challenges include: ensuring the educational and technical quality of training including routine quality assessment and the follow up and assessment of the "quality" of facilitators. Managerial capacity is often suboptimal at provincial and district levels; often there are no plans for update/refresher training; supervision is not linked to training follow and there is no identification of retraining needs; HRD action plans at sub-national levels, with timelines and future planning, are not in place.

The costs of repeated visits to health facilities are devastating for the poor. The impoverished need more facilities for TB diagnosis and treatment. These costs go beyond transportation and days of work lost: while the concept of TB treatment provided free of charge is enshrined in the DOTS strategy, the need for free TB diagnosis (free consultations and tests for all chronic coughers) is not so clearly endorsed and supported and needs more attention.

V. Improving progress

Technical assistance

A more proactive approach to addressing problems related to technical assistance capacity, coordination, financing and quality may be required.

One aspect of technical assistance that requires swift action is the shortage of global capacity to meet the needs of countries for assistance, in all technical areas. One solution may be to develop and offer large-scale training and mentoring programmes. Although such programmes could be offered globally, developing local capacity is critical. In the longer term, training should establish country and regional networks of high-quality experts trained according to the International Standards for TB Care.

In addition to greater access to technical expertise, countries would benefit from appropriate tools and guidance to better plan and coordinate the technical assistance they need and receive. Partners could facilitate this by developing consensually accepted standards for high-quality technical assistance. Information about how to deliver and monitor such assistance, and the standards that should be followed by Partners, would also be made more accessible through better information sharing among all.

Childhood TB

Greater effort must be made to facilitate information-sharing among programme managers on the challenges, lessons learnt and rewards of including management of childhood TB in NTP plans and activities.

NTPs from low-income and middle-income countries must be made aware of, and encouraged to apply for, grants from the GDF for child-friendly anti-TB drug formulations provided free of charge, and the Global Fund for financial support in implementing management of childhood TB. In order to do so, programmes need to demonstrate that their guidelines are in line with WHO recommendations for managing childhood TB.

Partners should provide assistance to help countries adapt their national registration and reporting systems in line with changes to the WHO TB recording and reporting system.

Laboratory strengthening and case detection rates

In Africa in particular, greater support is required to increase case detection rates and achieve and surpass the 70% target. This also includes expanding/strengthening laboratories services, community care and other innovative approaches.

Specifications for laboratory equipment, along with guidance on use, are necessary to ensure that programmes and laboratory leaders purchase only high-quality equipment that meets international standards. Such specifications, if published and broadly distributed, will help connect laboratories to the tendering processes and decrease the purchase of substandard and inappropriate equipment. This will be critical, especially as countries and partners use Global Fund monies and other resources to expand testing capacity for MDR-TB management.

Developing laboratory capacity to detect MDR-TB and XDR-TB is a priority in global TB control. Doing so will require guidance on biosafety practices for TB laboratory testing, the creation of safe facilities and establishment of procedures and practices to protect laboratory technicians. Providing risk assessment-based approaches and specific precautions for each testing method are critical to ensure worker protection and safety. Accreditation programmes to ensure safety standards for laboratory facilities will also be needed.

Public–private mix

In all regions, educational and advocacy efforts should emphasize the important role of PPM activities.

The contribution of PPM to national progress in TB control must be assessed among PPM initiatives. The WHO recording and reporting system for TB control now recommends that countries record and report data on PPM-related information. Partners should actively encourage countries to adopt this new system, and include PPM-related data in their routine recording and reporting.

Determining the contribution of PPM to TB control will require consensus among partners on the indicators and methods to be used. Several partners have begun to review the methods used in different settings to evaluate the contribution of PPM initiatives to TB control. Guiding principles on how to measure PPM contribution to TB control should be developed from this evidence-based exercise.

TB and poverty

All partners should reinforce the value of establishing poverty reduction strategies and aligning these with NTP plans, budgets and funding proposals to donors. Technical partners working on TB and poverty must quickly publicize and actively use existing guidelines for improving access to DOTS services among poor and vulnerable populations. The principle of free diagnosis for chronic cough must be endorsed and countries provided with support in making it a reality of health systems. It must be recognized that the burden of payment must shift from the poorest to the public health system.

Those partners working to develop and promote new laboratory techniques and technologies should emphasize the need for rapid diagnostic results. Techniques to ensure that sputum smear results are provided to the patient on the first clinical visit hold great promise for the future and should continue to be pursued. It may be necessary to prioritize the creation of new TB services for poor communities.

Health system strengthening and human resource development

A comprehensive strategic HRD plan for implementation of the Stop TB Strategy should provide long term overall guidance for implementation and financing to ensure the goal of an adequate, competent an performing workforce for TB control. The plan should be based on a recent HRD needs assessment, and should include, but is not limited to, (i) a clear vision, goal and strategies;(ii) training and staffing needs for all components of the Stop TB Strategy; (iii) up-to-date job descriptions; (iv) inclusion of TB based on the Stop TB strategy and National Guidelines in the training curricula of doctors, nurses and laboratory technicians, as well as any other staff category that is involved in TB control; (v) ongoing training for existing staff - both health service providers and health management and support workers, at all levels of the health system; and (vi) systematic supervision and monitoring of recruitment and training needs, for example to account for staff turnover and to enable to implementation of new strategy components. Increased assistance needs to be delivered for human resource planning as well as management and retention of qualified staff.

Recent international developments are expected to facilitate improved HRD in the coming years. Guiding principles on how NTPs can contribute to health system strengthening[1] were published by WHO in 2008. TBTEAM collaborated extensively with the Global Fund to help countries incorporate health system strengthening elements into Global Fund proposals[2].

C. Multidrug-resistant TB

MDR-TB is a form of TB resistant to, at least, isoniazid and rifampicin, the two most powerful anti-TB drugs. While drug-susceptible TB can be cured in six months, MDR-TB is more complex, demanding and costly to treat, and XDR-TB, a subset of MDR-TB, can be particularly lethal, especially among HIV-infected people.

A model (DOTS-Plus) for piloting the management of MDR-TB in resource-limited settings was launched in 1999 and, through the Green Light Committee[3] (GLC), it is now proven to be effective, feasible and cost-effective. The DOTS-Plus model was incorporated into the Stop TB Strategy and Global Plan as MDR-TB management.

The Global Plan requires that this model be drastically scaled up around the world: drug resistance surveillance and the management of MDR-TB must be integrated as routine components of TB control, providing access to diagnosis and treatment for all TB patients, and covering all health-care providers.

[1] WHO *Stop TB policy paper: contributing to health system strengthening: guiding principles for national tuberculosis programmes.* Geneva, World Health Organization, 2008 (WHO/HTM/TB/2008.400).

[2] http://www.who.int/globalfund/healthsystems/proposal_preparation/en/index.html and http://www.who.int/tb/dots/planningframeworks/en/

[3] http://www.who.int/tb/challenges/mdr/greenlightcommittee/

During 2007, the targets for the number of patients to be diagnosed and treated for MDR-TB were reviewed and revised to make the targets for 2010 comparable to the goal of universal access to ART (antiretroviral therapy) by 2010 (see sidebar).[1]

I. Global progress

Current estimates suggest that 511 000 new cases of MDR-TB occurred in 2007. As projected, the number of new patients in whom MDR-TB was diagnosed and who were notified to WHO increased during the reporting period (from 18 000 in 2005 to 29 000 in 2007), as did the number of patients that countries expected to treat (Table 3).[2]

Despite progress, the number of MDR-TB patients treated in 2006 and 2007, and projected to be treated in 2008, was far behind Global Plan expectations (Figure 5). The Global MDR-TB & XDR-TB Response Plan called for 100 000 MDR-TB patients to be enrolled in treatment in 2008, which is three times higher than notifications (for 2007) or country projections (for 2008 and 2009).

Differences between Global Plan expectations for 2008 and country projections vary by region. Forecasts of the number of patients to be enrolled in treatment in African countries with high HIV prevalence and the Latin American Region are ahead of Global Plan expectations, with relatively large numbers of patients to be treated in Brazil and South Africa (see Progress by region).

In the three regions with the greatest number of MDR-TB cases (Eastern Europe, South-East Asia and the Western Pacific), meeting the expectations of the Global Plan will require substantial efforts to scale-up diagnosis and treatment, especially in China and India.

Monitoring the drug resistance epidemic

The Global Plan calls for drug resistance data to be available from 130 countries by 2010.

THE GLOBAL MDR-TB & XDR-TB RESPONSE PLAN 2007-2008

Perhaps the most landscape-changing event in global TB control during the first three years of the Global Plan was the recognition of strains of MDR-TB with more severe drug-resistant pattern, called XDR-TB, a threat which leaves patients (including many people living with HIV) virtually untreatable using currently available anti-TB drugs.

Launched in 2007, the "Global MDR-TB & XDR-TB Response Plan" was, in effect, both an update to the Global Plan (among other things, it revised the target for patients -- from 800,000 to 1.6 million -- and set a new target for universal access) and operational plan for the global response.

Progress towards this target appears to be on track. In 2007, the WHO/IUATLD (International Union Against TB and Lung Disease) Global Project on Anti-tuberculosis Drug Resistance Surveillance[3] collected data from 85 of the countries included in the Global Plan, covering areas that contain more than 75% of the estimated smear-positive TB cases worldwide (compared with coverage in 2005 of 47%). Data have become available from new areas of three HBCs (China, India and the Russian Federation) and from three HBCs for the first time: Ethiopia, the Philippines and the United Republic of Tanzania. By the end of 2008, 36 countries had reported at least one case of XDR-TB.

Diagnosing drug resistance

Diagnosis of MDR-TB requires DST services to be available and used. According to the Global Plan, by 2010, all countries with a national reference laboratory (NRL) should be performing quality-assured culture and DST, and collaborating with a supranational reference laboratory (SRL). DST should have expanded to cover 92% of all new and previously treated cases in Eastern Europe and 60% of re-treatment cases in other regions.

Table 3: Global Plan Milestones for MDR-TB Management

INDICATOR	2006	2007	2008
Laboratory-confirmed mdr-tb cases treated by glc-approved programmes (thousands)			
Global Plan target	20	69	116
Actual	1.6	2.8	12
Mdr-tb cases diagnosed and notified (thousands)			
Actual	22	29	25*
Proportion of notified mdr-tb cases covered by new glc approvals (%)			
Actual	7.3%	27%	48%*

* projected numbers

[1] *The Global MDR-TB and XDR-TB response plan 2007-2008.* Geneva, World Health Organization, 2007 (WHO/HTM/STB/2007.387).

[2] The projections used in this table are from the Global Plan to Stop TB 2006-2015 and the Global MDR-TB & XDR-TB Response Plan 2007-2008; a further update of such projections were later presented at the Beijing Meeting on MDR-TB.

[3] http://www.who.int/tb/challenges/mdr/surveillance and the International Union Against Tuberculosis and Lung Disease (the Union) at http://www.theunion.*org*

DST nearly tripled during the reporting period (from 64 000 DSTs in 2005 to 172 000 in 2007) but remains behind the expectations of the Global Plan and the Global Response Plan (750 000 in 2007). In Eastern Europe, DST was only done for 20% of new cases and fewer than 5% of re-treatment cases. The target of performing DST for 60% of re-treatment cases in non-Eastern European countries also appears very unlikely to be met: approximately 0.5% of such cases reportedly received DST in the African Region in 2007 (see Progress by region).

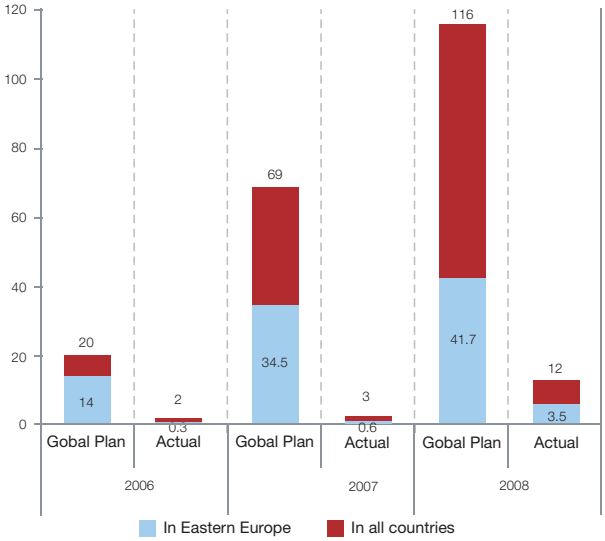
Improving the quality of treatment

The Global Plan calls for all detected MDR-TB patients to be treated with quality-assured second-line drugs in line with WHO guidelines.

Measuring progress towards this target is challenging. Outside GLC-approved programmes, the number of notified cases that are enrolled on treatment is not known, and of these it is not known how many receive treatment that is in line with WHO guidelines.

In recognition of this, the GLC has intensified its efforts to enable rapid expansion of MDR-TB diagnosis and treatment according to the latest WHO recommendations. In 2008, the GLC reviewed 43 applications, the highest to date, of which 39 were approved.

Figure 5: MDR-TB cases treated by GLC-approved programmes (thousands)



These programmes will treat a cumulative total of approximately 20 000 MDR-TB patients – more than triple the number of patients to be treated by programmes approved in 2007. The GLC is covering an increasing proportion of the new cases (69%) being detected, but still a tiny portion of the estimated global burden.

Increasing the availability of second-line drugs

Access to high-quality second-line drugs is central to the control of MDR-TB. The Global Plan calls for quality-assured production of second-line drugs to be established in several countries, including China, India, the Russian Federation and South Africa, by 2010.

To date, production capacity has been established in India and South Africa, but progress to establish capacity in other countries has been slow. Given the long lead times required to build such capacity and ensure its quality through formal prequalification procedures, it appears unlikely that this target will be met – although work is being done to lay the foundation for increased capacity beyond that date.

Supporting country implementation

Guidelines for the programmatic management of drug-resistant TB[1] were published in 2006 and subsequently revised in 2008 by WHO. It is clear that producing and disseminating guidelines has facilitate the adoption and adaptation of the WHO policy for MDR-TB at the country level, with a direct positive impact on progress in implementation – as reflected in the rapid increase in the number of MDR-TB management programmes approved by the GLC during the reporting period.

Improving research

Progress was made during the reporting period to better coordinate global MDR-TB research efforts.

The research agenda for scaling-up programmatic management of drug-resistant TB was updated with partners. A group of partners (TB-RESIST) to advocate for, and carry out, clinical trials of revised treatment regimens (including existing and new drugs) for drug-resistant TB was established.

GUIDING THE GLOBAL RESPONSE TO DRUG RESISTANCE

The Stop TB Partnership established the Working Group on MDR-TB in 1999. The Working Group on MDR-TB is composed of representatives of Stop TB Partners, including national disease control programmes, Ministries of Health, non-governmental organizations, community representatives, bilateral and multilateral aid agencies, supra-national laboratories, the corporate sector as well as technical experts who serve in a personal capacity. The goal of the Working Group is to urgently reduce human suffering and mortality due to MDR-TB.

To ensure that each aspect of MDR-TB receives the attention it requires, the Working Group has established three specialized collaborations:

- The Green Light Committee to enable access to affordable, high-quality, second-line anti-TB drugs for the treatment of MDR-TB.
- A subgroup on drug management to improve in-country management of second-line anti-TB drugs with respect to quantification, importation, registration, distribution and storage.
- A subgroup on research to develop an agenda for the main research needs for global MDR-TB control and coordinate activities to address needs.

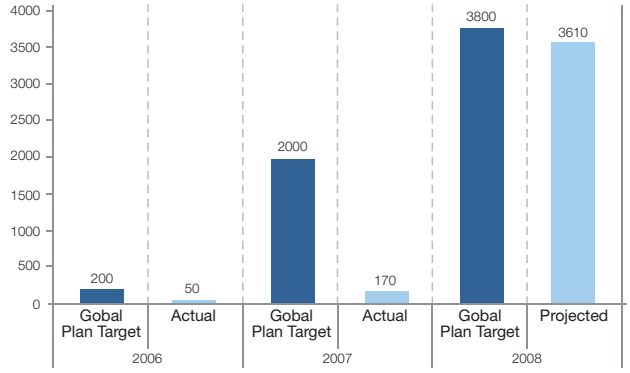
More: http://www.stoptb.org/wg/dots_plus

[1] *Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency update 2008.* Geneva, World Health Organization, 2008 (WHO/HTM/TB/2008.402).

