Progress Report on the Global Plan to Stop Tuberculosis

Stop TB Partnership

TB
Progress Report

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Contents

List of acronyms

AFRO	WHO Regional Office for Africa
AIDS	Acquired Immunodeficiency Syndrome
ARV	Antiretroviral
BCG	Bacille Calmette Guérin
CDC	Centers for Disease Control and Prevention
DEWG	DOTS Expansion Working Group
DOTS	Internationally recommended strategy for TB control
DST	Drug susceptibility testing
FDC	Fixed-dose combination
FIND	Foundation for Innovative New Diagnostics
GATB	Global Alliance for TB Drug Development (TB Alliance)
GDEP	Global DOTS Expansion Plan
GDF	Global Drug Facility
GFATM	Global Fund to Fight AIDS, TB and Malaria
GLC	Green Light Committee
GMP	Good Manufacturing Practice
GPSTB	Global Plan to Stop TB
HBC	High-burden countries
HIV	Human immunodeficiency virus
IEC	Information, education and communication
ILO	International Labour Organization
IUATLD	International Union Against Tuberculosis and Lung Disease
KNCV	Royal Netherlands Tuberculosis Association
MDR-TB	Multidrug-resistant tuberculosis
NGO	Nongovernmental organization
NIAID	National Institute of Allergy and Infectious Disease
NICC	National Interagency Coordination Committees
NTP	National Tuberculosis Control Programme
PIA	Phased implementation of activities
PLWHA	People living with HIV/AIDS
PPM	Public-Private Mix
R&D	Research and development
RICC	Regional Interagency Coordination Committee
SEARO	WHO Regional Office for South-East Asia
TB	Tuberculosis
TBCTA	TB Coalition for Technical Assistance
TBDI	TB Diagnostics Initiative
TDR	Special Programme on Research and Training in Tropical Diseases
UNAIDS	Joint United Nations Programme on HIV/AIDS
USAID	United States Agency for International Development
VCT	Voluntary counselling and testing
WG	Working group
WHO	World Health Organization

Message from the Chair Stop TB Coordinating Board

On behalf of the Stop TB Coordinating Board, I would like to express my appreciation for the remarkable work done by our partners in the fight against tuberculosis throughout the world. It is this hard work and dedication of the partners to the Global Plan to Stop TB that make the Stop TB Partnership a true collaborative global effort.

With a current membership of some 280 organizations, the Stop TB Partnership has enhanced political commitment to the Global Plan to Stop TB. In a short period of time, its constituent partners have achieved tangible successes.

- In just three years, the number of people being treated under DOTS has increased by more than 23%. All of the 22 high-burden countries now have national strategies in place for tuberculosis control.
- The Global Drug Facility has provided first-line drugs for over 1.9 million people in 49 countries, and its purchasing power has lowered the cost of tuberculosis (TB) drugs by over 30%, to less than US$ 10 per course of treatment.
- Guidelines have been developed for implementing collaborative TB/HIV projects, and prevention and treatment of TB have been recognized as critical factors for mitigating the impact of the HIV epidemic.
- The Green Light Committee for approving applications for DOTS-Plus pilot projects has facilitated streamlined access to life-saving second-line drugs for people suffering from multidrug-resistant tuberculosis. It has also reduced the price of second-line drugs by as much as 90%.
- Remarkable progress has been made with regard to the development of new tools. For the first time in 40 years we have a robust pipeline of promising drug candidates. A structure has been put in place to spearhead and accelerate development of new diagnostics. Two vaccine candidates are now entering Phase I clinical trials.

Tuberculosis, however, remains a formidable adversary. This progress report demonstrates that we still face a funding gap in TB control of at least US$ 1 billion per year. More resources must be mobilized if internationally agreed TB control targets are to be met. The Partnership has established a Resource Mobilization Task Force that will work to leverage additional funding and mount new advocacy efforts. Securing long-term financing for the Global Drug Facility is also crucial and continues to be a priority for the Partnership.

Building on the momentum it established during the first three years of operation, the Partnership must focus on results – especially regarding DOTS detection and treatment success rates. The severity of the TB/HIV co-pandemics and the threat that drug resistance poses to TB control demand a well-planned, well-executed, and rapid expansion of TB control efforts. This situation also requires the swift development of new tools including diagnostics, drugs and vaccines.

Following the course laid out in the Global Plan to Stop TB while addressing the challenges highlighted in this update is of critical importance in the years ahead.

Ernest Loevinsohn,
Chair of the Stop TB Coordinating Board

The Stop TB (STB) Partnership has made substantial progress towards achieving the strategic objectives of the Global Plan to Stop Tuberculosis (GPSTB). This update summarizes the Partnership's achievements and the challenges it faces in the struggle to control and eventually eliminate this devastating disease.

Progress since the launch of the Global Plan

The GPSTB identified DOTS expansion and adaptation to meet the emerging challenges of HIV and tuberculosis (TB) drug resistance as key to controlling TB worldwide. As a result of the work of the Stop TB partners, DOTS has been implemented in 180 countries and, by the end of 2002, 69% of the world's population was living in areas covered by DOTS. All of the 22 high-burden countries (HBCs) now have plans for expanding DOTS and improving case detection and cure rates. As the TB and HIV epidemics continue to fuel one another, the need for increased collaboration between HIV/AIDS and TB control efforts is more urgent than ever.

Development of an interim policy for collaborative TB/HIV activities has been completed; joint TB/HIV pilot projects have been established, with evaluations under way or completed, and scaling up has begun. Pilot projects to treat patients with multidrug-resistant TB (MDR-TB) have been established in 10 countries; and the Green Light Committee (GLC) has contributed to dramatic price decreases on second-line drugs. These accomplishments would not have been possible without the contribution of the Partnership's Working Groups on DOTS Expansion, TB/HIV, and DOTS-Plus for MDR-TB.

The GPSTB acknowledged the inadequate capability of current diagnostic tools, drugs and vaccines to address TB's growing scope and complexity, and emphasized the urgent need for research to improve and develop new tools for combating the disease. Recent years have witnessed unparalleled advances of new tools including new diagnostics, drugs, and vaccines. Much of this progress is the direct result of efforts by the Partnership's Working Groups on New Diagnostics, Drugs, and Vaccine Development. Since the launch of the Global Plan, the TB Diagnostics Initiative has supported commercial development of new diagnostics, while the newly created Foundation for Innovative New Diagnostics (FIND) has provided additional capacity for active co-development of critically needed tests. The Global Alliance for TB Drug Development (TB Alliance) has taken advantage of new technologies and approaches currently transforming drug discovery, and worked to ensure swift movement of promising compounds through the development and approval pipelines. For the first time in decades, new vaccine candidates have entered Phase I clinical trials.

Challenges remain

Despite these major achievements, serious gaps remain. Many African countries and states that belonged to the former Soviet Union have seen increasing numbers of TB cases and recorded treatment success rates substantially below the 85% target. Implementation of collaborative TB/HIV activities at country level is slow given the pace of the accelerating epidemics. Addressing the growing epidemic of MDR-TB requires intensified efforts to improve and maintain DOTS programmes and expand DOTS-Plus projects. The challenges of expanding DOTS, implementing collaborative TB/HIV efforts, and scaling up services for MDR-TB will require new thinking, programme innovation, intensified efforts, and additional resources.

The original GPSTB estimated US$ 9.1 billion of costs over a five-year period (US$ 1.8 billion annually) for TB control efforts, identified funding of US$ 5.35 billion (US$ 1 billion annually) and a likely gap

of US$ 3.8 billion (US$ 0.8 billion p.a.). This GPSTB Progress Report re-estimates the annual TB control needs for 2004 and 2005 at US$ 2.2 billion per year, an increase of US$ 415 million annually over the original GPSTB estimate. This updated estimate includes relatively conservative estimates of increased needs for DOTS expansion and new tool development. However, it does not yet include an estimate of the significantly increased needs for TB/HIV control efforts.

Despite an increase in overall resources for TB control (primarily from the GFATM), the previously identified funding gap has not been filled. The need, meanwhile, has increased, even before re-estimating increased needs for TB/HIV efforts. This leaves a conservatively estimated funding gap of at least US$ 1 billion per year for TB control.

Large-scale investment is also key to making new tools available. Streamlined evaluation processes are needed to apply the recent advances in biotechnology to the development of new TB diagnostic tools. Greater effort is required to translate promising basic research into drug discovery programmes. Continued support for vaccine development is also critical to ensure that current candidates are thoroughly evaluated as quickly as possible and, once a vaccine is approved, distributed to where the TB burden is the greatest.

The Stop TB Partnership

Since the launch of the GPSTB, the Stop TB Partnership has made significant strides in coordinating and catalysing global TB efforts. A strong Secretariat housed at the World Health Organization has helped to create the Global Drug Facility (GDF) and provided guidance and oversight to the Partnership's six Working Groups.

The Partnership has grown quickly and substantially, numbering over 280 member organizations by early 2004. Having catalysed political commitment and developed the operational mechanisms needed to control TB, the Partnership is poised to make rapid progress towards reaching the 2005 targets. However, renewed commitment to the plans and pledges from all partners will be crucial to ensuring success.