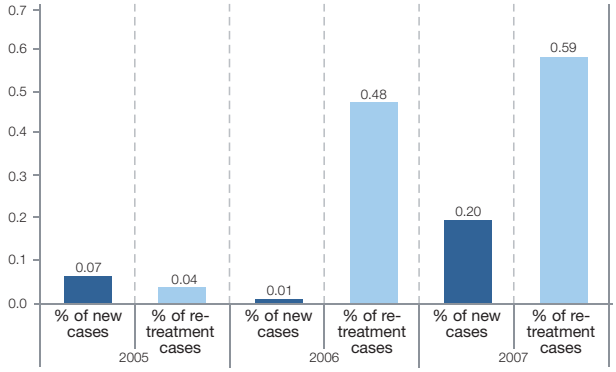
II. Progress by region

African countries with high HIV prevalence

MDR-TB cases treated by GLC-approved programmes

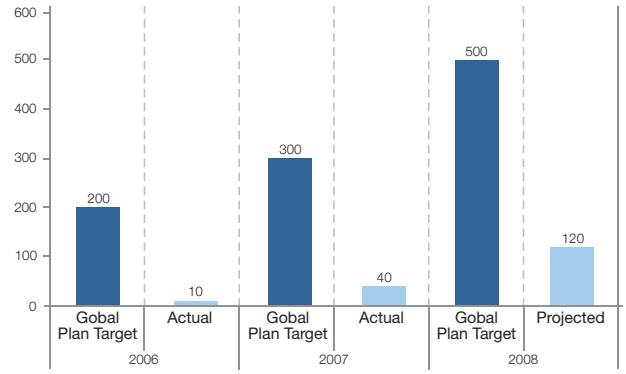


Proportion of TB cases for which DST was performed

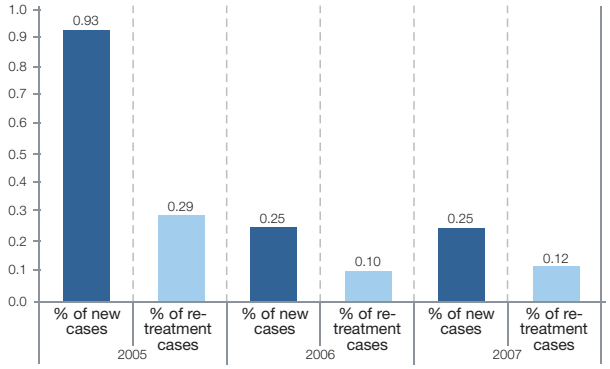


African countries with low HIV prevalence

MDR-TB cases treated by GLC-approved programmes

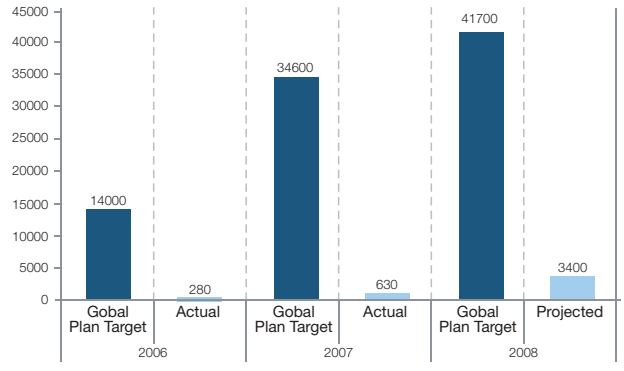


Proportion of TB cases for which DST was performed

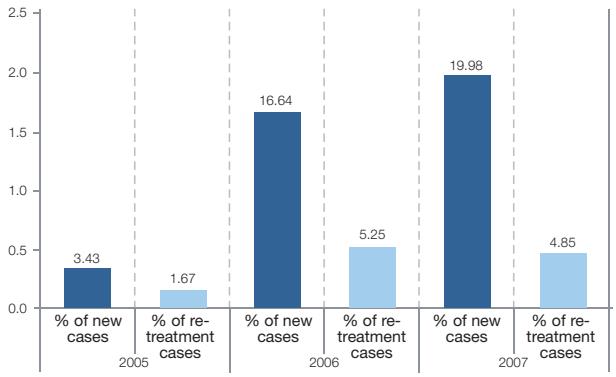


Eastern European countries

MDR-TB cases treated by GLC-approved programmes

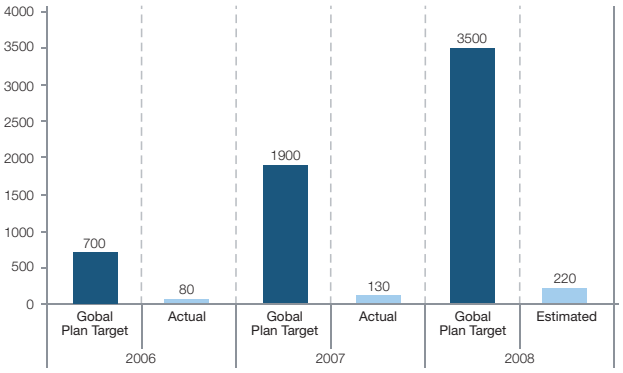


Proportion of TB cases for which DST was performed

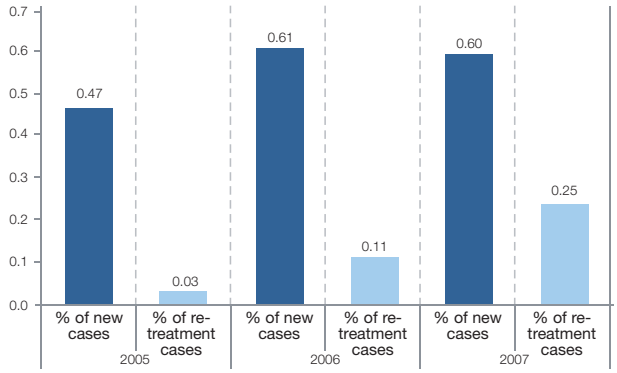


Eastern Mediterranean countries

MDR-TB cases treated by GLC-approved programmes

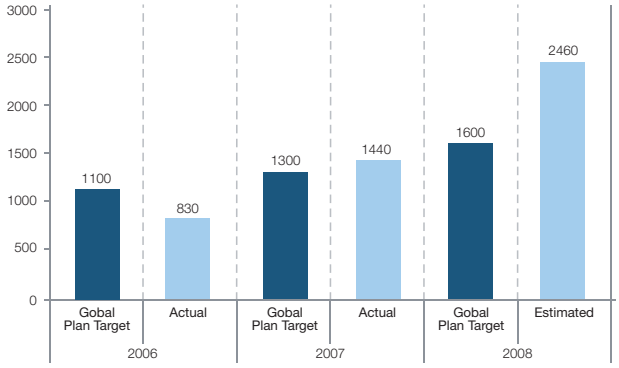


Proportion of TB cases for which DST was performed

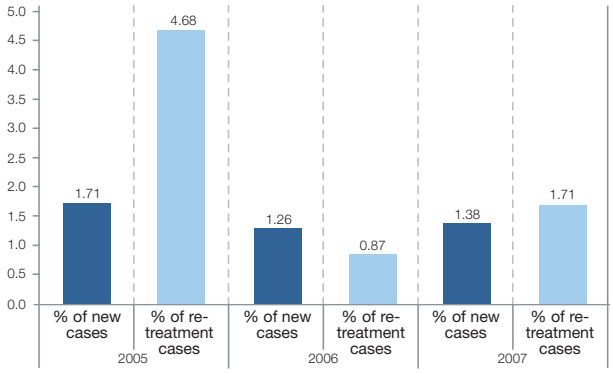


Latin American countries

MDR-TB cases treated by GLC-approved programmes

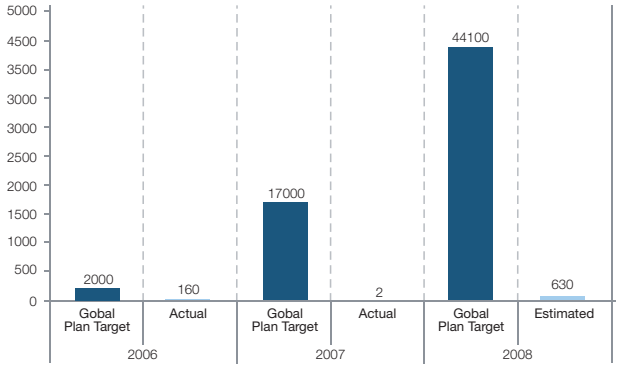


Proportion of TB cases for which DST was performed

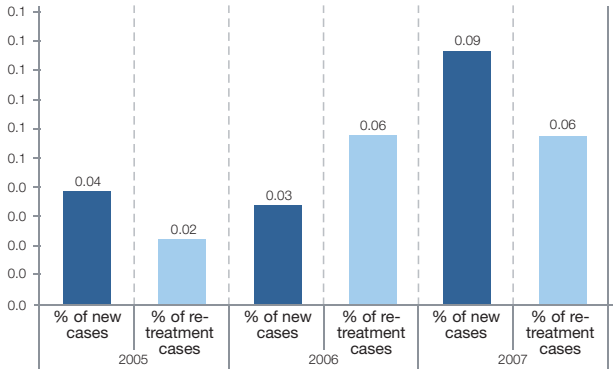


South-East Asian countries

MDR-TB cases treated by GLC-approved programmes

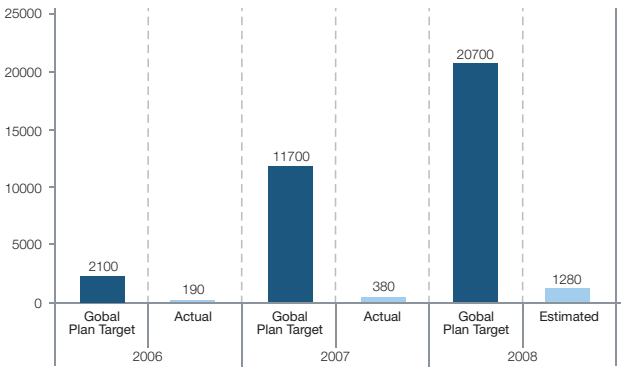


Proportion of TB cases for which DST was performed

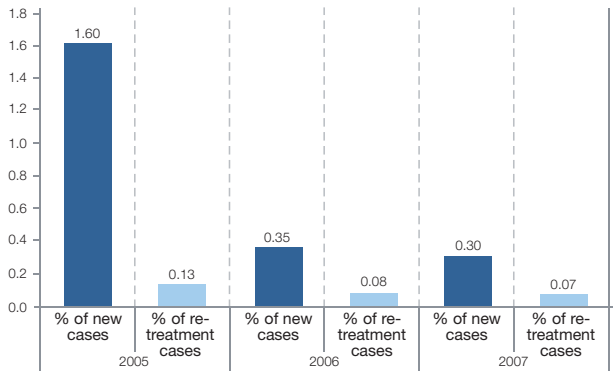


Western Pacific countries

MDR-TB cases treated by GLC-approved programmes



Proportion of TB cases for which DST was performed



III. Budget requirements and financial investment

The MDR-TB component of the Global Plan included costs for second-line drugs as well as all other costs associated with the management of MDR-TB (such as laboratory tests for diagnosis and monitoring, programme and data management, training, hospitalization and visits for direct observation of treatment, food packages where these were considered appropriate, drugs to manage side-effects). The original estimates of funding requirements for MDR-TB in the Global Plan were updated in 2007, based on the Global MDR/XDR-TB Response Plan.

Data reported through WHO's financial monitoring system allow the funding available and spent on MDR-TB during the three years 2006–2008 to be compared with funding requirements according to the Global Plan for 101 countries.[1] These 101 countries account for 93% of the world's TB cases.

Given the major differences in funding for MDR-TB in the Russian Federation and South Africa compared with other countries, analyses are presented separately for these two countries (which account for 6% of the world's TB cases) and for the remaining 99 countries (which account for 86% of the world's TB cases) in Figure 6 and Figure 7.

The Global Plan estimated that US$1.5 billion was required for MDR-TB in the three years 2006–2008, of which US$ 0.6 billion was for South Africa and the Russian Federation, and US$ 0.9 billion was for the other 99 countries.

In South Africa and the Russian Federation, the amount of funding actually available in 2006 was much higher than Global Plan requirements, and similar in 2007. Most of the available funding was from domestic sources. In 2008, the funding estimated to be required according to the national strategic plans of these two countries was similar to the Global Plan, but available funding was much lower than these requirements.

In the remaining 99 countries, funding for MDR-TB has fallen far short of Global Plan expectations. The shortfall was US$ 0.7 billion over three years, most of which was accounted for by the South-East Asia and Western Pacific regions, and within these regions by India and China respectively. Most of the funding that has been available for MDR-TB in these 99 countries has been

Figure 6: Funding required for MDR-TB in the Global Plan compared with available funding and expenditures reported by countries (excluding the Russian Federation and South Africa), 2006-2008

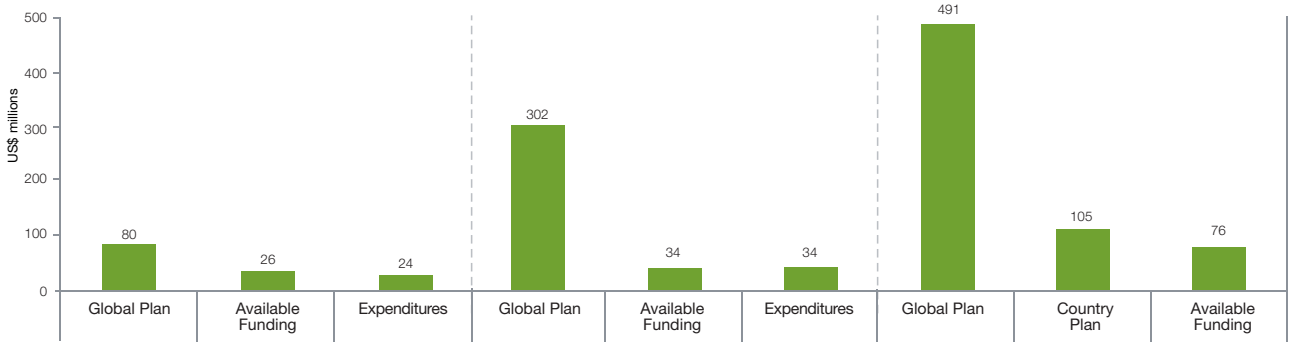
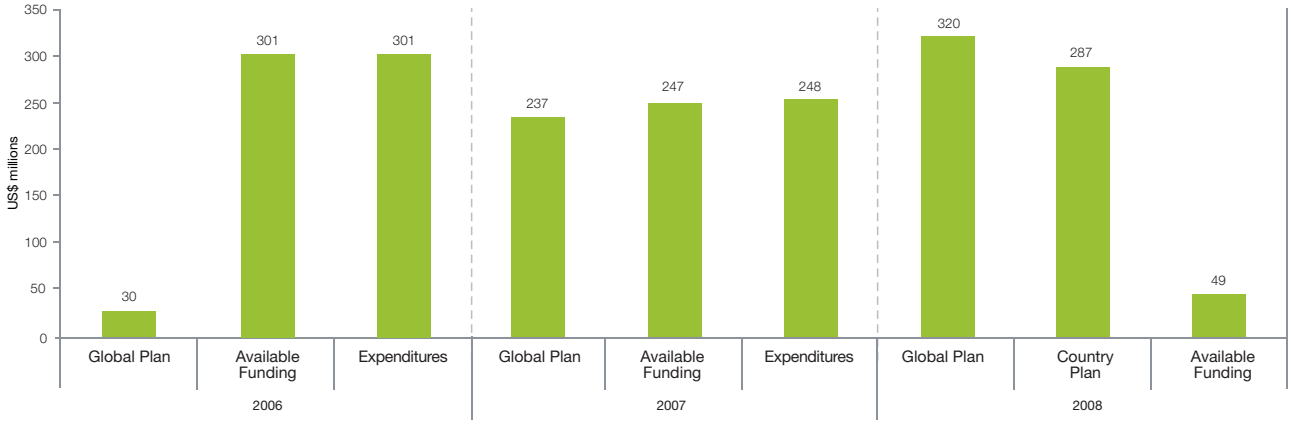


Figure 7: Funding required for MDR-TB in the Global Plan compared with available funding and expenditures, the Russian Federation and South Africa, 2006-2008



Note: Since expenditure data for 2008 have not yet been reported to WHO, funding requirements for 2008 in the Global Plan are compared with a) the funding required for MDR-TB according to country plans and b) the funding available for these plans.