The Global Drug Facility

The GDF was established in 2001 to facilitate global DOTS expansion by increasing the availability of high-quality TB drugs. The GDF provides grants, procures drugs directly, and maintains a white list of prequalified TB drug manufacturers and products. To date, the GDF has provided drugs to treat almost 2 million TB patients in 49 countries. Unfortunately, the success of this effort is threatened by a critical funding shortage.

GPSTB financial summary

The original five-year cost estimate of the GPSTB was US$ 9.1 billion, an average of roughly US$ 1.8 billion annually. Based on the revised estimates, the current annual need has increased to US$ 2.2 billion per year for 2004 and 2005. This increase reflects necessary intensification of efforts in many areas identified in the plan.

Conclusion

This GPSTB update demonstrates impressive strides in the fight against TB. Nonetheless, in many places, TB is spreading faster than TB control efforts. Continued large-scale investments of financial and human resources are needed to accelerate progress against TB and to eliminate the disease as a global health threat.

In the early 1990s, the nations of the world with the most advanced economies woke up to the reality that TB was still in their midst. In fact, inadequate TB control policies were allowing the disease to spread and its societal impact to worsen. The wealthy countries' experience mirrored, though much less acutely, a TB crisis facing countries with far fewer resources. Minimal commitment to public health infrastructure, poor access to health services for the most vulnerable people, inadequate prescribing norms and drug logistics, and a lack of patient follow-up were contributing to a rapidly worsening TB epidemic. The emergence of HIV/AIDS further fuelled the growing TB problem, as did the spread of MDR-TB.

This grave situation cried out for urgent and coordinated action, including efforts to mobilize resources, public awareness, and political commitment; stimulate public and private development of improved disease-fighting tools; scale up already proven, cost-effective disease-fighting strategies in low-income environments; and address the new menaces of HIV-associated TB and MDR-TB. Demands for action came from long-committed advocates for TB control in the affluent countries as well as from advocates in the highest-burden countries, who had worked for too long in relative isolation. The Stop TB Partnership resulted from their combined efforts.

The Stop TB partners made the development of a shared global plan to control TB one of their first priorities. Momentum for such an initiative already existed and manifested itself by support for the cost-effective DOTS approach for TB diagnosis and treatment, targets set by the World Health Assembly for the year 2005, some increases in funding for fighting the disease during the 1990s, as well as the development of realistic objectives for short-term, medium-term, and sustained progress in each of the major areas of TB control, from research and development to field implementation. These initiatives and targets, however, did not amount to a coherent agenda that could rally key new partners behind the effort to combat TB and forge commitment to the diverse courses of action needed to bring the disease under control. In 2000, at the Amsterdam Ministerial Conference on TB and Sustainable Development, 20 of the highest-burden countries mapped out their priorities for a plan of action that would have a rapid impact on TB in those areas suffering most from the epidemic. The Amsterdam Declaration for TB Control heralded a unique effort by hundreds of individuals and institutions to draft the Global Plan to Stop TB and win its endorsement.

This report is an update on the efforts to implement the Global Plan to Stop TB. The plan, a five-year, consensus-based business plan, was launched at the First Global Partners' Forum in Washington in 2001, which included the participation of 200 partners. Today, the Partnership has expanded to include almost 280 institutions; it has also evolved substantially in terms of the action it undertakes and the documented results achieved. The Washington Forum set benchmarks for the targets of the World Health Assembly for 2005 and beyond. The partner institutions are striving together to reach them.

The 21st century has already seen tremendous changes in the response to major global public health threats. Public health has today secured itself a place on the world's political and developmental agenda as at no other time in the past 50 years. There is growing recognition of the fact that improving public health has a critical impact on economic and human development. There is growing awareness of the huge risks associated with failure to ensure high quality and safe delivery of public health services. And there is a growing understanding that the worldwide TB epidemic is a critical impediment to alleviating global poverty and suffering. The Member States of the United Nations have pledged to meet eight Millennium Development Goals (MDGs) by the year 2015. The reversal of major communicable disease epidemics is the eighth of these 12 goals, and TB control indicators are among the defined markers of progress.

The Global Plan to Stop TB includes four strategic objectives:

- **To expand** our current strategy, DOTS, so that all people with TB have access to effective diagnosis and treatment.
- **To adapt** this strategy to meet the emerging challenges of HIV and TB drug resistance.
- **To improve** existing tools by developing new diagnostics, new drugs and a new vaccine.
- **To strengthen** the Global Partnership to Stop TB so that proven TB control strategies are effectively applied.

The progress of the Stop TB Partnership described in this report demonstrates that TB control is succeeding around the world and that it is possible to scale up interventions to serve millions of people. This update also demonstrates that new energy can be brought to the battles against TB and other diseases that mostly affect the poor.

The challenges confronting the Partnership and documented in this update are the same as those that face efforts to meet each of the United Nations health-related Millennium Development Goals. These challenges include increasing and sustaining new funding levels; strengthening public health systems, including the availability, capacity, and motivation of human resources; empowering households and communities; engaging providers in the private and other sectors; and creating and adopting new technology, such as diagnostics, drugs, and vaccines.

The Partnership is addressing the challenges that have clear solutions, and it is seeking new approaches to meet challenges whose solutions are not yet apparent. The Partnership will continue to strive to deepen the commitment of its partners, both individuals and institutions, in the TB control effort, while forging links with other individuals and institutions sharing its goal of improving health and human development.

The Global Plan to Stop TB has provided a road map to guide this work. We are still far from our goal and require renewed investment and energy to attain it. We must accelerate our pace to meet the challenges ahead. This update of our progress represents both a renewal of our shared commitment and a call for others to join us in our mission to stop TB.

Substantial progress has been made towards achieving two of the strategic objectives of the Global Plan to Stop TB: expanding DOTS coverage and meeting the emerging challenges of TB/HIV and multidrug-resistant TB. All the high-burden countries now have plans for expanding DOTS and improving case detection and cure rates. The development of interim policy and of recommendations for collaborative TB/HIV activities has been completed; joint TB/HIV pilot projects have been established and their evaluation is under way or completed; and scaling up is occurring in some countries. Pilot projects to treat patients with MDR-TB have been established in 10 countries; and the Green Light Committee has contributed to dramatic price decreases on second-line drugs.

The Partnership's Working Groups on DOTS Expansion, TB/HIV, and DOTS-Plus for MDR-TB have contributed significantly to these accomplishments. Despite these strides, major gaps remain. The challenges of expanding DOTS, implementing collaborative TB/HIV efforts, and scaling up services for MDR-TB will require new thinking, programme innovation, more resources, and intensified efforts.

TB control today: the challenge still before us

1a. DOTS expansion *(1)*

Progress since the Global Plan

The GPSTB identified DOTS (*2*) expansion as the key to controlling TB worldwide. As more than 80% of the world's TB patients live in 22 countries, the focus of the Partnership's effort has been on controlling the TB epidemic in these high-burden countries.(*3*)

DOTS has been implemented in 180 countries (out of 210) and by the end of 2002, 69% of the world's population was living in areas covered by DOTS. This represents a significant improvement since the launch of the GPSTB, when only 119 countries were implementing DOTS.

The targets for 2005 set by the World Health Assembly, and adopted by the Partnership, are to treat successfully 85% of detected smear-positive TB cases and to detect 70% of all such cases. In 2002, TB cases notified under DOTS programmes represented 37% of estimated new smear-positive TB cases. This is an increase from the 27% case notification rate presented in the GPSTB and more than halfway to the 70% goal for 2005. As a result of intensified efforts, case notification rose more quickly in 2002 than in any year since 1995. The country-specific concentration of increased case notification in 2002 – just six of the HBCs accounted for 60% of the additional cases detected – testifies to the potential gains if improvement spreads to the other 16 HBCs. Based on recent trends, the case detection rate is expected to be about 50% by 2005; at that time all TB patients reported in the public sector will receive the internationally recommended standard of care under DOTS. Treatment success under DOTS worldwide was 82% on average for the 2001 cohort, just below the 85% goal. See *Annex 1* for an epidemiological profile of the 22 HBCs.

Progress through the DOTS Expansion Working Group

Much of the progress to date is the result of the achievements of the Partnership's DOTS Expansion Working Group (DEWG), which includes national TB programme (NTP) managers from the 22 HBCs as well as technical and financial partners. The DEWG helps countries develop detailed DOTS implementation plans, supports technical and financial agencies in their TB control efforts, ensures that countries have adequately trained health care staff, and monitors and evaluates progress. See *Annex 2* for a summary of the activities and accomplishments of the DOTS Expansion Working Group in 2002.

With assistance and support from the DEWG and its network of partners, by the end of 2003 NTP managers in the 22 HBCs had formulated plans for DOTS expansion and improved case detection and cure rates. These plans attempt to address the most common constraints to improvement: lack of qualified staff, poor monitoring and evaluation systems, weak laboratory support, lack of coordination with private practitioners and other public providers of TB care, ineffective decentralization of health care services, ineffective efforts to improve drug supplies, and inconsistent drug quality. The best of the national TB control plans (such as those of India and Viet Nam) include detailed strategies for improving DOTS coverage, case detection, and programme quality.

Significant new resources have now been mobilized for TB control in most HBCs, reflecting both more government commitment and an increase in grant financing, particularly from the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM). Trends in case notification and cure rates in several countries demonstrate that progress is possible in all HBCs.

One of the key achievements of the DEWG together with the Partnership Secretariat has been the establishment of the GDF. The GDF was launched in March 2001 to provide drugs to treat up to 11.6 million people and assist countries to reach the 2005 global TB targets. In the GDF's first two years alone, six rounds of applications resulted in support for 46 countries and nongovernmental organization (NGO) programmes. As a recent evaluation (*4*) has demonstrated, the GDF has had a catalytic effect on DOTS expansion beyond the provision of drugs, as the application process itself necessitates developing plans for DOTS expansion and drug management. In just three years of operation, a total of 1 911 451 free patient treatments were approved; the pooled procurement mechanism has yielded drug prices that are on average one-third less than previous international tenders; and a white list of prequalified manufacturers and drugs that adhere to quality standards has been developed and updated.(*5*)

In addition to problems in drug supply, another key constraint to DOTS expansion in the HBCs has been inadequately trained health care staff. Consequently, since 2002 the DEWG has placed special emphasis on capacity building. Support for the development, revision, and implementation of comprehensive strategies for human resource development was provided through workshops for focal points in African and Asian HBCs. Close collaboration with the newly established TB Coalition for Technical Assistance (*6*) (TBCTA) task force on training ensured high-quality training and consistency worldwide. In addition, other tools and guidelines were developed (e.g. a competency checklist for TB consultants) and training manuals and materials were revised.

The DEWG has also helped improve coordination by assisting in the establishment of national- and regional-level coordination committees. Eighteen of the 22 HBCs created National Interagency Coordination Committees (NICCs), which now meet on a regular basis to support the implementation of DOTS expansion action plans. NICCs are central to the coordination of the technical and financial support in a given country. Regional Interagency Coordination Committees (RICCs) were established in the six regions and provide broad support for country activities.

Country experiences were highlighted during the Second ad hoc Committee meeting in 2003 (part of the annual DEWG meeting). This committee meeting provided countries with new insights and motivation for accelerated action. The report from this meeting indicates the achievements at country level and highlights the need for additional work in seven key areas: 1. Consolidating, sustaining, and advancing achievements – 2. Enhancing political commitment – 3. Addressing the health workforce crisis – 4. Strengthening health systems, particularly primary care delivery – 5. Accelerating the response to the TB/HIV emergency – 6. Mobilizing communities and the private sector – 7. Investing in research and development to shape the future. (*7*)

In response to low case detection rates, a Public-Private Mix (PPM) Subgroup and a Laboratory Capacity Strengthening Subgroup of the DOTS Expansion Working Group were established. In many countries, the NTP is not the sole provider of TB diagnosis and care. Private sector providers, which are largely unregulated, see a large percentage of patients. The mandate of the PPM Subgroup is to assist in formulating policy guidelines, to provide guidance on PPM DOTS strategies, and to assist in developing a research agenda. Progress in several countries in the development and implementation of PPM DOTS has been shown. For example in India, PPM activities are being scaled up in 14 cities; and in the Philippines, the NTP is in the process of implementing a phased national expansion of PPM DOTS. Analysis of data from PPM DOTS pilot projects shows major gains in case notifications, 25%–30% on average, and high cure rates ranging between 75% and 90% in most settings, proving that engagement of private health care providers is paramount for TB control in a community. The aim of the Laboratory Subgroup is to assess laboratory networks in the 22 HBCs and other countries requiring special assistance as well as to assist in the development and implementation of plans to enhance the capacity of these laboratory networks. In 2003, assessments of laboratory services, in collaboration with

partners, took place in Bangladesh, Kenya, Pakistan, and Uganda to determine capacities in line with DOTS expansion.

Other achievements of the DOTS Expansion Working Group include the development of an operational guide for NTPs on the introduction and use of fixed-dose combination drugs (FDCs), the development of a guide to expanding DOTS in the context of a changing health system as well as the revision of the treatment guidelines for NTPs.

Remaining challenges for DOTS expansion

The DEWG's accomplishments and the progress achieved since the publication of the GPSTB are encouraging. While progress has been apparent in almost all HBCs, some of these countries have moved more quickly than others toward the 2005 targets. In many places, TB is spreading faster than TB control efforts. There were an estimated 8.8 million new cases of TB in 2002; worldwide, new TB cases increased in 2003 at an annual rate of 2.4%; the rates of increase were greater, however, in sub-Saharan Africa and in countries of the former Soviet Union. Moreover, treatment success rates in many African and eastern European countries were substantially below the 85% target (71% and 70%, respectively), owing in part to HIV co-infection, to drug resistance, and to the failure of some NTPs to monitor treatment outcomes for all patients. These statistics underscore the need to accelerate progress in more of the HBCs. Unless demonstrable gains can be replicated in all the HBCs, the epidemic will continue to outstrip the efforts to control it.

Overcoming barriers requires innovative approaches to increase case detection and to raise treatment success rates, particularly in the countries with high burdens of HIV and MDR-TB. NTPs must be proactive in their approaches to increasing case detection and cure rates. Achieving this requires strengthening technical capacity. It also requires strong political commitment to DOTS, especially in the face of health sector reforms. Programme managers, national, regional, and community personnel, and their advisors need to adopt creative approaches to improving case detection and to ensure adequate budgets to support their activities.

The donor community must also rise to this critical challenge by ensuring that funds are available to support expanded detection and treatment efforts. There are clear indications that health ministries in the HBCs are underestimating the costs of reaching the global targets. In too many instances, national health budgets do not contain adequate funds for programme expansion, treatment supervision, training, and innovation. Staffing can be chronically underbudgeted owing to the assumption that staff levels cannot be changed.

Additional resources for TB control programmes must include support for technical assistance and sustained investments in health infrastructure, including training, supervision, and laboratory infrastructure. For example, it is notable that while substantial new funding has been granted to individual countries, there has been no increase in the funding available for international technical agencies. In the absence of an increase in funding for international technical assistance that is consistent with the increased funding for activities at country level, there is a considerable risk that funds will not be efficiently absorbed or effectively used and that patient care will not improve. The donor community has an important role to play in helping to facilitate these important investments.

The report of the Second ad hoc Committee meeting in 2003 calls for reaching out to those key players engaged in health improvement efforts and poverty reduction for further progress in TB control. To move forward, the governments of the 22 HBCs and the donor community need to address funding and staffing inadequacies in order to fulfil the Washington Commitment they endorsed in October 2001 and meet the targets defined in the Global Plan.

1b. TB/HIV

Progress since the Global Plan

As the TB and HIV epidemics continue to fuel one another, the need for increased collaboration between HIV/AIDS and TB control efforts is more urgent than ever. This is especially the case given the recent launch of the WHO "3 by 5" Initiative, which aims to start 3 million people living with HIV/AIDS (PLWHA) on antiretroviral therapy by 2005. This initiative will require, and provide opportunities for, strengthened collaboration between HIV/AIDS and TB control programmes.

Progress through the TB/HIV Working Group

Since the launch of the Global Plan, the TB/HIV Working Group has produced three major policy and strategy documents. The first document is the *Strategic framework to decrease the burden of TB/HIV*, which outlines the range of interventions available for TB control in populations where the prevalence of HIV is high. The second document is the *Guidelines for the implementation of collaborative TB and HIV programme activities,* which builds on the strategic framework by defining how interventions identified in the *Strategic framework* can be implemented, based on field experience gained in pilot projects. The third document is the *Interim policy on collaborative TB/HIV activities*, which provides clear recommendations about what TB/HIV collaborative activities should be implemented given the currently available evidence and the level of HIV prevalence. It groups TB/HIV collaborative activities into three major categories: 1. Mechanisms for collaboration (defined as coordinating bodies at all levels, surveillance of HIV among TB patients, joint planning, and monitoring and evaluation) – 2. Activities to decrease the burden of TB in PLWHA (defined as intensified case-finding, isoniazid preventive therapy, and TB infection control in care and congregate settings) – 3. Activities to decrease the burden of HIV in TB patients (defined as HIV testing and counselling, HIV prevention, co-trimoxazole preventive therapy, HIV/AIDS care and support, and antiretroviral therapy). The policy documents and economic data now emerging from countries implementing collaborative TB/HIV activities provide a solid foundation for updates currently being conducted on the GPSTB estimates of the resources required for TB/HIV.

Other important policy and strategy documents have been produced. The revised *WHO antiretroviral treatment guidelines* (*8*) indicate that most TB patients are likely to be eligible for antiretroviral treatment. The *Guidelines for HIV surveillance among tuberculosis patients* and the *Guide to monitoring and evaluation for collaborative TB/HIV activities (field test version)* provide national TB and HIV/AIDS programmes with a framework for strengthening implementation of surveillance, monitoring, and evaluation systems.