[1] WHO requests information about funding for TB control from all countries on an annual basis, using a system established in 2002. During the period 2006–2008, 101 countries reported complete data.

from domestic sources (59%) with 33% from the Global Fund, 7% from other grants, and 1% from loans.

UNITAID[1] donated US$ 20 million in 2007 and an additional US$ 33 million in 2008 for the supply of anti-MDR-TB drugs (through the GDF); it contributed a further US$ 26 million to fund tools for diagnosing MDR-TB, including provision of molecular line probe assays that allow diagnosis of MDR-TB in less than two days.

IV. Challenges

MDR-TB management is a public health intervention far more complex, demanding and costly than the management of drug susceptible TB. The political commitment of countries and several major partners, fundamental to mobilize the resources needed and to adapt the WHO policy to the local context, is still insufficient for the massive scale up needed to achieve the targets set in the Global Plan, and is a major reason why the progress that has been achieved is well below targets. However, the complexity of the intervention also explains why even in those countries, where the political commitment exists, progress in patient enrolment on treatment is slow. Capacity to manage MDR-TB is being built on, quite often, very weak health systems.

Progress appears to be slowing in regions (e.g. Eastern Europe) known to be hot spots for the disease. In other regions (e.g. Africa), reports indicate that MDR-TB is emerging but the full extent of the problem cannot be demonstrated because of weak diagnostic, surveillance and reporting systems.

There was progress in monitoring the drug resistance epidemic, but challenges remain. Only six countries in Africa provided drug resistance data because of a lack of equipment and trained staff to carry out investigations. Surveys do not include patients in the private sector and the methods employed are unable to determine acquired resistance. Furthermore:

> *There are operational, technical and methodological barriers to the implementation and repetition of drug resistance surveys in most high-burden countries. The foremost operational barrier is the laboratory capacity. In addition to the laboratory, considerable human resources to interview and verify patient classification are required, as well as extensive national and international transport networks required to ship sputum specimens, cultures, and M. tuberculosis isolates within and across national borders.*[2]

Surveillance of XDR-TB must also improve. Currently, DST of second-line drugs is not available in most countries and, where it does exist, there is insufficient quality assurance. Limiting such DST to only the highest risk cases restricts global understanding of the emergence of second-line resistance.

Limited improvement in diagnosing drug resistance contributes to slow progress towards Global Plan and Global Response Plan targets for MDR-TB management. Recent advances by the GLI and partners (such as the Foundation for Innovative New Diagnostics[3] (FIND)), the potential use of laboratories established for avian influenza, and the recognition of the potential of private laboratories may bring the acceleration that is urgently needed.

Treating all patients identified with MDR-TB is a different but equally important challenge. Although high-burden MDR-TB countries are now adopting and piloting appropriate MDR-TB treatment strategies, uncontrolled and erratic use of second-line drugs remains a problem, especially in the private sector.

Management of MDR-TB, and especially XDR-TB, raises ethical issues that should be carefully addressed in TB control (e.g. patient isolation, coercive treatment and confidentiality). The response to ethical issues cannot be based on a general global policy, however, but on an assessment of local law and values. Capacity building for countries to conduct such assessments and adapt WHO guidance on the ethical aspects of TB control is necessary. Lack of access to free diagnosis, treatment and monitoring also hampers efforts to expand universal access as described in the Global Response to MDR-TB.

Proper infection control to combat transmission has only recently received the attention it deserves. Investment is required to provide the technical assistance needed, and the necessary equipment and consumables such as respirators.

One of the most important challenges is the workforce crisis. As with the development of diagnostic networks, there is a lack of qualified human resources to consult and implement MDR/XDR-TB programmes. An increasing number of countries are now piloting MDR-TB management through the GLC, but expanding such complicated programme components is challenging, especially in light of the general crisis in human resources for health. MDR-TB management programmes are limited to localized projects, and scale-up to national levels is a work in progress in most countries.

Lack of access to second-line anti-TB drugs also contributes to poor progress towards Global Plan and Global Response Plan targets. During the reporting period, shortages of some second-line drugs were frequently reported and described as a factor limiting scale-up of MDR-TB management. A buffer stock of second-line drugs, recently established by GDF and UNITAID, is expected to be pivotal in addressing this problem. Progress to develop new second-line drugs continues, but too slowly to offer hope for the immediate future.

[1] http://www.unitaid.eu

[2] *Anti-tuberculosis drug resistance in the world: fourth global report.* Geneva, World Health Organization, 2008 (WHO/HTM/TB/2008.394).

[3] http://www.finddiagnostics.org

Although manufacturers of second-line drugs exist, few are prequalified by WHO to supply high-quality drugs, and the cost of their drugs is frequently prohibitive. In many countries, barriers constrain registration and procurement of quality-assured drugs from international suppliers in favour of national suppliers, regardless of drug quality. Efforts to expand the network of suppliers of second-line drugs (both in HBCs and elsewhere) are hampered by the perception that profits are not sufficient to justify the investments required to establish manufacturing capacity and undergo the rigorous process of becoming prequalified by WHO. However, new initiatives of the Stop TB Partnership to mobilize manufacturers in the high-burden MDR-TB countries and expedite prequalification are promising.

V. Improving progress

Only greatly improved political commitment from governments and private and public organizations can advance the fight against drug-resistant TB. The Global MDR-TB and XDR-TB Response Plan, 2007-2008[1] is the operational plan of the Working Group on MDR-TB, and describes in detail the goals, targets, objectives, activities, responsible bodies, and milestones in the scale up of MDR-TB management. Some of the most relevant areas that countries, WHO and the Stop TB Partnership should address to accelerate the scale-up of MDR-TB management are the following:

Political Commitment

It is essential that countries, especially the high MDR-TB burden countries responsible for 85% of the global estimated burden, commit to achieve the targets for MDR-TB, set in the Global Plan. That commitment should result in actions to strengthen health systems, including finding solutions to the crisis in the health workforce, regulation of access to anti-TB drugs, involvement of all health care providers in the response to MDR-TB, and the development of national TB plans that include a comprehensive response to MDR-TB drawing on the objectives, activities and milestones of the Global MDR-TB and XDR-TB Response Plan.

To address these pressing issues, WHO, the Bill and Melinda Gates Foundation and, the Government of the People's Republic of China convened a meeting in Beijing in April 2009, with the 27 high burden MDR-TB countries responsible for 85% of the world's estimated cases of MDR-TB.

Monitoring the drug resistance epidemic

Countries should produce better epidemiological data to explain geographic variations in drug resistance and to identify the greatest contributors to development of drug resistance. Countries should strengthen the capacity to monitor second-line drug resistance to develop an accurate understanding of its global magnitude and distribution.

Diagnosing drug resistance

New technologies for more rapid, accurate and cost-effective DST are already becoming available. Countries and donors should drastically increase their efforts to deploy these technologies in existing and new laboratories. WHO and technical partners should work towards building up greater international expertise in how to build laboratory capacity in countries. Laboratory networks to provide rapid diagnosis of drug resistance using molecular methods, particularly for HIV-infected patients, are of utmost importance. WHO should increase efforts to establish such networks and to define guidelines for case finding strategies drawing on these new technologies.

Improving the quality of treatment

Newly available policy guidance will assist in developing capacity to deliver quality treatment in accordance with international guidelines. WHO and technical agencies should support countries in the formation of the appropriate human resources for programmatic management of drug-resistant TB, and to dramatically increase the capacity to provide technical assistance to countries implementing or scaling up MDR-TB management programmes. Creating a network of Technical Assistance Centres, which can provide MDR-TB training and in-depth technical assistance to projects eager to expand, will be a step towards building such capacity.

Increasing the availability of second-line drugs

In addition to research into newer, cheaper products, WHO, GDF and technical partners should identify incentives for private and public sector investment in building supply capacity, which will likely require significant political involvement at high levels of government. Efforts should focus on consolidated supply policies to avoid fracturing the supply market, thus offering the greatest possible incentives for manufacturers and pooled procurement through high quality supply chains. The GLC needs to ensure that demands from countries that qualify for approval will be met.

Improving research

Investing in new and improved DST tools, particularly those that can be applied in peripheral facilities and at the point of care should be a top priority. Private and public research bodies, with the support of countries and donors, should run clinical trials to test the efficacy and effectiveness of simplified and shorter second-line treatment regimens as well as accelerating the evaluation of candidate second-line drugs.

D. Increasing TB/HIV collaboration

HIV/AIDS and TB are so closely connected that they are often referred to as co-epidemics or dual epidemics. HIV affects the immune system and increases the likelihood of people developing TB disease. HIV promotes both the progression of latent TB infection to active disease and the relapse of TB in

[1] The Global MDR-TB & XDR-TB Response Plan, 2007-2008. WHO/HTM/TB/2007.387

Table 4: Global Plan Milestones for TB/HIV Expansion

INDICATOR	2006	2007	2008
TB patients tested for HIV129 (millions)[1]			
Global Plan target	1.6	2.0	2.3
Actual	0.6	0.9	n/a
Proportion of all notified TB cases that were tested for HIV[2,3](%)			
Global Plan target	47%	56%	65%
Actual	19%	27%	n/a
Diagnosed HIV-positive TB cases (millions)			
Global Plan target	1.1	1.1	1.2
Actual	0.2	0.3	n/a
Diagnosed HIV-positive TB cases enrolled on CPT (millions)			
Global Plan target	0.5	0.6	0.7
Actual	0.1	0.2	n/a
Diagnosed HIV-positive TB cases enrolled on ART (millions)			
Global Plan target	0.2	0.3	0.3
Actual	0.1	0.1	n/a
HIV-positive people screened for TB (millions)			
Global Plan target	11	14	16
Actual	0.3	0.6	n/a
HIV-positive people offered IPT (millions)			
Global Plan target	1.2	1.5	1.9
Actual	0.03	0.03	n/a

[1] Maximum number included for each country is the number of notified cases multiplied by the population coverage of collaborative TB/HIV activities anticipated by the Global Plan.

[2] Numbers of notified TB cases are weighted according to the population coverage of collaborative TB/HIV activities anticipated by the Global Plan.

[3] Only countries that provided both the numerator and the denominator when reporting are included in this percentage.

previously treated patients. TB is among the leading causes of death in people living with HIV, particularly in sub-Saharan Africa, which bears the brunt of the epidemic.

Yet at the time of the launch of the Global Plan, NTPs reported that few TB patients were being tested for HIV; still fewer were being assessed for ART, and a very small fraction were receiving ART. There was little collaboration between TB and HIV/AIDS control programmes, although many were beginning to adopt elements of the WHO interim policy for collaborative TB/HIV activities. The Global Plan calls for collaborative TB/HIV activities to be scaled up globally, particularly in countries with a high burden of TB/HIV, such as in Africa.

I. Global progress

The latest data suggest that an estimated 1.37 million new HIV-positive TB cases occurred in 2007. This estimate is higher than figures previously published because the proportion of cases of TB estimated to be infected with HIV has been revised upwards, based on new information gained from the expansion of HIV testing since 2005–2006, notably in the African region (see Revised estimates, sidebar).

REVISED ESTIMATES OF THE NUMBERS OF TB CASES AND DEATHS AMONG HIV-POSITIVE PEOPLE

The WHO 2009 Global TB Control Report includes estimates of the number of HIV-positive TB cases and deaths that are higher than those previously reported.

Direct measurement of the prevalence of HIV in TB patients became available from more countries in 2008. These measurements suggest that the risk of developing TB in HIV-positive people compared with HIV-negative people is higher than previously estimated. Using this new incidence rate ratio, indirect measurements have been produced for countries for which direct measurement was unavailable.

As a result, current Global Plan targets and funding requirements for collaborative TB/HIV activities may need to be revisited to ensure they are sufficient for planning and monitoring the response to the HIV-associated TB epidemic.

According to these data, African countries with a high HIV prevalence accounted for approximately 75% of the estimated HIV-positive TB cases (and deaths from TB) in 2007. While the proportion of TB patients who are HIV-positive in these countries has remained largely unchanged during the reporting period (at 42%), the estimated mortality rate of HIV-positive TB patients in those countries has declined (from 66 per 100 000 population in 2005 to 59 per 100 000 in 2007).

Increasing collaboration

The Global Plan suggests that, as a prerequisite for scaling up collaborative TB/HIV activities, countries must establish national mechanisms for collaboration (e.g. a coordinating body for TB/HIV activities).

Dramatic progress was made during the reporting period to develop and implement such mechanisms (Table 5). For example, from 2005 to 2007, the number of countries that had a national policy to screen people living with HIV for TB increased from 27 to 118. Globally, 49 countries reported testing of more than half of their notified TB patients for HIV/AIDS by 2007, a remarkable achievement in a short period of time.

In addition, among 63 countries[1] that had been specifically identified as priorities for implementation of collaborative TB/HIV activities and which collectively accounted for 97% of estimated HIV-positive cases worldwide, approximately two-thirds had established coordinating bodies, developed a joint TB/HIV plan and were undertaking HIV surveillance by 2007.

This progress has been the result of much increased collaboration, commitment, and communication between national HIV/AIDS and TB control programmes, and among other national and international stakeholders, including civil society groups and technical agencies.

Based on the information available, the scope and quality of TB/HIV services worldwide have significantly improved during the reporting period, and national success stories have demonstrated that Global Plan targets are achievable (see Increased testing of TB patients for HIV in Kenya and Rwanda, sidebar).

International cooperation

During the first years of the Global Plan, civil society and community groups have become increasingly involved in the global and country-level responses to TB/HIV coinfection, particularly in advocacy and treatment literacy efforts.

But in-country collaboration can be more effectively achieved when the efforts and opinions of international partners are aligned. During the reporting period, much progress was made in building consensus between major global stakeholders, such as the Global Fund, the International AIDS Society,[2] the Stop TB Partnership, UNAIDS (Joint United Nations Programme on HIV/AIDS)[3], the United States President's Emergency Plan for AIDS Relief[4] (PEPFAR) and WHO. There were several examples of greater public support for collaborative TB/HIV activities among the global community and prominent and influential decision-makers. Recognition of the importance of TB/HIV collaboration is at an all-time high.

Reducing the burden of TB among HIV-positive people

To reduce the burden of TB among HIV-positive people, the Global Plan calls for greater screening for TB and provision of isoniazid preventive therapy (IPT) among HIV-positive people attending HIV care services.

Table 5: Scale-up of collaborative TB/HIV activities, 2005-2007

NUMBER OF COUNTRIES ESTABLISHING MECHANISMS FOR COLLABORATION	2005	2007
A national body responsible for coordinating TB/HIV activities	37	104
A national plan for collaborative TB/HIV activities	34	94
A national policy to offer CPT to HIV-positive TB patients	40	103
A national policy to offer ART to HIV-positive TB patients	45	125
A national policy to screen people living with HIV for TB	27	118
National policies for provision of IPT to HIV-positive people	28	81

INCREASED TESTING OF TB PATIENTS FOR HIV IN KENYA AND RWANDA	2005	2006	2007
TB patients tested for HIV (percentage)	50%	60%	80%

[1] Refers to 41 countries that were identified as priorities at global level in 2002 and that account for 97% of estimated HIV-positive TB cases globally, plus 22 additional countries that UNAIDS has defined as having a generalized HIV epidemic.

[2] http://www.iasociety.org/

[3] http://www.unaids.org

[4] http://www.pepfar.gov

GUIDING THE GLOBAL RESPONSE TO TB/HIV COLLABORATION

The Stop TB Partnership established the TB/HIV Working Group in 2001. The Working Group is composed of representatives of Stop TB partners with a track record of demonstrable global commitment, ongoing global policy and implementation work, and resource for TB/HIV. The mission of the working group is to accelerate the implementation of collaborative TB/HIV activities to reduce the global burden of HIV related TB through effective collaboration between National TB and AIDS Control programs and other stakeholders, and through generation of evidence based policy and programme guidance in order to achieve the global TB/HIV targets set for 2010-2015 in The Global Plan to Stop TB.