At the country level, results from the first six TB/HIV pilot projects in Malawi, South Africa, and Zambia have demonstrated that HIV/AIDS and TB control programmes can work together effectively at all levels towards the common goal of providing comprehensive prevention, care, and support services. Data on the costs of these projects are becoming available, and evidence on cost-effectiveness is due at the end of 2004. Since 2001, members of the Partnership have provided technical assistance to Ethiopia, Kenya, Malawi, Mozambique, Nigeria, South Africa, Uganda, the United Republic of Tanzania, Zambia and Zimbabwe for phased implementation of collaborative TB/HIV activities (PIA), based on experience with the initial pilot projects. Fifteen of the HBCs have now established TB/HIV coordinating mechanisms, and 12 of these countries are involved in joint TB/HIV planning. In 2004, PIA will be

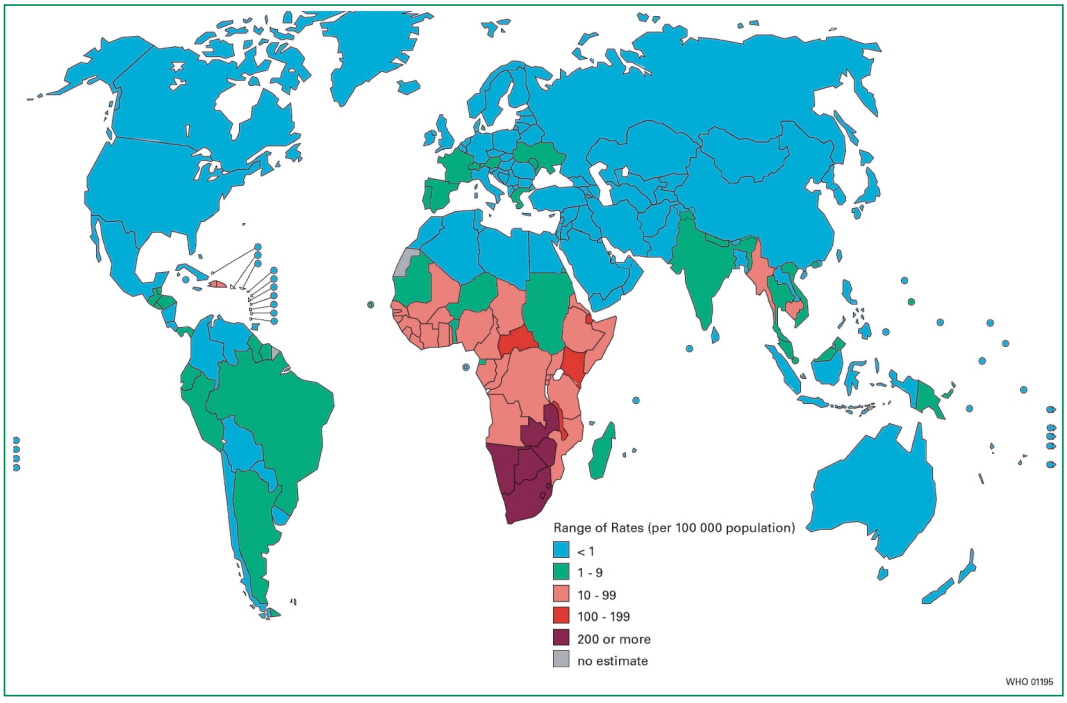
introduced in four francophone sub-Saharan African countries: Côte d'Ivoire, the Democratic Republic of the Congo, Rwanda, and Senegal. The GFATM supports most of these activities.

In support of country-level activities, the Working Group has developed a range of mathematical models. These are designed to help understand the impact that HIV will have on TB in different settings and to explore a range of control options in countries that have high rates of HIV and TB.

Under the aegis of the Working Group, four major analyses were conducted in HBCs. These have included analyses of: TB control options in high HIV prevalence settings (Kenya, South Africa, and Uganda); the cost-effectiveness of HIV and TB interventions in Kenya; the interactions between the HIV and TB epidemics in India; and the impact of ARV therapy on the incidence of TB. The results of these studies will aid national programme planning and development of future guidelines. See *Annex 3* for a summary of the activities and accomplishments of the TB/HIV Working Group in 2002 .

Remaining challenges for TB/HIV activities

Despite the achievements noted above, challenges remain. Implementation of collaborative TB/HIV activities at country level is still slow. More rapid progress will be needed to make a significant impact on the two epidemics and to enable TB programmes to make a large contribution to the WHO "3 by 5" Initiative. This contribution could be substantial: TB control programmes have the potential to recruit between 250 000 and 500 000 persons with HIV infection each year, most of whom would be eligible for ARV therapy. With additional training for health workers, TB control programmes can also assist in HIV prevention, delivery of ARVs, and provision of a package of HIV/AIDS care and support. For these things to happen, considerable new investment in human and financial resources will be needed, along with leadership and commitment from the governments of the HBCs and technical agencies.



Estimated numbers of HIV-infected TB cases per 100 000 population (all ages) by country in 2000 (9)

1c. MDR-TB

Progress since the Global Plan: achievements of the DOTS-Plus Working Group for MDR-TB

MDR-TB used to be considered a death sentence. Today, DOTS-Plus pilot projects are curing MDR-TB patients around the world.

The Partnership's Working Group on DOTS-Plus for MDR-TB (*10*) supports the development, testing, and monitoring of DOTS-Plus activities. As of December 2003, the GLC had reviewed 28 applications for support, of which 14 were approved and 11 were still under review. During 2002–2003, the Working Group firmly established nine new pilot projects for the proper management of MDR-TB in Bolivia, Costa Rica, Haiti, Malawi, Mexico, the Russian Federation (Arkhangelsk, Ivanovo, and Orel), and Uzbekistan; review of 11 new sites is under way. This is in addition to the existing pilot projects for DOTS-Plus in Estonia, Latvia, Peru, the Philippines, and the Russian Federation (Tomsk). Thus far, the GLC has approved more than 4500 patients for treatment at these sites.

Established by the MDR-TB Working Group in June 2000, the GLC has become a robust but flexible mechanism to prevent the misuse of second-line TB drugs, to promote access to quality-assured drugs, and to provide technical assistance to countries implementing DOTS-Plus. The GLC's vitality is maintained by renewing the membership to include representatives of leading partners of the Working Group on DOTS-Plus for MDR-TB. The GLC monitoring teams are currently developing and offering expertise that will form the basis for WHO global policy guidelines for management of MDR-TB to be issued in 2005.

The GFATM has decided that procurement and monitoring of second-line drugs for MDR-TB should go through the GLC in order to prevent their misuse and allow access to high-quality drugs and GLC technical assistance. This collaboration will increase the access to second-line drugs in resource-limited settings; the GLC has already reviewed six applications through this mechanism. Should the projects adhere to the GLC requirements, the GFATM will support them financially.

Thanks to the work of the GLC and several partners – including WHO, Médecins Sans Frontières, Harvard Medical School, and the International Dispensary Association – prices for second-line TB drugs have fallen remarkably over the past few years. This is partly due to an ongoing agreement with Eli Lilly and Company, Jacobus Pharmaceutical, and other manufacturers. These companies are continuing their support of DOTS-Plus by extending concessional pricing and increasing the quantities of drugs provided to the programme.

Training of health care staff and in-country monitoring support ensure that DOTS-Plus projects use the most effective and efficient treatments. In-service training enhances the skills and abilities of health care providers and managers to implement DOTS-Plus treatment strategies. MDR-TB management training was provided in Bolivia, Costa Rica, and Mexico in 2002, and in Cairo in 2003. Several workshops to introduce and explain the process of applying to the GLC have been held, attended by participants from Bangladesh, Costa Rica, India, Kazakhstan, Malawi, Mexico, Nepal, the Russian Federation, and South Africa.

MDR-TB pilot projects are being closely monitored and evaluated for effectiveness and cost-effectiveness. To date, treatment success rates of 70% and higher have been reported from DOTS-Plus pilot projects; these can be improved upon if drug resistance is diagnosed early and appropriate treatment initiated promptly.

A 2002 publication (*11*) on the national programme in Peru indicated that the treatment strategies used were cost-effective in middle-income countries. Economic evaluations of pilot projects are under way

in Estonia, Peru, the Philippines, and the Russian Federation (Tomsk). Based upon this demonstrated success of DOTS-Plus projects, planning is proceeding on integrating MDR-TB treatment with DOTS expansion plans in more settings with a high prevalence of MDR-TB.

Stop TB partners have developed a global research agenda for DOTS-Plus. This research agenda outlines priority topics and issues that need to be addressed in order to develop global policies for the management of MDR-TB. MDR-TB research projects around the world are now being tracked in a common database and project summaries are accessible through the WHO website.

See *Annex 4* for a summary of the activities and accomplishments of the DOTS-Plus Working Group for MDR-TB in 2002.

Remaining challenges to controlling MDR-TB

Despite the expansion and notable success of DOTS-Plus activities, the emergence of MDR-TB in nearly every country of the world continues to present a serious threat. Inconsistent supplies and inadequate quality of first-line TB drugs continue to limit the effectiveness of TB control efforts in some countries and contribute to the emergence of drug-resistant strains of TB.

Since 1994, the Global Project on Drug Resistance Surveillance has reported every three years on worldwide drug resistance; its next report was released in the first quarter of 2004. The project has identified 22 settings reporting MDR-TB prevalence greater than 3% among new TB cases; 11 of these settings reported MDR-TB prevalence above 6.5%. Six of these 11 settings had been identified in previous survey reports, but an additional five new settings (in Latin America, eastern Europe, and the western Pacific) were recently identified as having reported rates of MDR-TB among new cases ranging from 6.6% to 14.2%. Areas of eastern Europe, some provinces in China, and a few other countries are reporting the highest rates of MDR-TB.

The growing MDR-TB numbers illustrate the need for new diagnostics and TB drug development. Currently, most patients with MDR-TB are not identified until they have failed one or more courses of conventional therapy over a period of months or years – delays that result in increased resistance and further transmission. Additionally, new drugs are needed to provide more effective, shorter, and simpler treatment regimens to reduce significantly the burden of drug-susceptible TB as well as MDR-TB.

Clearly, addressing the growing epidemic of MDR-TB requires intensified efforts to improve and maintain DOTS programmes and expand DOTS-Plus projects under the stringent supervision of the GLC. Halting the spread of MDR-TB also requires investment in controlled clinical trials to answer complex questions concerning optimal treatment regimens and targeted operations research to design sound programmes in resource-poor settings.(*12*)

Recent years have witnessed noteworthy advances in the development of new tools for diagnosis of TB, new drugs for treating TB, and a new vaccine for preventing TB. The GPSTB acknowledged the inadequate capability of current diagnostic tools, drugs, and vaccines to address the growing scope and complexity of TB, and emphasized the urgent need for new research and development to improve and develop tools for combating the disease.

Much of the progress in these areas is a direct result of work by the Partnership Working Groups on New Diagnostics, Drugs, and Vaccine Development. Since the launch of the Global Plan, the TB Diagnostics Initiative of the Special Programme for Research and Training in Tropical Diseases (TDR) has supported commercial development of new diagnostics; since the creation of the FIND, there is additional capacity for active co-development of critically needed tests. The Global Alliance for TB Drug Development has ensured swift movement of promising compounds through the development and approval pipelines, and two new vaccine candidates have entered Phase I clinical trials. Progress has been impressive, yet large-scale investment will be necessary to make these tools available for use.

The future of TB control: the promise of TB research

2a. New diagnostics

Progress since the Global Plan: achievements of the Working Group on New Diagnostics

The poor performance of currently available TB diagnostic tests lets the disease go undetected in large numbers of patients, erodes faith in public health services, impedes the expansion of DOTS and, most importantly, allows continued transmission of the disease.

To achieve the goals set out in the Global Plan, the Partnership established a Working Group on New Diagnostics, a strong network of partners from industry, the public health sector, academia, and NGOs. The purpose of the Working Group on New Diagnostics is to facilitate the development of priority diagnostic tools for TB control and to ensure their effective and affordable use in low-income HBCs. The initiatives of the Working Group can be categorized into three broad areas: 1. Funding development of new tools – 2. Fostering an enabling environment for commercial development of tools – 3. Reviewing the performance of new tools and technologies. Achievements in each of these areas have been promising.

Launched in May 2003, FIND is a new non-profit entity designed to speed up the development of improved diagnostic technologies for patient care and disease control. FIND will collaborate with TDR to support the ongoing enabling activities formerly managed through the TB Diagnostics Initiative (TBDI) and otherwise encourage R&D in TB diagnostics around the world. FIND will co-invest in promising new technology platforms and manage a portfolio of promising test systems. Beyond this, FIND will set quality standards for diagnostic evaluation and strive to overcome the many philosophical obstacles to implementation of improved tools.

Funding of new tool discovery and development

Over the past three years, the TBDI has funded research and development projects in TB diagnostics in order to prime the development pipeline, to create a mechanism for screening new technologies and to attract new tool developers to the field. The "Bright Ideas Programme" has awarded more than US$ 1.1 million in competitive grants since 2001 for exploration of novel concepts or mechanisms to detect *Mycobacterium tuberculosis,* its products, or host responses. Early successes of the "Bright Ideas Programme" have included the development of a high-speed portable device for the simultaneous detection of *M. tuberculosis* antigens and TB antibodies. This battery-powered, hand-held device has proved highly effective in preliminary laboratory testing.

Enabling environment for commercial tool development

Research and development of TB diagnostics by large and small biotechnology companies must have an enabling environment that will promote information sharing, clarification of need for specific new diagnostic methods and tools, market analyses, reference banks for clinical materials, and support for the identification and improvement of clinical trial sites.

The TBDI aimed to clarify the need for new diagnostics through a number of activities, including a quantitative study designed to evaluate the economic and health impact of TB diagnostic delays and

dropouts, the development of a mathematical model that predicts the impact of implementing new diagnostics, and a document on the importance of diagnostic laboratories to improve the detection of TB cases.

Industry has found that attracting investment capital for TB diagnostics requires objective analysis of the global market size. In response, TBDI initiated a market analysis that will define market problems and needs, estimate global TB diagnostic expenditures, determine market size and the outlook for new tools, outline the costs of tool development, and estimate financial and social returns on investment in diagnostics R&D.

Most TB-endemic countries have only a limited capacity for laboratory evaluation of new diagnostic tools. To address this problem, TBDI maintains a list of sites where high-quality, supervised trials have been carried out; TBDI also performs a liaison function, putting test developers in direct contact with clinical investigators. TBDI has also established a programme to increase operational research capacity by providing training, monitoring, proficiency testing, and quality-assurance assistance in laboratories in selected HBCs. A survey of diagnostics regulation in 2001 (*1*) showed great variability, and in many poorer countries a complete lack of regulatory oversight, of diagnostics for infectious diseases. In response, TBDI developed the technical framework for its own regulatory-quality diagnostics evaluation system and began to work with regulators from advanced developing countries to strengthen their own capacity.

A Tuberculosis Specimen Bank has been assembled through prospective enrolment in a network of expert TB diagnostic sites (*2*). To date, more than 12 000 samples have been collected, and nearly 5 000 have been released to 40 groups with significant TB diagnostics programmes that target developing-country markets. In addition, TBDI plans to develop a bank of pedigreed *M. tuberculosis* isolates collected from around the world that exhibit a variety of drug-resistant phenotypes, to promote the development and evaluation of novel technologies for drug susceptibility testing and to provide reference materials to support quality control and proficiency testing programmes in endemic countries.

Performance review of marketed or near-market diagnostics

New technologies coming to market must demonstrate regulatory quality and performance in Phase III trials. However, many previous trials – including published and unpublished studies performed as commercial demonstration projects – have had major flaws in design or execution that negated the value of the performance data collected. TBDI and other members of the Working Group have been doing preparatory work to improve the value of future diagnostic evaluations, including identifying good trial sites, developing instruments to train and monitor trial site personnel, collecting and archiving reference materials to support laboratory-based evaluations, and developing standardized best-practices protocols.

Remaining challenges for new diagnostics

In spite of the increased international attention focused on developing TB diagnostic tools, no new tools have emerged. At present, microscopic examination of sputum is still the only widely available means of diagnosing TB in developing countries. This technique, invented more than 100 years ago, is insensitive and requires well-equipped laboratories that are difficult to maintain in the developing countries with the highest burden of TB.

Current tools are also inadequate for rapid drug susceptibility testing (DST) and the detection of latent TB infection. Delays in diagnosing MDR-TB result in increased morbidity, the selection of drug-resistant populations of bacteria, and the continued transmission of MDR-TB. The lack of a convenient and reliable diagnostic test for latent infection – one that can accurately predict the risk of active TB, especially in HIV infected patients – impedes efforts to diagnose and treat latent TB infection.

Success in TB diagnostics, however, will require more than just improved tools. Solid information on how to use these tools is also needed, including better data on the impact of early case detection on TB transmission, on the cost-effectiveness of routine or targeted DST, and on the appropriate role for treatment of latent or subclinical TB in HBCs. Lastly, as improved tools are developed and their usefulness demonstrated, mechanisms will be needed to ensure that these tools are made available and properly used in areas of greatest need, and that precious health care resources are not wasted on other poorly functioning or inappropriate diagnostic kits that are rapidly becoming commercially available.

Thus, rapid and accurate TB diagnostic tests are urgently needed. Recent biotechnical advances have fuelled a revolution in infectious disease diagnostics. TB has been included to some extent in these advances, but accelerated efforts and streamlined evaluation processes are necessary to apply these technical advances for new TB diagnostic tools.

2b. New TB drugs

↘ *Overall progress since the Global Plan*

A faster and simpler therapy for TB is essential to fighting TB's rapid spread, deadly synergy with HIV/AIDS, and ability to mutate into drug-resistant strains. It will also enable health care workers to reach and treat more TB patients, thereby expanding access to DOTS, and help achieve TB control targets. Since the publication of the first Global Plan, a robust portfolio of drugs has been assembled and managed, and is advancing towards clinical trials – for the first time in 40 years.

Several groundbreaking discoveries and scientific advances have revealed new avenues for TB drug development. In particular, the 1998 genome sequencing of *M. tuberculosis* was a major advance in the efforts to find better ways to combat this infectious agent. By clarifying the interactions between pathogen and infected host, this genomic information can lead to new drug candidates.

Other scientific advances hold great promise for transforming TB drug research and development. New technologies and approaches, including high-throughput screening, rational drug design and combinatorial chemistry, are transforming drug discovery and can now be applied to TB drug development. Screening existing compound libraries for TB activity may also reveal fast-acting therapies to help conquer this devastating epidemic.