The TB Infection Control subgroup of the Working Group facilitates development of policies, strategies, and guidelines for implementing effective TB infection control practices, monitoring and evaluation systems. It builds strategic partnerships and capacity for effective TB infection control of HIV, TB and other stakeholders active in infection control.

More: http://www.stoptb.org/wg/tb_hiv

The estimated number of HIV-positive people screened for TB in 2007 was far off Global Plan targets (0.6 million people screened against a target of 14 million), although some progress was made in screening for TB during the reporting period. The number of patients screened doubled from 2006 to 2007 (Table 4[1]).

Based on country reports, approximately 30 000 people worldwide were started on IPT in 2007, short of the Global Plan target (1.5 million people) (Figure 8).

[1] Global figures include countries in the Global Plan, i.e. countries in Central Europe and Established Market Economies are excluded here.

Figure 8: Number of HIV-positive people without active TB started on IPT (thousands)

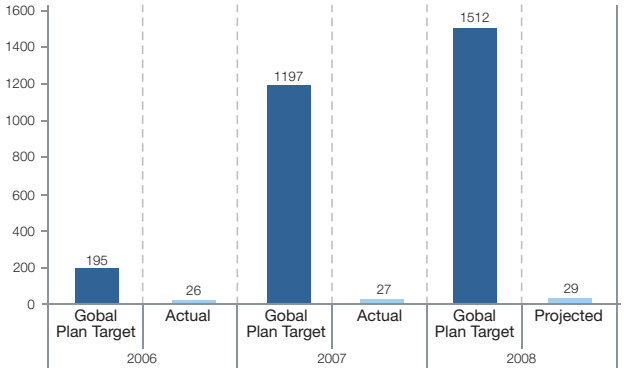
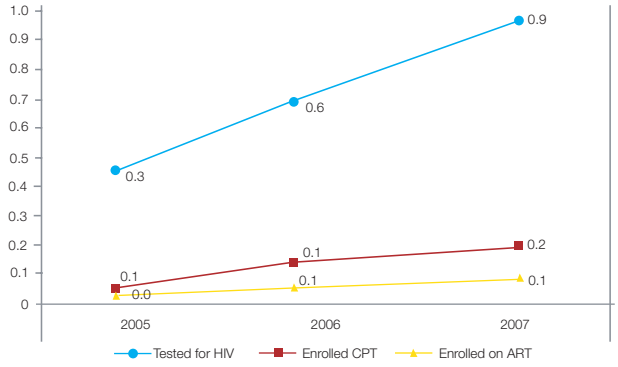


Figure 9: Reported HIV testing, CPT and ART among TB patients 2005-2007 (million)



THE THREE I'S: ISONIAZID PREVENTATIVE TREATMENT, INTENSIFIED CASE-FINDING AND TB INFECTION CONTROL

To enhance the uptake and visibility of collaborative TB/HIV activities among HIV stakeholders, the WHO Stop TB and HIV/AIDS Departments, in collaboration with other key partners, convened a meeting of international stakeholders in April 2008. The meeting led to the Three I's, a package of three key strategies to decrease the impact of TB on people living with HIV – isoniazid preventive treatment (IPT), intensified case-finding (ICF) for active TB, and TB infection control (IC). The meeting was an important step on the path towards improved services for people living with HIV and there was clear consensus on several key conclusions and concrete actions:

- TB is a major public health threat for people living with HIV and the community. TB threatens the significant health benefits achieved with scale-up of HIV care and treatment.
- The Three I's should be a central part of HIV care and treatment and are critical for the continued success of ART scale-up. All people living with or at risk of HIV in areas of high HIV and TB prevalence should be screened for TB and either diagnosed with TB or placed on IPT. Infection control is a key part of the screening process.
- People with HIV, health care workers and the community have a right to a safe clinical environment including immediate implementation of the Three I's including WHO recommended TB infection control policies.
- Implementation of the Three I's should be "owned by" HIV programmes and seen as indispensable as patient monitoring or cotrimoxazole prophylaxis.
- There is an urgent need to strengthen public health laboratory capacity and referral systems for the timely diagnosis of TB.
- There is an urgent need to strengthen the Three I's supply chain, particularly the development of INH/CTX co-formulation and/or co-packaging.
- Advocacy "Push" and "Pull": Top down and bottom up approach will be necessary to ensure implementation progress. Advocacy should focus on the importance of the Three I's and the need to create community demand for TB screening, IPT and IC as positive actions to fight TB.
- Monitoring and Evaluation is critical to monitor progress in scaling up the Three I's to people living with HIV and their communities.
- Resource mobilization is essential for success and we will need to mobilize political commitment and resources for Three I's implementation.
- Urgently develop national level policies and operational guidance to implement the Three I's.

More: http://www.who.int/hiv/pub/meetingreports/WHO_3Is_meeting_report.pdf

Reducing the burden of HIV among TB patients

The Global Plan calls for countries to reduce the burden of HIV among TB patients by providing HIV counseling and testing of TB patients, and co-trimoxazole preventive therapy (CPT) and ART to HIV-positive TB patients.

HIV testing of TB patients is an important gateway to interventions for both treatment and prevention. During the reporting period, there was notable improvement in this critical area: the reported number of TB patients tested for HIV more than doubled between 2005 and 2007 (from 336 000 to 858 000; Figure 9[1]).

[1] Global figures include countries in the Global Plan, i.e. countries in Central Europe and Established Market Economies are excluded here.

At least 27%[1] of all notified TB patients were tested for HIV in 2007. Although behind the Global Plan target (56%), it reflects a trend of increasing numbers of TB patients being tested for HIV. For example, African countries with a high HIV prevalence (accounting for approximately 75% of the HIV-positive TB cases) tested 41%[2] of their notified TB cases for HIV in 2007, an important step forward during the reporting period (from 14% in 2005).

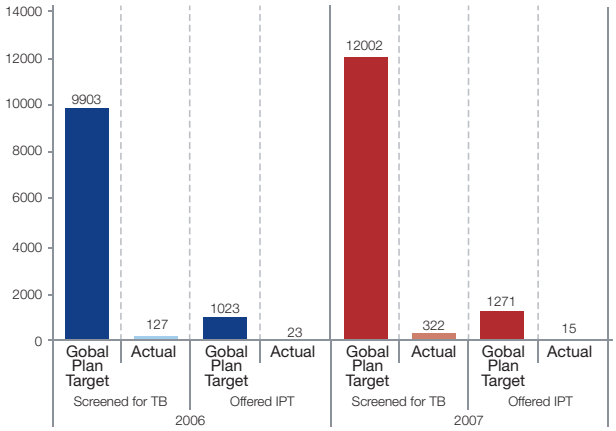
As with HIV testing of TB patients, provision of CPT and ART has not yet reached the level anticipated by the Global Plan: the number of HIV-positive TB patients enrolled on CPT in 2007 (197 000) was one third of the Global Plan target (567 000). Starting TB patients on CPT requires that they first be tested positive for HIV, however, and thus progress in this area is constrained by limited testing services. The percentage of TB cases found to be HIV-positive and that were enrolled on CPT exceeded Global Plan targets in 2006 and 2007.

In 2007, fewer than 100 000 HIV-positive TB patients were enrolled on ART, compared with a Global Plan target of almost 300 000. The percentage of diagnosed cases enrolled on ART (34%) was also behind the global target (51%) and fell from a year earlier (40%). This shows that while HIV testing rates have increased, delivery of treatment services for HIV-positive people cannot keep pace.

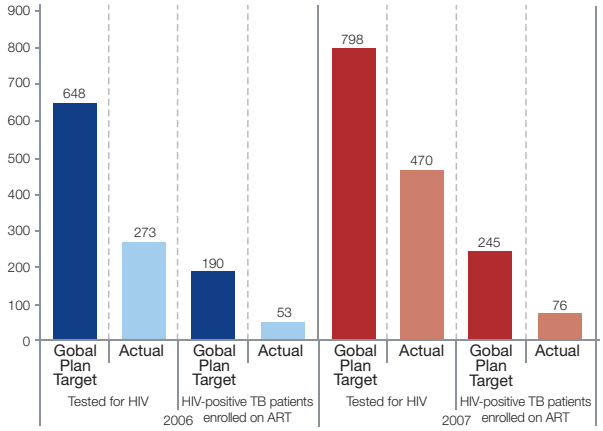
II. Progress by region

African countries with high HIV prevalence

Reported TB screening and IPT among HIV-positive people, 2006-2007 (thousands).

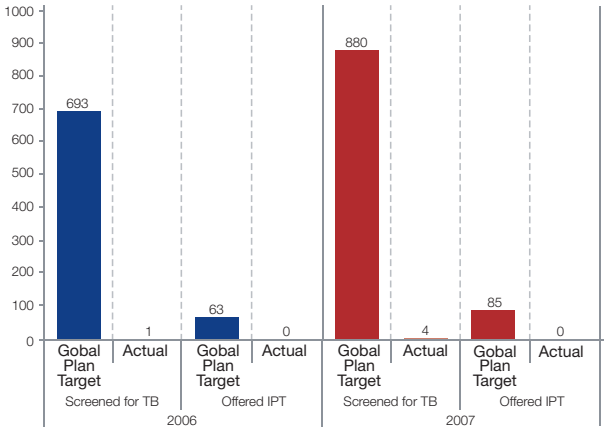


Reported HIV testing and ART among TB patients, 2006-2007 (thousands).

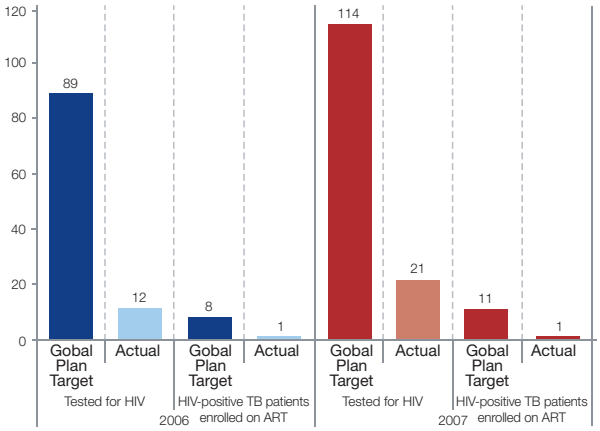


African countries with low HIV prevalence

Reported TB screening and IPT among HIV-positive people, 2006-2007 (thousands).



Reported HIV testing and ART among TB patients, 2006-2007 (thousands).

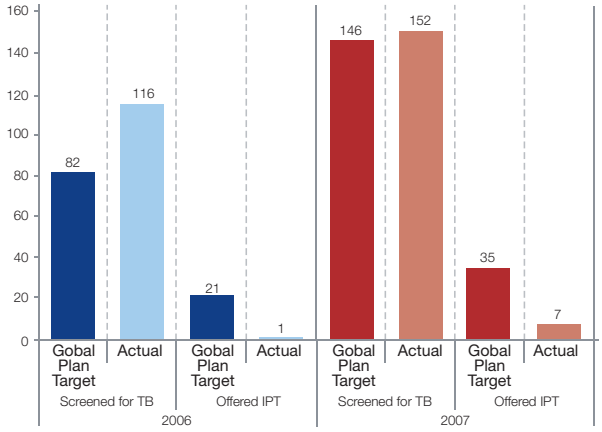


[1] There is a difference between world estimates and estimates in the Global Plan because the latter does not include Central Europe and countries classified as Established Market Economies. For example, an estimated 17% of all notified TB patients worldwide were tested for HIV in 2007.

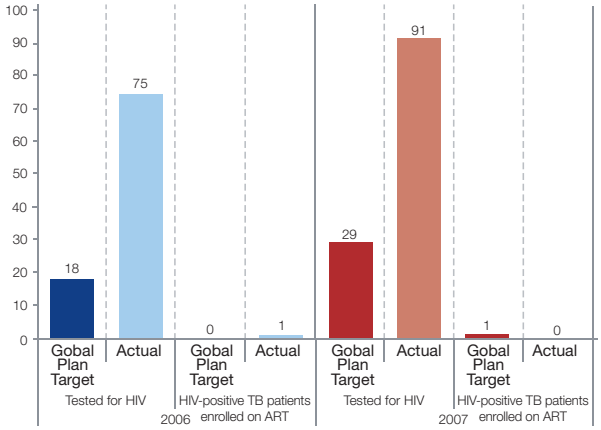
[2] Calculations based on the assumption that the maximum number of TB patients tested for HIV for each country is the number of notified cases multiplied by the population coverage of collaborative TB/HIV activities anticipated by the Global Plan.

Eastern European countries

Reported TB screening and IPT among HIV-positive people, 2006-2007 (thousands).

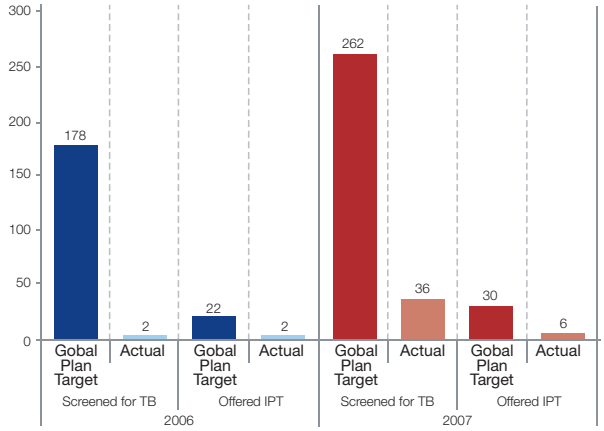


Reported HIV testing and ART among TB patients, 2006-2007 (thousands).

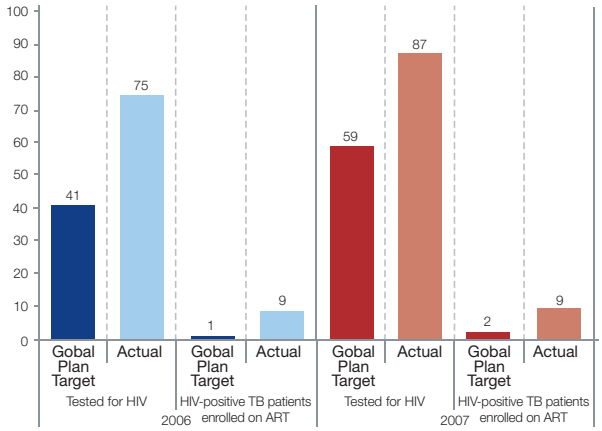


Eastern Mediterranean countries

Reported TB screening and IPT among HIV-positive people, 2006-2007 (thousands).

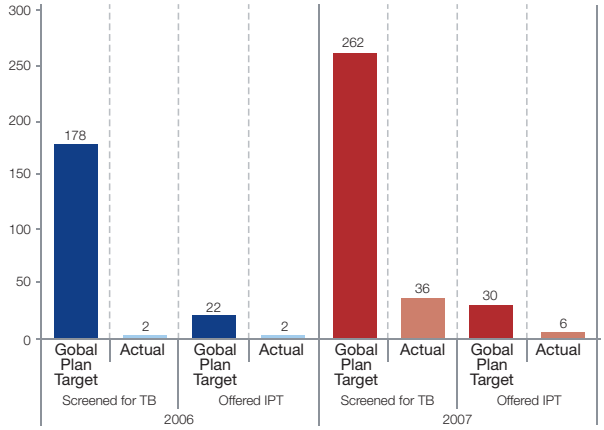


Reported HIV testing and ART among TB patients, 2006-2007 (thousands).

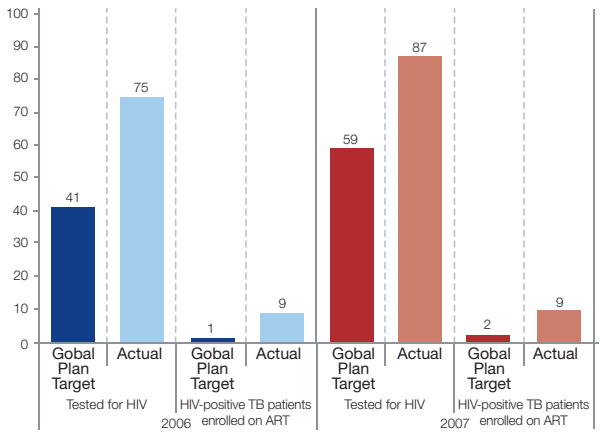


Latin American countries

Reported TB screening and IPT among HIV-positive people, 2006-2007 (thousands).