The Stop TB Working Group on TB Drug Development, led by the TB Alliance, coordinates worldwide R&D activities aimed at delivering an affordable and faster TB cure. The activities of the Working Group's members span a wide spectrum from basic research to discovery, clinical development, and registration.

The TB Alliance was created to reinvigorate a TB drug development process that had come to a virtual standstill owing to a lack of market incentives. Even though the market for TB drugs is forecast to reach US$ 700 million by 2010, its concentration in poor countries deterred any single industry player from

pursuing the full development of a TB drug.(*3*) The TB Alliance is a public-private partnership designed to ensure that promising TB drug candidates will move quickly through all stages of development, receive rapid and appropriate regulatory approval, and be promptly transferred into effective and accessible clinical use.

Each Working Group member pursues its own drug development activities. Through the Working Group, these organizations collaborate on joint initiatives. For example, experts from many member institutions contributed to the two core publications by the TB Alliance, *Scientific blueprint for TB drug development* (*4*) and *Economics of TB drug development* (*5*). Working Group members also contribute expertise to the TB Alliance Scientific Advisory Committee, its Board of Directors and its staff. This helps in the design of scientific and strategic plans to accelerate the development of new TB drugs.

Achievements of the Working Group on TB Drug Development

For the first time in 40 years there is a pipeline of promising compounds that are meeting development milestones. These compounds are poised to become the cornerstone drugs of TB control. This recent progress is the result of new collaborations between public and private partners that have leveraged the potential of industry, the public health sector, and academic laboratories.

To ensure that at least one new TB drug is registered by 2010, the Working Group has targeted the need to have at least five drug candidates through preclinical development by 2005. The Working Group has also identified a number of support activities required to meet these targets. Several compounds, both novel leads and candidates from existing families of drugs, are already in preclinical and even clinical development. For example, newer fluoroquinolone antibiotics (e.g. moxifloxacin and gatifloxacin) have shown potent activity in vitro against *M. tuberculosis*. Findings from animal studies indicate that moxifloxacin may significantly shorten TB treatment.

Progress on the development of new compounds like PA-824 – which will provide the cornerstone of future TB treatment, particularly for MDR-TB – has been dramatic. Innovative chemistry is helping to optimize compounds such as quinolones and other novel agents as well as to synthesize derivatives and analogues of various first-line drugs, including ethambutol and isoniazid, which show promising activity. Two new compounds are currently undergoing preclinical testing, and one may be entered into clinical studies in 2005.

The Working Group supports activities related to R&D platform technologies and facilitation of partnerships. These activities entail mapping of TB drug R&D initiatives, the establishment of partnerships with industry, further studies to define surrogate markers, investments in building controlled clinical trials capacity, and the harmonization of regulatory requirements.

The Working Group also facilitates the exchange of information and perspectives on the latest developments and prospects for TB drug development. Members participate in mapping the environment to identify promising lead compounds and technologies. The first such study was initiated by the Special Programme for Research and Training in Tropical Diseases (TDR) in 2000. Other consultations of experts, orchestrated by the TB Alliance, reviewed the prospects for further development of several families of compounds (e.g. fluoroquinolones and rifamycins), surveyed progress on surrogate markers and, in 2003, convened a scientific workshop on targeting latency in tuberculosis to determine the state of the science to shorten treatment. See *Annex 5* for a summary of the activities and accomplishments of the TB Drug Development Working Group in 2002–2003.

Remaining challenges for new TB drugs

Despite progress on many fronts, greater effort is required to translate promising basic research into drug discovery programmes. Employing the latest technologies, such as high-throughput screening and rational drug design, Working Group members are now transforming drug discovery processes to find additional compounds. A number of chemical compounds, or "leads", are providing the basic components of a healthy portfolio, but significantly greater resources are needed to support a pipeline from discovery to registration.

Additional investment is also essential for technology platforms and clinical trials capacity. Animal models of persistence and studies of surrogate markers that can give an early indication of treatment outcome would facilitate clinical trials. Long-established entities such as the Tuberculosis Trials Consortium (TBTC) and Tuberculosis Research Unit (TBRU), respectively supported by the U.S. Centers for Disease Control and Prevention (CDC) and NIAID, are working to increase capacities for clinical trials. New initiatives such as the European Developing Countries Clinical Trials Programme are also supporting this effort, but capacity for clinical trials is still a potential bottleneck and will be a major area of need and focus.

A new, shorter treatment regimen will radically transform the fight against TB. Shortening treatment from 6 or 8 months to 2 months or less, or otherwise simplifying the regimen, will lower the incidence of side-effects, improve patient adherence, and increase cure rates. A shorter regimen will also reduce the costs of TB treatment for both patients and health systems. By shortening and improving treatment of latent infection, a new drug has the potential to decrease TB disease morbidity, especially in patients co-infected with HIV. Furthermore, by effectively treating resistant strains, a new drug would have a profound impact on the treatment and control of MDR-TB. The challenge of the next two years will be to fund the continued development of these compounds and ensure a healthy and balanced pipeline with adequate investments in discovery projects.

Recent discoveries indicate that a new TB cure is within reach. The promise of TB control efforts will be fully met only when health care workers are given the best tools that modern science can deliver. The tools are now available to find the next generation of TB medicines, and the coordination mechanisms are in place. Today is the time to invest in new tools for tomorrow's TB control and ensure that TB patients have access to new, faster-acting TB therapies.

2c. New vaccines

Progress since the Global Plan: achievements of the Working Group on TB Vaccine Development

In order to address the critical need for new vaccines, the Partnership established a Working Group on TB Vaccine Development. The Working Group provides a global forum that brings researchers involved in publicly and privately funded TB vaccine initiatives together with officials from regulatory agencies responsible for licensing vaccines and representatives from the HBCs, the countries that will be the major consumers of new vaccines. The Working Group includes representatives from major public sector funding organizations, private philanthropy groups, commercial and non-profit institutions

involved in TB vaccine development, representatives from four HBCs, and experts in regulatory issues associated with vaccine development. The Working Group sponsors two specialist task forces focusing on issues related to preclinical development and clinical trials.

The Working Group's objectives are to facilitate exchange of scientific information, to develop standards for preclinical testing and assessment of immunogenicity, and to coordinate global plans for clinical trials. The Working Group's underlying rationale is that, since the current level of scientific understanding is insufficient to identify a single optimal strategy for vaccine design, prospects for development of a new TB vaccine will be promoted most effectively by encouraging communication between multiple investigators pursuing multiple strategies.

A new public-private partnership, the Aeras Global TB Vaccine Foundation, was launched in 2003 to facilitate the development of new TB vaccines. Aeras has recently received a major grant. Through support to vaccine trials, study of improved animal models, and research on next-generation vaccines, Aeras plans to use this grant to achieve the goal of licensing and delivering a more effective TB vaccine within 10 years.

Advances in mycobacterial genetics and immunology over the past decade, including the elucidation of the genome sequence of *M. tuberculosis,* have allowed formulation of a wide range of new vaccine candidates. The Working Group has focused on the following vaccine development prototypes.

Live mycobacterial vaccines

The current BCG vaccine is an attenuated strain of *Mycobacterium bovis* that, when given at or near birth, has been shown to protect against severe childhood forms of disease, including the often-fatal tuberculous meningitis. However, it has failed to provide reliable protection against adult pulmonary tuberculosis in endemic countries. Attenuation of *M. bovis* to generate the current family of BCG vaccines involved a series of gene deletion events that are now well understood. Restoring lost genes, or increasing expression of remaining genes, presents an attractive route to an improved BCG. A pilot lot preparation of the most advanced candidate has been produced for use in clinical trials, which are likely to begin in 2004. A complementary strategy for developing an improved live mycobacterial vaccine is based on engineering highly attenuated mutant strains of *M. tuberculosis.* Stringent safety evaluation is clearly essential for moving these candidates forwards into clinical trials.

Subunit vaccines

A protective response similar to that induced by BCG can be generated in experimental models using individual components of *M. tuberculosis* delivered in the form of isolated protein preparations, as DNA molecules, or as part of recombinant viral vaccines. This approach has potential advantages over live mycobacterial vaccines in terms of safety and quality control of the manufactured vaccine. Vaccine manufacturers and national regulatory entities prefer subunit vaccines because of their safety and quality control advantages. Thus, subunit vaccines represent the most advanced class of experimental TB vaccines. One candidate in the United Kingdom is the first of all new TB vaccine candidates to enter a Phase I safety trial. It is currently undergoing further safety evaluation in an endemic African population. Phase I trials of a second new vaccine have recently been initiated in the United States, and two additional vaccine candidates are expected to enter clinical evaluation in 2004.

In addition to promoting R&D in the above areas, the Working Group has undertaken a series of specific initiatives to achieve its objectives. The first is to bring together information about the current state-of-the-art in TB vaccine development in the form of a published "road map" and a readily accessible and updated web site. A second initiative is to develop an economic case for TB vaccines that can be used as an advocacy tool to encourage further interest from vaccine developers. The Preclinical R&D Task Force is currently focusing on the transition from preclinical to clinical evaluation by addressing production and regulatory issues related to preparation of vaccine lots for Phase I trials. The Clinical R&D Task Force is compiling a global directory of potential sites for clinical trials of TB vaccine candidates and evaluating assays that may be suitable for Phase II immunogenicity trials. Finally, the Working Group is sponsoring an evaluation of the issues related to the manufacture and comparison of BCG substrains.

Remaining challenges for new vaccines

Despite these advances, and even in the best of circumstances, a usable TB vaccine is probably a decade away. The transition from laboratory to clinical trials has a wide range of strategic and technical implications. Facilities and funding need to be identified for the production of clinical vaccine lots, an issue that is difficult to tackle for the new vaccine candidates containing live organisms; regulatory hurdles need to be overcome; and protocols and trial sites need to be developed for clinical efficacy trials, in particular Phase III trials. Preparing such sites will require a significant investment in human resources to ensure progress.

Recent years have witnessed an intensification of international research activity focused on TB vaccine development, including the establishment of Aeras. The world cannot afford to lose the momentum this activity has started. Continued support for vaccine development efforts is critical for ensuring that current candidates are thoroughly evaluated as quickly as possible, and that a vaccine, once approved, is distributed to where the TB burden is the greatest.

Since the launch of the GPSTB, the Stop TB Partnership has made significant strides. A strong Secretariat housed at WHO has helped to create the Global Drug Facility and provided guidance and oversight to the Partnership's six Working Groups.

The Global Partnership to Stop TB

3a. The Stop TB Partnership

The Stop TB Partnership structure includes a Partners' Forum, a Coordinating Board, a Secretariat, and the six Working Groups described in the previous chapters.

In pursuit of GPSTB's vision and mission (*1*), the Stop TB Partnership Secretariat coordinates and carries out activities as operational support to the Stop TB Coordinating Board. The Secretariat is a group of core staff housed within WHO and headed by an Executive Secretary. The Secretariat's functions are defined in the Partnership's Basic Framework. These functions include preparing an annual work plan and budget; mobilizing resources for vital activities of the Partnership; coordinating and monitoring the progress of activities; disseminating information inside and outside the Partnership; developing communication strategies to support its campaign; promoting greater awareness of the social, economic, and political aspects of the global TB epidemic; supporting and facilitating coordination of the Working Groups; providing administrative support to the Coordinating Board, the Working Groups, and the Forum; and contracting various functions of the GDF with pre-qualified agencies.

The Stop TB Coordinating Board formulates priorities for action for the Partnership, represents the Partnership, and acts on its behalf. The Coordinating Board's members track the progress of the Partnership's activities and address issues and problems the Partnership encounters. Board members also take on a number of activities in support of the Partnership. These include participation in high-level missions to countries, resource mobilization, and advocacy on behalf of the global fight against TB.

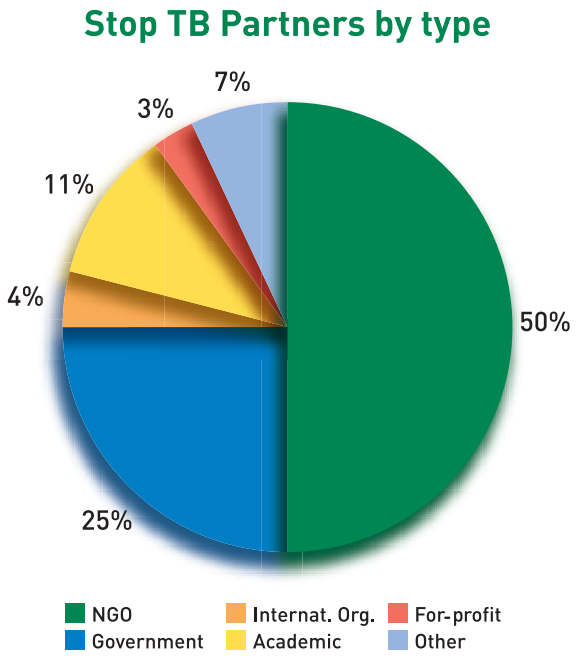
↘ *Achievements during 2001–2003*

In 2001, the Stop TB Partners met for the first time in a full Partners' Forum at the World Bank in Washington, DC, where the Partnership Framework and the GPSTB were endorsed. The partners voiced their dedication to implementing the GPSTB and attaining the 2005 Stop TB Targets in the Washington Commitments cited below:

Within the next 50 days – by the end of 2001	→ Finalize national plans to achieve 2005 goals → TB included in the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM)	ACHIEVED ACHIEVED
Within the next 50 weeks – by the end of 2002	→ Achieve global DOTS detection rate of 35% → Provide GDF drugs for one million additional patients	ACHIEVED ACHIEVED
Within the next 50 months – by the end of 2005	→ Achieve DOTS detection (70%) and cure (85%) rate targets	WORK IN PROGRESS
Within the next 50 years – by 2050	→ Eliminate TB as a public health problem	WORK IN PROGRESS

Thanks to the Secretariat's active work, the Partnership has grown quickly and substantially, from 75 organizational partners in 2000, to 210 in 2001, to 280 in early 2004.

The Secretariat has supported the implementation of the key recommendations set by the Board, including developing a Draft Memorandum of Understanding with the GFATM, establishing the Stop TB Trust Fund with the World Bank, and disbursing to date more than US$ 10 million from donors via this mechanism to GDF agents, Stop TB evaluators, and meeting organizers.



The Stop TB Partnership has achieved substantial success in raising concern for the TB epidemic and eliciting political commitment at both the global and national levels for fighting the disease. The Partnership has heightened awareness of the magnitude of the TB epidemic and its devastating impact on people, especially in the HBCs. Above all, it has succeeded in raising the profile of the TB epidemic and global response to the disease in high-level political forums such as the United Nations General Assembly, the World Health Assembly, the G8 (Okinawa Summit), and regional institutions such as the Organization of African Unity (OAU – now the African Union). The commitment of these forums to action against TB have created an enabling environment both for coherent fulfilment of policy objectives and for significant capacity gains within partner agencies. The Partnership has also been instrumental in championing the inclusion of TB in the GFATM and in bringing about significant increases in support from additional funding partners.

At the request of the Coordinating Board, in 2003 the Partnership commissioned an independent external evaluation of the Stop TB Partnership. Through interviews, fieldwork, document reviews, and observation, the Partnership was evaluated in the following eight areas: relevance, efficacy, efficiency, sustainability, institutional development impact, process, governance, and implementation. The evaluation concluded:

The Global Stop TB Partnership has established itself in a very short time as a widely respected global health partnership. The perception of partners themselves is that it has both added value to what they were already doing and has moved swiftly to introduce widely appreciated new initiatives such as the Global Drug Facility and the Green Light Committee. The Partnership has scored some major achievements in only three years. It has built and is sustaining a broad network of partners; established a partnership architecture which commands broad support; heightened political commitment... [and] made significant progress against TB, even in difficult environments... This is a formidable record.(2)

Working Groups, regional and national partnerships to Stop TB

The Partnership's Basic Framework identifies the six Working Groups as the primary means for coordinating activities mandated by the Board. In addition to meeting the 2005 targets of 70% case detection and 85% treatment success, the Partnership agreed that by 2005 it would define, adopt, and implement effective strategies to address HIV-related TB; incorporate DOTS-Plus protocols for MDR-TB in the DOTS strategy; and develop at least five new diagnostic tools for clinical evaluation, five new TB drug candidates for initial clinical trials, and one new vaccine candidate. The GPSTB maps input from the Working Groups covering major aspects of TB prevention and control. The activities and achievements of the Working Groups are described in Chapters 1 and 2.

The Partnership has built and is sustaining an effective umbrella network that has brought together diverse groups sharing a common vision. In a short time, the Partnership has gathered a broad alliance of national governments, bilateral and multilateral funding agencies, foundations, national and international NGOs, and public–private partnerships around a common agenda and strategy for action in the GPSTB. This common platform is evident not only at the global level but also at the regional and

country levels, albeit with less intensity. There is a widespread perception that such a broad consensus could not have been achieved in so short a time by any one partner alone. TB-dedicated partnerships bring country experiences together in a region-specific perspective and will provide a platform for advocacy and coordinated action in support of country activities. Regional partnerships were established in the Western Pacific and in South-East Asia and are being established in Africa and the Americas, while interagency coordinating committees became operational in all but one HBC. National partnerships have been formally established in Indonesia, the Philippines, and the Russian Federation; formation of other national partnerships is ongoing.

The Partnership has added value at the country level and provided tangible benefits, for example through the GDF and the generation of increased funding flows to national TB efforts, technical support (through strategy-development, problem-solving in the field, partner coordination, and training events), and advocacy work from Partnership members, which has helped build up the visibility of TB control and the Partnership itself. Peer interaction at the ministerial and senior government official levels has been critical and will continue to be encouraged.

Business partners

Internationally, significant progress has been made in engaging the corporate sector in the fight against TB. Private pharmaceutical companies have provided specialist support and drug donations. The World Economic Forum through its Global Health Initiative is working closely with the Partnership to develop strategies for wider involvement of the corporate sector. A notable success in this regard has been the production of *Guidelines for workplace TB control* together with WHO and the ILO.