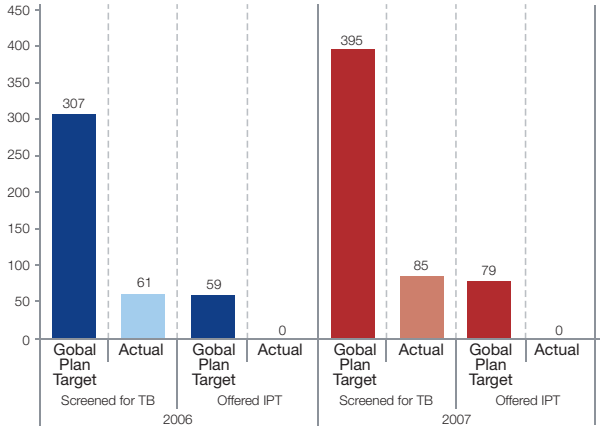


Reported HIV testing and ART among TB patients, 2006-2007 (thousands).

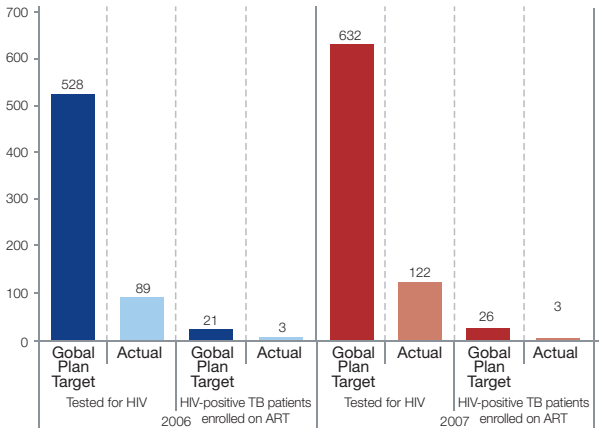


South-East Asian countries

Reported TB screening and IPT among HIV-positive people, 2006-2007 (thousands).

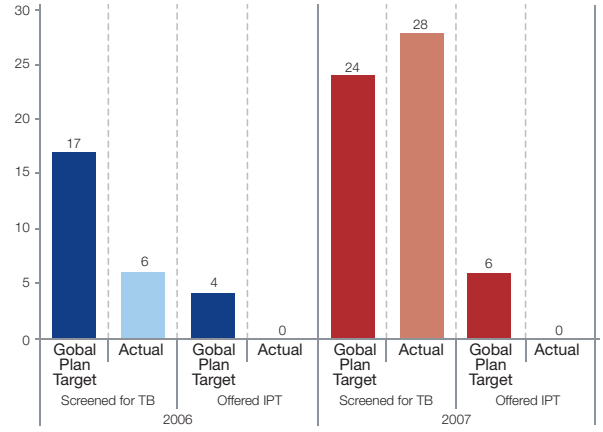


Reported HIV testing and ART among TB patients, 2006-2007 (thousands).

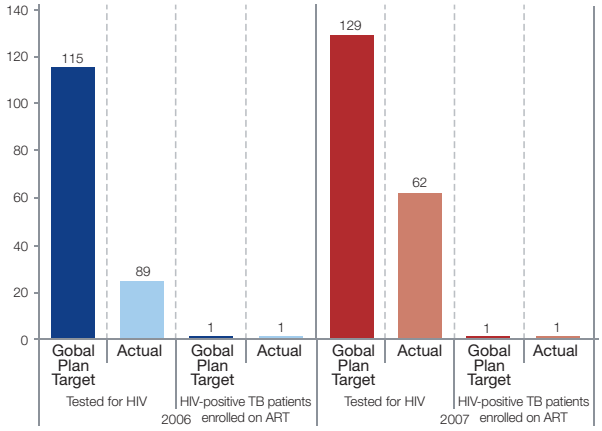


Western Pacific countries

Reported TB screening and IPT among HIV-positive people, 2006-2007 (thousands).



Reported HIV testing and ART among TB patients, 2006-2007 (thousands).



III. Budget requirements and financial investment

The TB/HIV component of the Global Plan included costs for all of the twelve collaborative TB/HIV activities recommended by WHO. Data reported through WHO's financial monitoring system allow the funding available and spent on TB/HIV during the three years 2006–2008 to be compared with funding requirements according to the Global Plan for 101 countries.[1] These 101 countries account for 93% of the world's TB cases.

The Global Plan estimated that US$1.4 billion was required for TB/HIV in the three years 2006–2008, of which approximately two-thirds was for African countries with a high prevalence of HIV (Figure 10). In contrast, countries reported expenditures of US$ 0.1 billion, with almost the entire shortfall compared with the Global Plan accounted for by two regions: Africa and South-East Asia. Of the US$ 136 million reported to be available in 2006–2008, 43% was from domestic sources, 33% was from grants from sources other than the Global Fund, and 24% was from the Global Fund.

The funding shortfall is consistent with the scale-up of activities such as HIV testing and provision of ART being behind Global Plan targets (see above). However, it should be highlighted that the funding shown in Figure 10 includes only funding reported by NTPs to WHO. This usually does not include funding for collaborative TB/HIV activities that is channelled via National AIDS control programmes or NGOs. In many of the countries with a high burden of TB/HIV, substantial funding has been made available through these mechanisms, including for ART for HIV-positive TB patients. The available funding for TB/HIV shown in Figure 10 is therefore underestimated. More comprehensive monitoring of funding for TB/HIV is needed.

[1] WHO requests information about funding for TB control from all countries on an annual basis, using a system established in 2002. During the period 2006–2008, 101 countries reported complete data.

IV. Challenges

Several challenges stand in the way of Global Plan targets for collaborative TB/HIV activities and threaten the achievement of the most important target of all: universal access. These challenges range from limitations of available technologies, to insufficient integration of TB and HIV service delivery and health systems, to failure to recognize the importance of TB for HIV services. Implementation of IPT is made difficult by operational challenges.

These challenges are compounded by a lack of effective monitoring and evaluation systems to document HIV/AIDS care and TB prevention and treatment activities in the field and inform the performance of programmes. There are many unanswered questions about the effects that combinations of drugs have on people undergoing ART and TB treatment.

Despite recent increases in HIV testing of TB patients, such testing should be expanded and HIV treatment services decentralized in order for activities to take place nationwide – essential for attainment of Global Plan targets.

V. Improving progress

To improve progress in the coming years and ensure that Global Plan targets are met in the future, partners should work closely to expand HIV testing of TB patients, and vice versa, including greater funding for HIV-related TB services in countries. Laboratories, particularly those at the peripheral level, must be enhanced to support both HIV and TB diagnostic capacity.

Research efforts (and funding) should also be intensified to identify better TB prevention tools for HIV-infected people. This will include establishing more and greater capacity to carry out clinical trials in key areas, such as combined treatment of HIV and TB for people who are HIV positive.

Although communication and collaboration among country programmes, donors and technical partners are beginning to yield greater funding for TB/HIV activities and for the infrastructure they require, these efforts must continue and be built upon.

E. Advocacy, communication and social mobilization

Expanding advocacy, communication and social mobilization (ACSM) in donor and endemic countries must be a priority in the next few years. ACSM is directed at building and financing a multilevel, multisectoral social movement to reverse the TB epidemic and achieve the Millennium Development Goals and the Stop TB Partnership's targets. Achieving a high level of social commitment within health service delivery systems is particularly crucial in the context of TB.

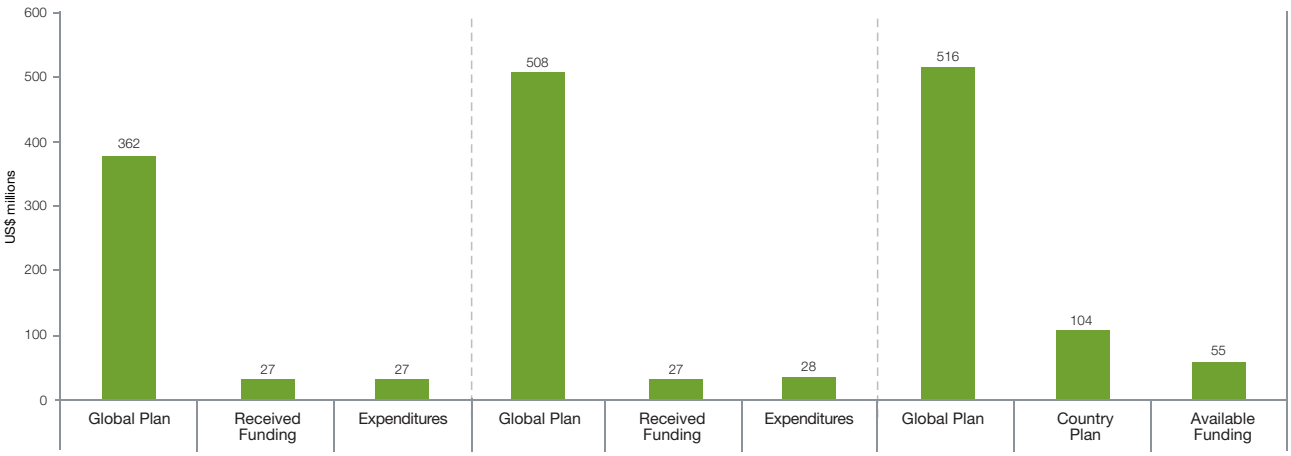
I. Global progress

Effective global advocacy is essential to place TB high on the political and development agendas in donor countries and in countries with high or medium TB incidence, to foster political will, and to increase financial and other resources on a sustainable basis.

The performance of global advocacy for TB during the first three years of the Global Plan was a success. Certainly, the development of the Global Plan itself, and the global and regional launch activities, contributed to unprecedented global awareness of TB.

In areas such as responding to emerging TB issues, broadening the coalition of Stop TB advocacy partners, and raising the profile of TB among policy-makers, legislators, funding institutions and the media, advocacy efforts performed very well. During the reporting period, the Stop TB Partnership grew from 463 partners in 2005 to 967 in 2008.

Figure 10: Funding required for TB/HIV in the Global Plan compared with available funding and expenditures reported by countries, 2006-2008.



Note: Since expenditure data for 2008 have not yet been reported to WHO, funding requirements for 2008 in the Global Plan are compared with a) the funding required for TB/HIV according to country plans and b) the funding available for these plans.

The appointment of the first-ever United Nations Secretary-General's Special Envoy to Stop TB, the former President of Portugal Dr Jorge Sampaio, has elevated the position of TB control on the political and development agendas of world leaders and national policy-makers (see sidebar).

Further to the great strides made in generating commitment among governments, global advocacy partners helped raise the profile of TB among politicians and world leaders, as evidenced by the focus in global fora on MDR-TB and TB/HIV. The prominence of TB as a discussion point during events such as the G8 summits (held in the United Kingdom and Russian Federation), the Berlin Conference on TB, the New York HIV/TB Global Leaders' Forum, the World Congress on Lung Health (Paris and Cape Town), the World Economic Forum (Davos) and the HIV/AIDS conferences (Toronto and Mexico) are to a great extent attributable to the work of Stop TB stakeholders.

The Stop TB Partnership Coordinating Board led several high-level missions to donors and endemic countries during the reporting period, meeting with heads of states, governments and agencies as well as policy-makers and key country stakeholders. Country missions included Canada, Indonesia, Nigeria, Italy, Germany, Thailand, the United Kingdom, the United Republic of Tanzania and the United States of America.

The European Ministerial Forum, '"All Against Tuberculosis" was held in Berlin, Germany on 22 October 2007. Representatives from ministries of 49 countries attended the forum, which was called on an emergency basis to advance the development of a Europe-wide approach to controlling and eventually eliminating TB. The gathered Ministers endorsed the Berlin Declaration[1] on Tuberculosis, which also called for the adoption of the Stop TB Strategy in all its components, including addressing the funding gap between the total resources available and the resources needed to control TB and accelerating the development of new diagnostics, drugs and vaccines to achieve the 2015 Millennium Development Goal for TB.

The number of donor countries implementing advocacy activities between 2006 and 2008 (Table 6) far exceeded the Global Plan target every year, begging the question of whether the target should be reviewed in light of its relevance to the overall objective of securing funds for implementation of the Global Plan.

[1] http://www.euro.who.int/Document/E91369.pdf

THE FIRST SPECIAL ENVOY TO STOP TB: FORMER PRESIDENT DR JORGE SAMPAIO

In 2006, the TB community welcomed former President of Portugal Dr Jorge Sampaio as the first UN Secretary-General's Special Envoy to Stop TB. Since that time, Dr Sampaio has elevated TB to previously unknown heights on the international political and development agenda and inspired strong commitment to the Global Plan to Stop TB among countries worldwide.

In one of his first international actions as UN Special Envoy to Stop TB, Dr Sampaio was a keynote speaker during WHO's 56th Africa Regional Committee in Ethiopia, urging Health Ministers to develop without delay the national emergency plans required to combat the TB epidemic. Less than a month later, Dr Sampaio met with former USA President Bill Clinton to discuss plans to work together on political advocacy around TB/HIV. Dr Sampaio continued his work, meeting with Mr José Manuel Barroso, President of the EU Commission, weeks later to encourage EU leadership to support the Global Plan. The Special Envoy then gave an opening address at the European CEO Summit on Business and AIDS, promoting improved collaboration between TB and HIV/AIDS programmes and opportunities for private sector involvement in the TB fight.

In 2007, Dr Sampaio toured southern African countries – including Malawi, Mozambique and South Africa – leading to the declaration of a TB Emergency in Malawi and a series of high level meetings in South Africa. Later that same year, Dr Sampaio addressed the European Parliament Development Committee, calling for EU-Africa Action plans to mirror the domestic TB Action Plan for the EU. He subsequently joined EU President Barroso for the announcement of additional EU funding for the Global Fund to fight AIDS, Tuberculosis and Malaria. In October, Dr Sampaio spoke at a Center for Strategic and International Studies policy event alongside US Senator Sherrod Brown, Head of PEPFAR Mark Dybul and Director of the WHO Stop TB Dr Mario Raviglione and discussed appropriations with several Members of Congress. These efforts, combined with the hard work of Stop TB partners, saw US commitments spending for global TB control double for the 2008 financial year, in addition to an increase in funding from the US President's Emergency Plan for AIDS Relief to address the TB/HIV co-epidemic.

In March 2008, President Sampaio joined by the WHO Director General and the Executive Directors of UNAIDS and the Global Fund launched the WHO Global TB Report in Geneva, Switzerland. Dr Sampaio then convened the first ever HIV/TB Global Leaders' Forum at UN Headquarters in New York, bringing together heads of government, public health and business leaders, heads of UN agencies including the Secretary General of the UN, and activists. Among other contributions to the TB community in 2008, the Special Envoy to Stop TB was a key speaker at the 2008 Annual Meeting of the Clinton Global Initiative, urging participants to intensify their commitment to collaborative action on HIV and TB, in particular preventing and treating TB among people living with HIV. The meeting brought together a diverse group of leaders from government, business, and civil society to examine pressing global challenges and transform that awareness into action.

The emergence of XDR-TB was a very serious but relatively unknown health threat when it raced to the forefront of public attention in 2006 through independent media reports. Advocacy partners played a key role in helping to develop a plan for the global response to XDR-TB.

II. Progress (country-level)

The Global Plan's vision for ACSM at country level is to bring about sustainable societal and behavioural change. To achieve the goals of the Global Plan, developing and implementing multisectoral, participatory and sustainable ACSM plans and forging national coalitions and partnerships around TB need to be supported by adequate in-country commitments to human and financial resources. Additionally, assistance to countries must be mobilized in the form of tools and franchising, training, technical advisers, opportunities for information exchange and regular formal assessments to ensure effective ACSM programming. Specific plans must be developed to provide training opportunities and tailored needs-based inputs to individuals and public sector institutions, with the aim of rapidly strengthening in-country ACSM capacities.

The Global Plan emphasizes that programme managers, medical officers, nurses, social workers and affected communities should work together to improve access to high-quality treatment for all populations. This acknowledgement is a critical step forward and provided the leverage needed to catalyse change in many countries during the reporting period. As a result, the first three years of the Global Plan have seen greater involvement by patient organizations and in-country, grass-roots organizations in TB care: in 2006 alone, 20 of the 22 HBCs reported community involvement in TB care. In 2008, all HBCs report implementing ACSM activities that target the general public, TB suspects and patients, health-care providers and policy-makers.

Facilitated by this change, many countries were able to successfully develop multiyear ACSM plans and to secure the finances needed to implement those plans: for example, 22 countries succeeded in raising grants from the Global Fund for ACSM amounting to US$ 43 million in round 8 alone.

Additional funding for grass-roots civil society organizations that seek to help shape policy at local and national levels was made available during the reporting period through the newly launched Challenge Facility for Civil Society.[1] In its first round of applications in 2007, 22 NGOs were awarded small grants in 12 endemic countries. In 2008, 23 NGOs were given grants in 17 endemic countries.

The number of endemic countries implementing ACSM activities in 2006–2008 exceeded Global Plan expectations (Table 6). One explanation may be that these first three years were spent cultivating the political and social change required to develop strategic ACSM plans and in securing the finances needed; and that ACSM activities will increase as those plans are put into action.

The first three years of the Global Plan also saw increasing interest for coalition building to bring together civil society, private sector, affected communities and other key constituencies at the local level. In addition to already existing national partnerships (e.g. in Brazil, Canada, Mexico, the Philippines and Uganda), several national partnerships emerged, including in Afghanistan, the Islamic Republic of Iran, Italy, Peru, Switzerland, the United Kingdom and the United States.

A great deal of international effort was expended during the first three years of the Global Plan on building ACSM capacity in countries and establishing a platform to provide the technical assistance that is so often required by countries. There has recently been an increase in the amount of assistance being provided to countries for strategic planning and implementation. However this assistance has frequently been in the very early phases of ACSM planning, such as the targeting of activities based on data from knowledge, attitude and practice (KAP) surveys and revising existing ACSM plans to better align ACSM objectives to TB control goals.

Table 6: Global Plan Milestones for Advocacy, Communication and Social Mobilization

INDICATOR	2006	2007	2008
Number of donor countries in which advocacy activities are being carried out			
Global Plan target	4	6	8
Actual	5	7	12
Number of HBCs in which advocacy activities are being carried out			
Global Plan target	8	12	16
Actual	9	13	17
Number of HBCs in which communication and social mobilization activities are being carried out			
Global Plan target	2	7	12
Actual	11	15	19

[1] http://www.stoptb.org/bi/cfcs

Nonetheless, the increasing participation of patient-centered organizations and networks, combined with the availability of funds and the existence of ACSM plans would appear to validate the assumption that continued progress and scale-up of activities can be expected in the coming years.

III. Budget requirements and financial investment

Data reported through WHO's financial monitoring system allow the funding available and spent on ACSM during the three years 2006–2008 to be compared with funding requirements according to the Global Plan for 101 countries.[1] These 101 countries account for 93% of the world's incident cases of TB.

The funding required for ACSM implementation in these 101 countries for the three years 2006–2008, according to the Global Plan, was US$ 0.6 billion (Figure 11). The funding reported to be available was US$ 0.2 billion. This shows that the funding available at country level was much less than the funding needs set out in the Global Plan. The main source of funding for ACSM was the Global Fund (45%), followed by the national governments (33%) and other bilateral sources (17%).

IV. Challenges

Full implementation of the Global Plan requires significantly increased funding for all TB activities, but particularly for ACSM, MDR-TB, TB/HIV, and research and development of new tools. If Global Plan targets are to be met, advocacy efforts must be sustained and improved in the coming years.

Advocacy efforts have not always been effectively packaged and coordinated to raise the funds necessary for full implementation of the Global Plan. While progress has been made to increase domestic funding for TB control, a significant amount of funding for national programme activities is dependent on contributions from external donors. Such reliance on donor funding puts at risk the long-term sustainability of national activities and requires greater attention from both global and national advocacy partners.

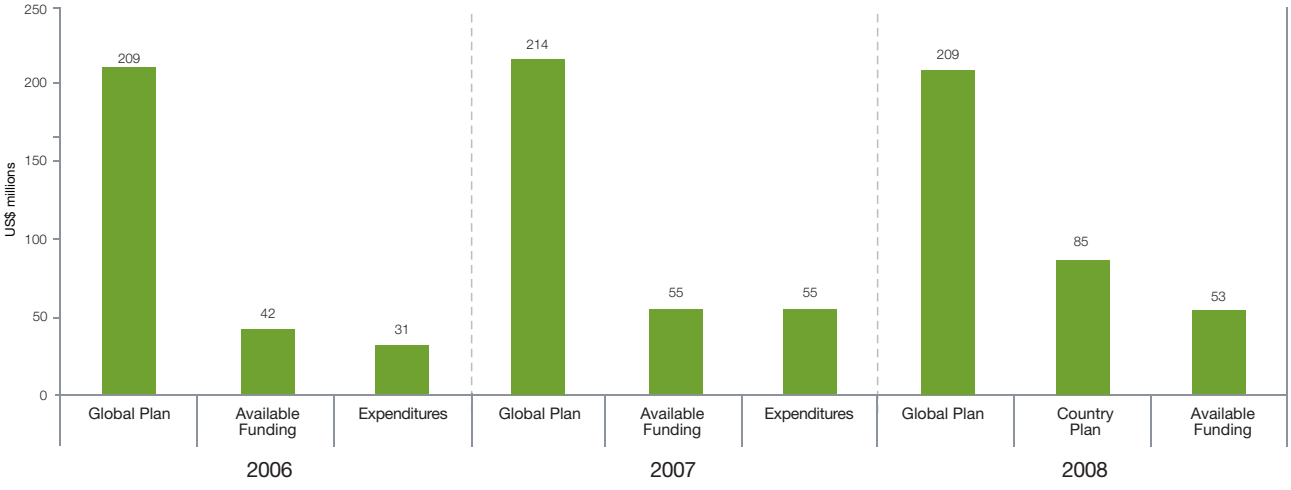
Despite the progress that has been made in ACSM for TB control, in-country capacity for planning, implementing and monitoring and evaluating ACSM initiatives needs to be further developed. This will require even greater commitment from endemic and donor countries to make strategic ACSM a priority in TB control.

V. Improving progress

To address the gap between the resources available for TB control and what countries need to achieve Global Plan targets, partners can:

- communicate to governments and other donors that humanity is at a moment of great opportunity, seeing progress with existing tools and with new, more powerful tools on the horizon. TB can be made a rare disease within a lifetime. Great success is possible if the will and resources are made available.

Figure 11: Funding required for ACSM in the Global Plan compared with available funding and expenditures reported by countries, 2006-2008.



Note: Since expenditure data for 2008 have not yet been reported to WHO, funding requirements for 2008 in the Global Plan are compared with a) the funding required for ACSM according to country plans and b) the funding available for these plans.

[1] WHO requests information about funding for TB control from all countries on an annual basis, using a system established in 2002. During the period 2006–2008, 101 countries reported complete data.

- stress that in a period of economic difficulty, to reduce efforts against TB would be extremely dangerous. Resistant TB would become widespread; TB/HIV co-infection would become even more common; access to effective treatment would continue to be denied to almost 40% of those individuals who develop active TB; and thus millions more people will continue to die unnecessarily.
- encourage governments of HBCs, especially those whose economies are growing, to significantly increase the resources they allocate for TB control. To facilitate this, efforts should be made to stimulate the creation of national Stop TB Partnerships in as many countries as possible.
- encourage existing donors to further increase their support for both operational TB work and research and development of new tools.
- encourage new donors to contribute to work against TB. This will mean dialogue with the emerging wealthier nations of the Middle East and of Asia.
- work with all partners to maximize public awareness of the need to accelerate TB control efforts.
- encourage governments to work with partners in their country who have the expertise that they may lack. This is key in ACSM, as some NTPs do not have a full-time ACSM expert to guide their activities.

The infrastructure required to engage with civil society groups (which make up nearly 50% of Stop TB partners) must be established to ensure that ACSM is as effective as possible.
Increases of domestic funding may be facilitated by further expanding country ACSM activities and engaging with national programme managers, and by providing them the tools and resources they require to more easily and effectively advocate for funding increases within their country.

Training will need to be mainstreamed into all TB training activities, to a greater or lesser extent, reflecting the mainstreaming of ACSM into national TB control. Training materials to support these efforts must continue to be developed, and aligned with other training materials, so as to ensure that Global Fund proposals reflect the entire reality of country. NTPs, civil society and community organizations must be given the tools they need to communicate the benefits of ACSM within their country and negotiate with corporate sectors, other ministries and within the ministry of health.

Finally, it will be essential that on-going ACSM efforts and their results are widely publicized and shared, so as to ensure that there is continued recognition of the added value of ACSM by countries and by donors. If results are not demonstrated, there is the risk that donors will decrease funding for such activities.

Chapter 2:
Achievements in Research

A. Overview

- Four new or improved TB diagnostics technologies and approaches endorsed by WHO and rolled-out at country level. Nine TB vaccines candidates enrolled in clinical trials.
- Nine TB drugs candidates in clinical trials, with several in advance stages. Great hope to shorten TB treatment to 3/4 months.

B. Achievements in TB Research

New tools for diagnosing, preventing and treating TB are needed. New tools that are effective and efficacious in people of all ages, including people with HIV, against all forms of TB should be developed and introduced in TB control. Such tools should be able to deliver quicker results, be affordable to the poor and less complex in terms of infrastructure requirements.

Developing, evaluating and implementing more effective diagnostics, drugs and vaccines not only requires large-scale investment, but the coordinated, concentrated efforts of all those with a stake in research: academics, scientists, manufacturers and pharmaceutical companies, donors and multilaterals, governments and national programmes, physicians, advocates and patients themselves.

Given the many contributors to research, and the diversity of work that must be carried out to reach development goals (including basic, translational and operational research), precisely measuring the financing that has been invested in new tools so far and the gap that remains is challenging. Nonetheless, evidence-based reports on financing for new tools recommend that funding must increase exponentially in order to achieve Global Plan goals.

1. Developing new tools to diagnose TB

New diagnostic tools for TB are desperately needed. WHO reports that although treatment success rates are improving every year, case detection rates have decelerated globally. In Africa, less than 50% of estimated cases are being detected in DOTS programmes. Compounded by new challenges, such as drug resistance and TB/HIV co-infection, the lack of effective, quality controlled diagnostic tools and systems endangers the gains that have been made in TB control.

The Global Plan calls for the development and introduction of cost-effective and appropriate new diagnostic tools that are accessible and affordable to patients, especially the poor.

I. Progress

The introduction of a new diagnostic technology for the diagnosis of MDR-TB (molecular line probe assays) for referral laboratories, endorsed by WHO in 2008, was a major breakthrough. The newly endorsed tool is nearly as accurate as culture but is capable of providing results in a few hours or days instead of weeks. Work is currently under way for its introduction in 16 countries (see box “Collaboration between Stop TB partners and donors delivers quick laboratory results”).

In addition, the last three years have seen the creation of a rich pipeline of potentially useful products.

Of seven promising tools currently in late stage development and evaluation, four require only basic laboratories and limited training. This emphasis on reaching peripheral contacts is even more obvious in tests in early phases of development: the majority of these tests intend to serve that purpose. Much more progress is needed to develop and evaluate tests to detect active TB at the first point of care (e.g. for use by rural health workers).

There has also been progress in evaluating and endorsing methods to improve existing tests and techniques (Table 7). In addition to evaluating existing tools, partners have worked closely to address gaps in scientific knowledge in order to support research of new tools. A number of systematic reviews of the literature have successfully synthesized knowledge about TB diagnostics and been used to inform global policy and to forge an urgent research agenda.

Progress has been made in bringing together the diverse partners involved in diagnostics development, evaluation and implementation. Recognition of the importance and value of collaboration is evidenced by the tripling in size of the Working

Group on New Diagnostics (see Coordinating research in new diagnostics, sidebar), convened by FIND and the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases[1] (WHO/TDR).

The Working Group on New Diagnostics and the Retooling Task Force[2], in collaboration with other partners, have published a guide[3] to the diagnostics pipeline for NTP staff to help assist and inform the selection of new tools by countries.

II. Challenges

Several challenges impede the development of appropriate new diagnostic tools for TB. Although a wide range of research institutions are involved in developing and evaluating new tools, a pronounced lack of funding hampers this work. More funding is also needed to establish and maintain a platform of clinical trial sites for evaluation and demonstration studies.

The amount of research being carried on is not sufficient in some areas, and incentives must be provided to advance further work in this vital field. In particular, more research to enhance the impact of existing diagnostics (or combinations of diagnostics) on case detection within clinical algorithms and more biomarker basic research for antigen discovery is needed.

Furthermore, while much progress has been made in delivering new tools, many of these tools require expensive, complicated biosafety infrastructure that limits their use to district facilities

COORDINATING RESEARCH IN NEW DIAGNOSTICS

The Stop TB Partnership established the Working Group on New TB Diagnostics in 2001. The Working Group coordinates and facilitates development, evaluation and implementation of new and modified diagnostics in a scientifically acceptable and timely manner by linking all stakeholders involved in the diagnostic development and evaluation pathway. The Working Group was established to develop a toolbox of cost-effective and appropriate new diagnostic tools, which perform equally well in HIV-infected subjects, to:

- improve TB case detection, through increased sensitivity and specificity and improved accessibility - simple, accurate, inexpensive tests that can be performed at low levels of the health care system and that produce results on the same day are the ultimate goal;
- rapidly and inexpensively identify drug-resistant TB, permitting timely, effective treatment to reduce both individual morbidity and continuing transmission;
- reliably identify latent TB infection and determine the risk of future progression to active disease, allowing rational use of preventive therapy.

More: http://www.stoptb.org/wg/new_diagnostics

Table 6: Global Plan Milestones for New Diagnostics

GLOBAL PLAN INDICATOR	TARGET	PROGRESS
REFERRAL LEVEL		
Rapid culture (+DST) for M. tuberculosis and diagnosis of MDR-TB	2006	Endorsed by WHO in 2007
Rapid speciation test for confirming M tuberculosis grown in culture	2008	Endorsed by WHO in 2007
Manual nucleic acid amplification test (NAAT) for detection of M tuberculosis and isoniazid and/or rifampicin resistance	2008	Endorsed by WHO in 2008
Automated NAAT for detection of M tuberculosis and rifampicin resistance	2008	Expected 2010
PERIPHERAL LABORATORY		
Improved microscopy	2006	More sensitive definition of a smear positive case: endorsed by WHO in 2007 Reduced number of smear examinations required: endorsed by WHO in 2007 Light-emitting diode (LED) flurorescene micros-copy - approval by WHO expected in 2009 Front-loaded smear microscopy - approval by WHO expected in 2009
Introduction of simplified NAAT (1)	2008	Expected 2011

[1] http://www.who.int/tdr/

[2] http://www.stoptb.org/retooling/

[3] New laboratory diagnostic tools for tuberculosis control (ISBN 978 92 4 159748), World Health Organization, 2008.

and national reference laboratories. Much greater effort must be made if partners and countries are to achieve the goal of faster substitutes to culture for detecting smear-negative TB, improved antibiotic susceptibility testing, and tests for the detection of latent infection at primary health care level (health post) and at the peripheral laboratory level.

The development of new diagnostics for the early detection of TB is also held back by a lack of understanding of the basis of latent TB infection, and the processes involved in latency. Typically, patients are not diagnosed until they develop active TB – meaning they are already transmitting the disease as well as suffering the biological, economic and social consequences of the disease. Treating patients with active TB reduces, but does eliminate transmission. Diagnosing and treating patients with latent TB – before they started transmitting it to others – would vastly reduce the number of new TB cases each year, and reduce socio-economic toll of the disease, especially on the poor.

III. Improving progress

One of the reasons for the lack of funding for new diagnostic tools is that there are few organizations that are willing and able to champion a new tool and guide it through the complex, lengthy process of development, evaluation and ultimately endorsement by WHO. Without such champions, many potential tools are "orphaned" after proof of principle and therefore do not attract donor funding.

The creation of a scientific blueprint outlining the steps and procedures for development and evaluation of new diagnostics is a strategy being pursued by partners that is expected to reap benefits and serve as an objective basis for describing and staging diagnostic technologies in an up-to-date and inclusive pipeline of diagnostic technologies under development. Based on this blueprint, partners would be able to easily identify where products are not progressing – making it clear to donors and industry where a financial investment can do the most good.

Although still a major challenge for partners, there is hope that recent developments will help move diagnostic tools to the periphery of health-care systems in the coming years. The launch of the GLI established a dedicated mechanism to strengthen integrated TB laboratory networks and enable accessible high-quality laboratory services for all and especially the poor. Several diagnostic tools currently under development and evaluation may offer less expensive, high performing alternatives for peripheral diagnostic centers.

The challenge of diagnosing latent TB, when met, will have a profound impact on TB control worldwide. Fortunately, this is now a topic for research identified by the Grand Challenges Exploration Grant Initiative[1] supported by the Bill & Melinda Gates Foundation, the Canadian Institutes of Health Research, the National Institutes of Health and the Wellcome Trust.

COLLABORATION BETWEEN STOP TB PARTNERS AND DONORS DELIVERS QUICK LABORATORY RESULTS

People in low-resource countries who are ill with MDR-TB will benefit from faster diagnosis – in two days, not the standard two to three months – and appropriate treatment thanks to close collaboration between members of the Stop TB Partnership and international donors. After WHO recommended molecular "line probe assays" for rapid MDR-TB diagnosis worldwide, the Stop TB Partnership, the Foundation for Innovative New Diagnostics (FIND), UNITAID and WHO announced that over four years – as laboratory staff are trained, laboratory facilities enhanced and new equipment delivered – 16 countries will be eligible for grants to use rapid methods to diagnose MDR-TB, including the molecular tests. Funded by UNITAID, the countries receive the tests through the Stop TB Partnership's Global Drug Facility, while the Global Laboratory Initiative and FIND help countries prepare for installation and use of the new tests, ensuring necessary technical standards for biosafety and the capacity to accurately perform DNA-based tests.

2. Developing new drugs to treat TB

Today's TB drug regimens take too long to administer and require too many medications. Treatment of drug sensitive disease requires 6-9 months while treatment of drug-resistant TB is even more lengthy, taking 18-24 months or longer. Second-line drugs are also much more toxic and considerably more expensive than the standard first-line anti TB-regimen. Furthermore, current first-line treatment regimens are not compatible with certain common antiretroviral therapies (ART) used to treat HIV/AIDS.

The Global Plan aims for the development, trial and introduction of new drugs, preferably with novel mechanisms of action that would allow a shorter TB regimen for both drug-sensitive and drug-resistant disease. Shortening treatment to four or two months or even less should improve patient adherence and lessen the likelihood of patients developing drug resistance. New drugs are needed that will also be effective in treating children, and latent TB infection, and will be compatible with ART. Furthermore, new regimens need to be affordable and easily managed in the field.

The main goal of the Global Plan is to introduce the first new TB drug in 40 years in 2010 and – by 2015 – to be on the verge of a new TB regimen that will achieve cure in 1–2 months. That treatment would be effective against MDR-TB and be compatible with ARV treatment. By 2015, clinical trials for a new treatment of latent TB infection should also be under way.

I. Progress

Because of the uncertainty surrounding a new drug until the very moment it is approved for use, and the high attrition

[1] http://www.grandchallenges.org/explorations

CASE STUDY: UNITED REPUBLIC OF TANZANIA

The Tanzanian National TB and Leprosy Programme (NTLP) has made progress in recent years, successfully treating 85% of its cases detected and expanding its TB/HIV coordinated activities. Nonetheless, it faces challenges. Two of its greatest ambitions are to improve detection of new, smear-positive TB cases and detection of drug-resistance. New diagnostics were identified by Tanzania as one way to help achieve these goals.

In 2007, the NTLP began evaluating LED fluorescence microscopy as a more appropriate tool for improving case detection at the periphery. Standard light microscopes were converted to LED using an adaptor. Conventional fluorescence microscopy, not LED-based, is on average 10% more sensitive than traditional Ziehl-Neelsen microscopy but also more prone to false positive results. Because it builds upon existing techniques, it does not require costly infrastructure or extensive training. The positive response to the LED trials has prompted the NTLP to begin rapidly scaling-up its availability at all district hospitals and high-volume sites. The adoption and implementation of such new tools requires large programmatic changes, unfortunately making it impossible to implement immediately at peripheral laboratories, where the need for the poor (and potential impact in high-volume laboratories) is likely to be greatest.

Tanzania has also begun introducing faster, more sensitive liquid culture and DST at national and regional reference laboratories. The availability of these tests is expected to improve the diagnosis and management of TB patients. Increasing detection of drug resistant cases poses different challenges at the periphery. As in most countries, samples from patients failing treatment are sent to a central reference laboratory. Transporting these samples can be a challenge – and specimens may be delayed for long periods or even lost. Long delays and other adverse conditions of transport can result in the specimens being not suitable for culture (because of contamination) or falsely considered negative. Delayed detection of resistance can have tragic results.

In 2009, the NTLP will assess the feasibility of introducing rapid testing for detecting drug resistance. Studies have shown that line probe assays (endorsed by WHO in 2008) adequately detect rifampicin resistance when used directly on smear-positive patients, thus confirming their potential value for screening suspected MDR-TB patients.

rate of candidates, drug development is a highly resource intensive process. To increase the chances of success, a variety of candidates must be actively pursued and sustained. Furthermore, the complexity and safety requirements of clinical trials place limits on the number of clinical trials that can be carried out simultaneously.

Careful coordination between all members of the global TB drug development community is of paramount importance if the limited human, financial and logistic resources available are to be maximized.

During the reporting period, partners facilitated TB drug development by bringing together an encouraging discourse between actors working at different stages of the TB drug research and development. This approach improved communication between constituencies, helped build a common vision for TB drug development, and rallied diverse stakeholders to advocate with one voice for sustained and significant financial and political commitment to the development of new TB drugs.

Through the Working Group on New Drugs (see sidebar), convened by the Global Alliance for TB Drug Development[1] (TB Alliance), partners have monitored the progress of global TB drug development programs. This work has revealed an expanding, but insufficient, pipeline of products in the early stage of development. The 2007 pipeline included five novel TB drug candidates in clinical trials, 12 trials of new approaches to treatment, and eight preclinical candidates – too few to assure new drugs will be available by target dates in the Global Plan.

More promisingly, actors in both private and public sectors, often working in collaboration, have broken ground with key clinical studies during the reporting period:

- gatifloxacin (OFLOTUB) and moxifloxacin (Bayer[2], TB Alliance, University College London[3], and the Medical Research Council[4]) entered Phase III clinical trials;
- TMC207 (Tibotec, Inc.[5]), OPC-67683 (Otsuka Pharmaceutical Co., Ltd.[6]) and PA824 (TB Alliance) entered Phase II clinical trials; SQ109 (Sequella, Inc.[7]) and the pyrrol LL-3858 (Lupin) entered clinical development Phase I; Linezolid (CDC TBTC, NIH/NIAID[8]) completed an early bactericidal activity (EBA) study; Rifapentine (CDC TBTC, sanofi-aventis, Johns Hopkins) containing regimens were studied in trials;
- TMC207 and OPC-67683 became the first novel TB drug candidates to be in clinical development for resistant disease.

COORDINATING RESEARCH IN NEW DRUGS

The Stop TB Partnership established the New Drugs Working Group in 2001.

The Working Group was established to facilitate global collaborations for the development of new TB drugs, promoting coordination of all stakeholders in TB drug development. The purpose of the Working Group is to ensure that scientists, academics, pharmaceutical companies, donors, multilaterals, and patients themselves are working together to speed the development of new drugs for TB. The Working Group serves as a mechanism through which members individually and collectively support the field of TB drug research by providing input into core publications and public policy recommendations developed by the Partnership. It also aims to ensure close coordination between researchers working on new tools and public health stakeholders involved in TB control.

More: http://www.stoptb.org/wg/new_drugs

In addition, promising drug discovery is being undertaken and sponsored by many organizations (eg. Novartis, GlaxoSmithKline, Astrazeneca, New Medicines 4 TB, Sequella, TB Alliance, Vertex Pharmaceuticals, sanofi-aventis, Bill and Melinda Gates Foundation, Eli Lilly TB Drug Discovery Initiative, NIH/NIAID) and individual academic investigators. Critical initiatives such as the TB Alliance Clinical Trials Site Assessment have made progress to enable more efficient clinical development of TB drugs in the future.

Finally, studies have been published during the reporting period, providing information crucial to success of the global TB drug research and development endeavour, such as the TB Alliance's Pathway to Patients[9] – the first comprehensive analysis of how today's TB drugs reach patients on a global scale.

II. Challenges

Years of sustained collaborative effect and commitment are nonetheless still required to reach the Global Plan's goals regarding new TB drugs and regimens.

Although there may be promising new drugs in the global TB drug pipeline, there are several challenges ahead:

- Drug candidate attrition. At best, only 10% of drug candidates that enter the clinical pipeline advance to registration. Thus, a

[1] http://www.tballiance.org
[2] http://www.bayer.com
[3] http://windeyer.ucl.ac.uk
[4] http://www.mrc.ac.uk
[5] http://www.tibotec.com
[6] http://www.otsuka-global.com
[7] http://www.sequella.com
[8] http://www.clinicaltrials.gov
[9] Pathway to Patients: Charting the Dynamics of the Global TB Drug Market. Global Alliance for TB Drug Development, 2007.

robust and sustained pipeline of new candidates and backup discovery programs are absolutely essential to success. The current portfolio is simply too small to expect entirely new regimens by the dates outlined in the Global Plan;

- Lack of understanding of the biology of persistence: to achieve the objective of radical treatment shortening, validated drug targets relevant to persistent M. tuberculosis are still required;
- Lack of tools and knowledge to ensure we succeed in capturing the potential of a drug, for example an understanding of pharmacokinetics and pharmacodynamics and the drivers of TB drug safety;
- Clinical trial site capacity: the paucity of Good Clinical Practice-compliant sites severely limits the progress of clinical development of TB drug candidates as well as optimization of existing TB drugs.
- Lack of funding for TB drug research and development.

III. Improving progress

Continued multi-year worldwide commitment, research and vigilance will be required to achieve the Global Plan goals regarding new drugs for TB. But the coordination and planning carried out in the first three years of the Global Plan has positioned partners to enter a new phase of work, more focused on intra-constituency activities designed to address challenges.

To improve progress towards Global Plan targets, Stop TB partners (i.e. sub-groups of the New Drug Working Group) will focus on five key challenge areas. Each sub-group is composed of experts committed to addressing obstacles that, when overcome, will move the whole field forward. These sub-groups address:

- Biology/Targets: will focus on M. tuberculosis biology, and to identify, and prioritize validated drug targets;
- Candidates: will efficiently identify advance compounds capable of becoming candidate drugs;
- Tools and Critical Knowledge: will promote and advance technologies and understanding needed for better, shorter clinical trials and to ensure the candidates and regimens with most potential are recognized as such;
- Clinical Trials: will support successful clinical development with several initiatives, including trials site capacity and identification of regulatory issues.

During the first half of 2009 these teams will prepare detailed mappings of the activities, capabilities and resources currently available and needed in the future, and establish priorities for each of their areas. During the second half of 2009, teams will scale-up advocacy and project activities while maintaining frequent communication to ensure all partners remain aware of each other's developments. During 2010-2011, the focus will shift to implementing those collaborative activities judged by each team to be most likely to realize their strategy and, hence, move closer to delivering new TB drugs.

3. Developing new vaccines to protect against TB

Today's TB vaccine, Bacille Calmette-Guérin (BCG), was developed more than 85 years ago and is routinely given to infants in much of the world. While it provides some protection against severe forms of TB in infants and children, it is unreliable against pulmonary TB.

There is an urgent need for a modern, safe and effective vaccine that would prevent all forms of TB, including drug-resistant TB, in all age groups and among people with HIV. Improved vaccines and vaccination strategies will make a crucial contribution to achieving the Stop TB Partnership's target to reduce the global incidence of TB disease to less than one case per million people by 2050. Facilitating the development of new vaccines for TB is an essential part of the Stop TB Strategy and the Global Plan. The goal is to have a safe, effective, licensed TB vaccine available at reasonable cost by 2015.

I. Progress

Between 2006 and 2008, tremendous progress was made to develop new vaccines and vaccination strategies for TB, however much work remains to be done if the goals outlined in the Global Plan are to be realized.

Several vaccine candidates have entered into early stage clinical trials. Given the high attrition rate of candidates, however, it is essential that new candidates continually enter into trials. Since 2006, the pace at which new candidates have entered clinical trials has accelerated.

Non-profit organizations such as Aeras Global TB Vaccine Foundation[1] and the Tuberculosis Vaccine Initiative[2] and other researchers from the public, private and academic sectors have contributed extensively to develop and catalyse new TB vaccine candidates. Some candidates would improve BCG, while others would "boost" BCG or an improved BCG, thereby extending its protective effects. At present there are several new vaccine candidates in various stages of clinical trials, with many more in preclinical development.

The Global Plan calls for at least 20 vaccine candidates to enter Phase I clinical trials by 2015. To date, nine vaccine candidates have entered clinical trials, and some have moved beyond Phase I (Table 8). Several candidates are in preclinical development and are anticipated to enter clinical trials in the coming years.

The Global Plan also calls for nine candidates to be evaluated in Phase II trials: by 2008 there should be at least two vaccines in Phase IIb or "proof of concept" trials. By the end of the reporting

[1] http:// www.aeras.org
[2] http:// www.tbvi.eu

Table 8: TB vaccine candidates by phase of development

STRATEGY	CANDIDATES
PRIMING	
Preclinical	13
Phase I clinical trial	2
Phase II clinical trial	0
BOOSTING	
Preclinical	17
Phase I clinical trial	3
Phase II clinical trial	2
Phase III clinical trial	1
IMMUNOTHERAPY	
Preclinical	11
Phase I clinical trial	1
Phase II clinical trial	1

Note: *Includes vaccine candidates as of September 2008. For more information on the type and names of the candidates, check the vaccines pipeline: www.stoptb.org/retooling. Please note that some candidates fall under multiple categories.*

period, three vaccine candidates had entered Phase II clinical trials and one candidate is planned to enter Phase IIb in early 2009.

No candidates, with the exception of a therapeutic vaccine preparation (Boosting Strategy, Table 8), were expected to enter Phase III efficacy trials during the timeframe of this report. Nonetheless, partners have laid the groundwork for future Phase III trials by defining clinical endpoints, developing functional assays, strengthening regulatory capacity and capacity at field sites in high burden countries, and enhancing advocacy and communications efforts.

II. Challenges

Several significant challenges must be addressed to realize the Global Plan vision of a new TB vaccine by 2015. These challenges include:

- *Scientific challenges.* One of the greatest scientific challenges in developing new TB vaccines is related to the uncertainty about identifying vaccine candidates, including measuring vaccine immune responses that will provide consistent protection against TB and the lack of experience with new TB vaccines in human populations. As a result, the scientific community is pursing a dual strategy of maintaining support

for relevant activities in vaccine discovery research while maximizing the number of candidates introduced into clinical trials. This approach increases the chances for developing an effective vaccine.

- *Diagnosing TB in children.* A key operational challenge in developing new TB vaccines is the difficulty in determining a definitive diagnosis in infants and children who are the main targets for new vaccines and are critical in clinical testing. Newer, experimental diagnostics are currently being evaluated to determine if they will provide a solution to this dilemma.
- *Field site development.* The development of vaccine trial sites appropriate for large-scale Phase III efficacy trials is also a challenge. Vaccine trial sites must be created within communities with both a high prevalence of TB and a sufficient research infrastructure. Preparation of these sites involves substantial investment in physical infrastructure, local research capacity and human resource capacity. The Working Group has committed its members to a goal of supporting the development of clinical trial field sites in order to meet aggressive targets for testing of new vaccines. The most advanced site, which is equipped to conduct such large-scale trials, is in the Western Cape region of South Africa. Efforts are being made to develop additional sites in African and Asian countries, including Cambodia, India, Kenya, Mozambique, and Uganda, but greater investment is needed.
- *Financial challenges.* Despite impressive commitments by philanthropic organizations and the public sector, the Global Plan estimates a funding gap of over US$ 1 billion to achieve the goal of developing a new, more effective TB vaccine.

III. Improving progress

As with the TB Drug Development community, Stop TB partners (i.e. task forces within the Working Group on New TB Vaccines) will focus on five key areas in order to address the challenges faced in TB vaccine development. These task forces consist of experts in their respective fields, and their purpose is to build consensus in the vaccine community regarding critical issues, and to identify common approaches to advancing vaccine candidates.

- The *Innovative Approaches to TB Vaccine Development* task force brings experts in TB and immunology together with specialists from other disciplines to promote "out-of-the-box" thinking in TB vaccine development. The task force held its first meeting in July 2007, and plans to convene a meeting in 2009 specifically on issues related to live vaccines.
- The *Harmonization of Laboratory Assays for TB Vaccine Development* task force was formed (a) to promote the harmonization of immune assays in use at various clinical trial sites and (b) to develop a robust functional assay for use in clinical trials. The task force will coordinate a collaborative research project in 2009-2010 that focuses on determining the reproducibility of different mycobactericidal assays under field conditions. This could have broad implications for the field of TB vaccine research in terms of identifying correlates of protection and determining if a vaccine is likely to be effective.
- The *Clinical Research Issues in TB Vaccine Development* task force was formed to address issues such as defining clinical endpoints and developing new diagnostic paradigms to improve TB diagnosis in difficult populations, particularly children and people who are immunocompromised. This task force will also support efforts to strengthen capacity at clinical trial sites through a network of endemic country clinical trial sites.

COORDINATING RESEARCH IN NEW VACCINES

The Stop TB Partnership established the Working Group on New TB Vaccines in 2000. The Working Group was established to foster and coordinate collaborative efforts to develop novel vaccination approaches that will be effective in reducing TB disease. The Working Group is responsible for catalyzing and coordinating the discussion between members of the community and ensuring that members of the community collaborate and communicate effectively.

More: http://www.stoptb.org/wg/new_vaccines

One of the main challenges to TB vaccine development is mobilizing sufficient resources to support the broad continuum of activities inherent in this work – ranging from basic research and discovery through to product development, field site development, clinical testing, manufacturing, licensure and distribution.

- The *Advocacy for TB Vaccine Development and Implementation* task force was formed to raise awareness at the global and country level of the critical need for new TB vaccines. The goal of these advocacy efforts is to create an environment that is amenable to mobilizing resources for the global efforts to develop new vaccines. The task force convened in October 2008 and has begun to develop a strategic workplan based on the discussions that took place.
- The *Economics and Product Profiles* task force was formed to develop estimates of the economic value of new TB vaccines to support the case for increased investment in vaccine research and development, and to analyse financing models and incentive programs intended to spur private sector involvement in TB vaccine development. The task force commissioned a landscape analysis to provide information that will support a well-informed discussion on a range of economic issues critical to the rapid development and deployment of improved TB vaccines. In addition, this analysis identified existing resources and gaps in knowledge to help the sub-group focus its activities on areas where value can be added and to formulate a research action plan covering the short, medium and long-term. These issues were discussed at the first meeting of the task force (London, UK, December 2008).

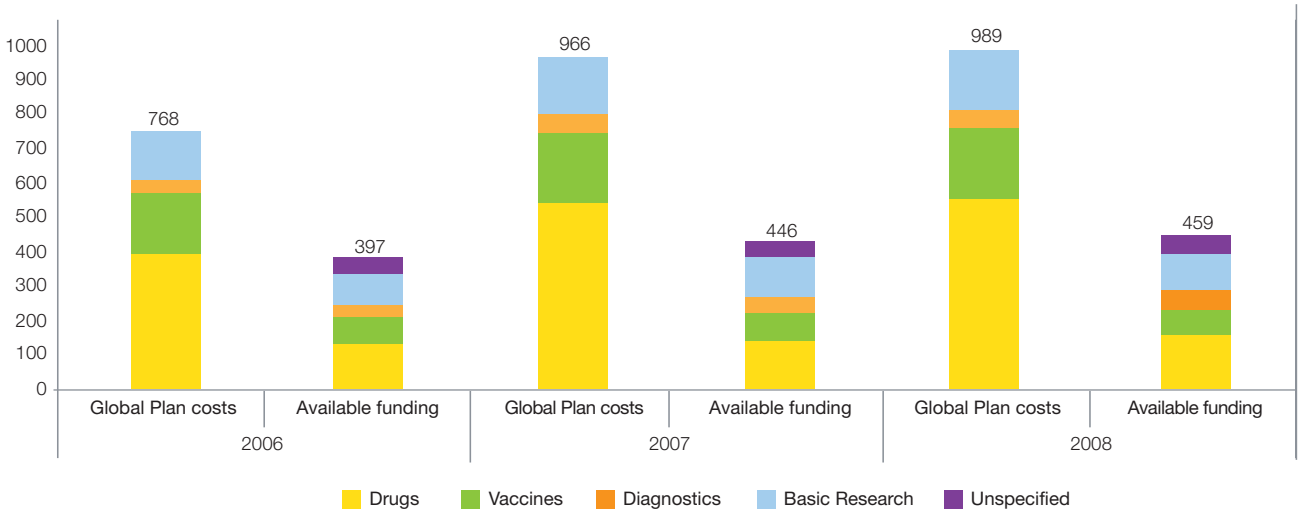
C. Funding trends for TB Research and Development

A report by TAG[1] reported that funding for TB research and development reached US$ 429 million in 2006 and US$ 483 million in 2007. The TAG report includes information on expenditures for basic research, diagnostics, drugs, vaccines, unspecified, and operational research. The latter two were not costed in the Global Plan.

Comparing the TAG report with the Global Plan estimates for 2006 and 2007 suggests that the funding gap for new tools was around US$ 500 million[2], still far behind the ideal funding needs.

Another report[3] suggested that TB research and development reached US$ 410.4 million in 2007. Operational research funding was not part of the data gathered by the G-Finder. Nevertheless this figure is very close to the one reported by TAG for 2007.

Figure 12: Global Plan costs compared to available funding for TB research and development, 2006-2008*



*2008 is an estimate based on the TAG summary.

[1] Tuberculosis Research and Development: A Critical Analysis of Funding Trends, 2005–2007: An Update. Treatment Action Group, 2009.

[2] Note that in Figure 12 operational research and unspecified research funding from TAG have been excluded for the calculation of the funding gap. These two categories have not been costed in the Global Plan.

[3] Moran M, Guzman J, Ropars AL, et al. Neglected disease research and development: how much are we really spending? PLoS Medicine, February 2009, 6:2;e100030

Annex 1:
Evaluation of the Stop TB Partnership

In 2007–2008, McKinsey & Company independently evaluated the impact, effectiveness and efficiency of the Stop TB Partnership and recommended ways to maximize its impact in the future. The assessment was based on data and publication reviews, an Internet-based survey, and visits to eight countries and over 200 interviews.

The evaluation concluded that, from 2001 to 2006, the Partnership had contributed significantly to efforts to stop TB; and that progress in global TB control and research during that time was greater for its contribution. The Partnership had demonstrated impact in five important ways, by:

- strengthening the coalition of organizations involved in TB control and research;
- broadening and increasing consensus on the agenda for TB control and research;
- expanding the reach and increasing the impact of global advocacy,
- coordinating and supporting Partner activities, some of which benefited other functions and disease control programmes;
- improving TB control in countries.

The Partnership has set high aspirations for its impact over the next 5–10 years. The evaluation recommended:

- identifying the biggest opportunities to drive progress in TB control and research,
- integrating strategies of individual Partnership bodies into a unifying Partnership strategy,
- concentrating Partnership efforts and resources,
- maximizing the use of Partnership levers to influence countries, Partners, and other actors;
- increasing performance transparency.

Annex 2:
TB Epidemiological regions

This annex lists the countries and territories in each of the eight TB epidemiological regions: (1) Africa, high HIV prevalence (AFR High); (2) Africa, low HIV prevalence (AFR Low); (3) Latin American Region (LAC); (4) Eastern European Region (EEUR); (5) Eastern Mediterranean Region (EMR); (6) the Established Market Economies (EME) and Central Europe (CEUR); (7) South-East Asian Region (SEAR); and (8) Western Pacific Region (WPR).

1) Africa, High HIV Prevalence (AFR High)

Botswana	Democratic	Mozambique	Swaziland
Burundi	Republic of Congo	Namibia	Uganda
Cameroon	Ethiopia	Nigeria	United Republic of Tanzania
Central African Republic	Gabon	Lesotho	Zambia
Congo	Kenya	Rwanda	Zimbabwe
Côte d'Ivoire	Malawi	South Africa	

2) Africa, Low HIV Prevalence (AFR Low)

Algeria	Comoros	Guinea-Bissau	Niger
Angola	Equatorial Guinea	Liberia	Sao Tome & Principe
Benin	Eritrea	Madagascar	Senegal
Burkina Faso	Gambia	Mali	Seychelles
Cape Verde	Ghana	Mauritania	Sierra Leone
Chad	Guinea	Mauritius	Togo

3) Latin American countries (LAC)

Anguilla	Colombia	Jamaica	Suriname
Antigua & Barbuda	Costa Rica	Mexico	rinidad and Tobago
Argentina	Cuba	Montserrat	Turks & Caicos Islands
Bahamas	Dominica	Netherlands Antilles	Uruguay
Barbados	Dominican Republic	Nicaragua	US Virgin Islands
Belize	Ecuador	Panama	Venezuela
Bermuda	El Salvador	Paraguay	
Bolivia	Grenada	Peru	
Brazil	Guatemala	Puerto Rico	
British Virgin Islands	Guyana	Saint Kitts and Nevis	
Cayman Islands	Haiti	Saint Lucia	
Chile	Honduras	St Vincent and the Grenadines	

4) Eastern Europe (EEUR)

Armenia
Azerbaijan
Belarus
Bulgaria
Estonia
Georgia
Kazakhstan
Kyrgyzstan
Latvia
Lithuania
Republic of Moldova
Romania
Russian Federation
Tajikistan
Turkey
Turkmenistan
Ukraine
Uzbekistan

5) Eastern Mediterranean (EMR)

Afghanistan
Bahrain
Djibouti
Egypt
Islamic Republic of Iran
Iraq
Jordan
Kuwait
Lebanon
Libyan Arab Jamahiriya
Morocco
Oman
Pakistan
Qatar
Saudi Arabia
Somalia
Sudan
Syrian Arab Republic
Tunisia
United Arab Emirates
West Bank & Gaza Strip
Yemen

6) Established Market Economies (EME)

Andorra
Australia
Austria
Belgium
Canada
Czech Republic
Denmark
Finland
France
Germany
Greece
Iceland
Ireland
Israel
Italy
Japan
Luxembourg
Malta
Monaco
Netherlands
New Zealand
Norway
Portugal
San Marino
Singapore
Spain
Sweden
Switzerland
United Kingdom
USA

and Central Europe (CEUR)

Albania
Bosnia and Herzegovina
Croatia
Cyprus
Hungary
Poland
Serbia and Montenegro
Slovakia
Slovenia
The Former Yugoslav Republic of Macedonia

7) South-East Asia (SEAR)

Bangladesh
Bhutan
Democratic People's Republic of Korea
India
Indonesia
Maldives
Myanmar
Nepal
Sri Lanka
Thailand
Timor-Leste

8) Western Pacific (WPR)

American Samoa
Brunei Darussalam
Cambodia
China
China, Hong Kong SAR
China, Macao SAR
Cook Islands
Fiji
French Polynesia
Guam
Kiribati
Lao People's Dem. Republic
Malaysia
Marshall Islands
Micronesia
Mongolia
Nauru
New Caledonia
Niue
Northern Mariana Islands
Palau
Papua New Guinea
Philippines
Republic of Korea
Samoa
Solomon Islands
Tokelau
Tonga
Tuvalu
Vanuatu
Viet Nam
Wallis & Futuna Islands

The 22 TB high-burden countries, 2008

Afghanistan
Bangladesh
Brazil
Cambodia
China
Dem. Republic of Congo
Ethiopia
India
Indonesia
Kenya
Mozambique
Myanmar
Nigeria
Pakistan
Philippines
Russian Federation
South Africa
United Republic of Tanzania
Thailand
Uganda
Viet Nam
Zimbabwe

Annex 3: Methods

Implementation of TB control: DOTS, MDR-TB, TB/HIV and ACSM

The analytical work that underpinned the Global Plan included projections of how interventions to control TB would need to be scaled up during the period 2006–2015 for four major components of TB control: DOTS, MDR-TB, TB/HIV and ACSM. These four components corresponded to the four "implementation" working groups of the Stop TB Partnership. For each of these four components, key indicators that could be used to measure progress were defined. These indicators were as follows:

- DOTS: the number of new smear-positive, new smear-negative and extrapulmonary cases notified and treated under DOTS; the case detection rate for smear-positive cases; the case detection rate for new smear-negative and extrapulmonary cases; the treatment success rate for new smear-positive cases; and funding for DOTS implementation;
- MDR-TB: the number of TB cases tested for drug resistance; the number of laboratory-confirmed cases of MDR-TB treated in GLC-approved projects, or programmes of an equivalent standard; and funding for diagnosis and treatment of MDR-TB;
- TB/HIV: the number and proportion of TB patients tested for HIV; the number and proportion of HIV-positive TB patients enrolled on co-trimoxazole preventive therapy (CPT) and antiretroviral therapy (ART); the number of HIV-positive people screened for TB and offered isoniazid preventive therapy (IPT); and funding for collaborative TB/HIV activities;
- ACSM: the number of HBCs in which ACSM activities were being implemented, and funding for ACSM activities.

For each indicator, milestones or targets were defined for each year of the plan. These milestones or targets were set out in seven Excel spreadsheets (one for each epidemiological region), and also stored in a WHO database (in Stata).

To compare actual progress with the milestones/targets included in the plan, data for each of the major indicators included in the Global Plan were extracted from the WHO TB database. The latter is based on data that are collected from all countries on an annual basis, using a standard collection form (see www.who.int/tb). These data are used to produce the annual WHO report on global TB control (www.who.int/entity/tb/publications/global_report). The one exception was data on the number of MDR-TB cases treated in GLC-approved projects and programmes, which were taken from a GLC-specific database.

Analyses were conducted for the years 2006–2008, for each of the seven epidemiological regions and for all regions combined, in Stata.

Research and Development

The Global Plan set out the vision, goal, objectives, indicators and related milestones for each of the three major areas (new drugs, new diagnostics, new vaccines) where research and development to improve TB control is needed, as well as estimates of the funding required in each year 2006–2015. The plans for each of these three components of the Global Plan, including estimates of funding requirements, were developed by the corresponding Working Group of the Stop TB Partnership i.e. the working groups for new drugs, new diagnostics and new vaccines, respectively.

To review progress against the milestones for development of new drugs, new diagnostics and new vaccines, discussions were held with the Chairs and secretariats of each of the Working Groups, and available documents describing progress in the period 2006–2008 were reviewed. The secretariats of each group also provided a short report of progress in their respective area.

To assess the funding that was available during the period 2006–2008, data from two sources were used. These were:

- reports on funding and expenditures for TB research and development published by TAG.[1] TAG has published two reports, one in 2008 and the second in 2009, which in combination provide data on funding for TB research and development during the period 2005–2007;
- a report from a survey of funding for research and development.[2] The survey provided estimates of funding for TB research and development in 2007.

The surveys conducted by TAG and G-Finder provided consistent results, suggesting that funding for TB research and development was in the range US$ 400 million to US$ 450 million per year during the period 2005 to 2007. For the purposes of this report, it was assumed that the level of funding in 2007 was maintained in 2008.

[1] Treatment Action Group (TAG), 2008. Funding Trends in TB Research and Development, 2005-2007: A Preliminary Report; and Treatment Action Group (TAG), 2009. A critical analysis of funding trends 2005–2007 - an update.

[2] The George Institute for International Health, Health Policy Division, 2008. G-Finder survey: Neglected disease research and development - how much are we really spending?

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Stop TB Partnership

WHO/HTM/STB/2009.59.

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THE GLOBAL PLAN
TO STOP TB
2006-2015