Advocacy, communications and social mobilization

Information, communication, advocacy, and social mobilization are central to the Partnership's activities and cut across all of the Partnership's components from the global to the community level. The Secretariat leads the Stop TB Advocacy and Communications Task Force by means of a new 15-member Core Group set up to strengthen planning, implementation, coordination, and reporting of activities. The country visit reports from the Partnership's external evaluation indicate that, where advocacy and communications efforts of the Partnership have been effective, the commitment of governments has demonstrably increased.

Global advocacy to keep the problem of TB high on public and political agendas has been achieved through annual World TB Days that now regularly involve more than 50 countries. The Partnership has encouraged countries to mount year-long campaigns that engage TB patients as spokespeople and focus on specific themes such as "DOTS: TB cure for all" (2001), "Stop TB, fight poverty" (2002), and "DOTS cured me, it will cure you too!" (2003). The Partnership has undertaken advocacy initiatives and built a network of high-level spokespeople such as the Director-General of WHO, the President of the World Bank, and government ministers from the HBCs. In late 2003, the Partnership recruited its first Global Ambassador, India's musical superstar A.R. Rahman, who will participate in a programme of public events in 2004.

The Partnership has built close working relationships with UNAIDS and other key HIV/AIDS organizations to advocate collaborative efforts to combat TB/HIV. High-intensity social mobilization projects have been launched in India (Kerala State) and Kenya, and a strategic framework has been developed to build communication capacity at country level to support DOTS expansion.

Information management

The Secretariat produces and coordinates a vast amount of information for its global constituency through the Stop TB web site, web alerts, communiqués, newsletters, and audiovisual materials. To enhance partner-to-partner communication, the Secretariat has developed a web-based Partners Directory, which provides an accurate and updated overview of the activities that Stop TB partners are undertaking or planning.

Remaining challenges for the Partnership

The first GPSTB represented a landmark consensus strategy document that is unique in the world of public health partnerships. Strategic overlap and complementary goals between and among Working Groups, the governance structures of the Partnership, and important outside actors need to be further enhanced in the next Global Plan.

The Global Plan development process itself should serve as a mechanism to identify and create these synergies, particularly among the Working Groups and with key external entities, through support from the Coordinating Board and its Secretariat. This process should therefore be a core Partnership activity in the period leading up to the 2006 Global Plan launch.

The Global Stop TB Partnership is making significant progress, even in some difficult environments, but there is still work to do. While there is some evidence of improved DOTS coverage and success rates, these still fall short of the 2005 targets. Better coordination among all partners could be achieved through the use of Interagency Country Coordinating Committees, Consultative Forums, and Technical Meetings. HBCs should develop medium-term plans for TB control supported by in-country technical assistance and NGO activities. There is a clear need for more national and international funding, training activities, IEC activities, and attention to laboratory services, drug quality, case-finding, and treatment outcome information.

Further work is needed in specific policy areas, such as the link between TB and poverty. First steps in this area have been taken. The Network on TB & Poverty, established following the 2002 World TB Day, supported a systematic analysis of existing evidence on the relationship between TB and poverty. The Network could be a useful tool in producing innovative approaches for reaching out to the poor and stimulating operational and social research to increase understanding of how barriers for the poor can be identified and subsequently reduced.

The fieldwork undertaken during the external evaluation focused on advocacy and communications within the Partnership Secretariat and the Advocacy and Communications Task Force. The evaluation concluded that this area of activity has not received the necessary attention and support. The external evaluation recommended that structures within the Stop TB Partnership dedicated to advocacy and communications be strengthened and formalized at the global level. To move forward, these structures will need more resources to mount more intensive and sustained media activities and parliamentary outreach efforts. These should be aimed at enhancing case detection at country level by providing technical assistance for NTPs to leverage GFATM, TBCTA, and other existing funding resources and by activating HIV/AIDS groups in a joint advocacy strategy to promote understanding of the linkages between the two diseases and to support TB/HIV interventions at country level.

As a start-up, the Partnership has had success in establishing effective mechanisms with minimal resources. However, the evaluations of the GDF and the Stop TB Partnership both indicate that more systematic and business-like management and reporting systems are needed in the Secretariat. Changes in this area are under way. There is also serious underfunding of the Partnership's core functions.

Thus far, the Partnership has a formidable record of accomplishment. Having secured the political commitment and operational mechanisms needed to control TB, it is poised to make rapid progress towards attaining the 2005 targets on time. Renewed commitment to the plans and pledges from all partners is needed now more than ever.

3b. The Global Drug Facility

Shortages of TB drugs are frequent in many parts of the world and are most often caused by financial constraints, inefficient drug procurement systems, and poor management. These drug shortages create a significant barrier to rapid DOTS expansion. Furthermore, erratic supplies contribute to the emergence of MDR-TB (*3*). Recognizing the urgency of these issues, and in response to a call at the March 2001 Amsterdam Ministerial Conference on TB and Sustainable Development, the Partnership launched the Global Drug Facility (*4*).

Progress since the Global Plan

The goals of the GDF are: 1. To ensure uninterrupted access to high-quality TB drugs for DOTS implementation – 2. To thereby catalyse rapid DOTS expansion in order to achieve the WHO global targets for TB control – 3. To stimulate worldwide political and public support for public funding of TB drug supplies – 4. To secure sustainable global TB control and eventual elimination of TB. The GDF seeks to fulfil its mission by providing grants, by direct procurement, and by maintaining a White List of pre-qualified TB drug manufacturers and products. All countries receiving GDF grant and drug procurement services have access to technical support and monitoring from Stop TB partner organizations as well as to a standardized list of quality-assured drug products in user-friendly packaging.

The GDF grant programme provides standardized, high-quality TB drugs free of charge to people in the poorest countries. Grants of TB drugs are tied to the performance of NTPs in adhering to the DOTS strategy, so that GDF-donated drugs are used appropriately and promote stronger general health planning and better drug management. The GDF is able to provide timely and efficient services by drawing on the expertise of partner agencies and organizations. To date, the GDF has provided drugs to treat almost 2 million TB patients in 49 countries in Africa, Asia, and eastern Europe. The total value of the GDF's approved grants has exceeded US$ 23 million.

As a result of standardization of products, pooled procurement, and competitive bidding, the GDF has also significantly reduced TB drug prices. Drug prices have decreased by more than 30% to less than US$ 11 for a standard 6-month course of treatment. This price reduction, while not a paramount aim of the GDF, ensures efficient use of GDF resources and enables GDF recipients to benefit from considerable savings on TB drugs. In 2002, the GDF introduced a Direct Procurement Service, which enables countries to procure low-cost, high-quality drugs directly through the GDF, while also benefiting from the technical assistance facilitated by the GDF through Stop TB partners. Ninety-five countries and more than 60 organizations and agencies committed to DOTS are eligible to use this mechanism.

The GDF developed and continues to update a White List of manufacturers and products that meet international quality standards, through a standardized prequalification process, in collaboration with the WHO Department for Essential Drugs and Medicines Policy/Quality Assurance and Safety: Medicines. This process is based on a review of TB product dossiers and inspections of manufacturing sites to assess compliance with Good Manufacturing Practices (GMP). The White List of manufacturers and products is published on the GDF web site and regularly updated, enabling agencies and countries procuring TB drugs to identify sources of quality-assured drugs.

The GDF is a pooled procurement mechanism, yet there are three key elements that make the GDF different from previous procurement mechanisms: 1. The GDF links demand for drugs to supply and to monitoring and technical assistance, which decreases the risk of developing drug-resistant TB – 2. The GDF outsources most of its work to partners on a collaborative and contractual basis through a competitive bidding process – 3. The GDF is actively involved in drug management, i.e. the GDF simplifies in-country drug management and use by providing a standardized list of products in user-friendly drug packaging, such as patient kits and blister packs.

The work of the GDF has proved to be groundbreaking for other diseases. WHO is currently adopting the GDF model for diseases such as HIV/AIDS and malaria.

In 2002, the Coordinating Board commissioned an external evaluation of the GDF. The evaluation showed that the GDF is having positive effects at the country level and offers multiple benefits at a systems level by reducing prices, promoting standardization and innovation in drugs and packaging, and encouraging patient compliance and rational use. Further, GDF services are being delivered in a resource-effective manner, and its three-component model, which bundles grant-making, procurement, and partner mobilization for technical assistance, is critical to its success. The evaluation concluded that maintaining the grant-making function is crucial to the GDF's continued progress and achievement.

"In summary, based on the results in its first two years of operations, GDF has demonstrated proof of concept as an innovative and potentially high impact model. It has shown positive results at a country and system level, in addressing drug access issues, and to a lesser extent, catalysing DOTS expansion." (5)

Remaining challenges for the GDF

The accomplishments of the GDF thus far are impressive. Nonetheless, there is room for improvement. The independent evaluation of the GDF made selected recommendations for operational improvements in advocacy, partner-mobilization, and procurement; in strengthening the management team; and in developing flexible and responsive administrative support. The evaluation also suggested that clearer governance structures be put in place. These recommendations also resulted in the convergence of the GDF and GLC, now an ongoing process, with the aim of ensuring uninterrupted access to both first- and second-line drugs.

The establishment of the GFATM, the GDF's shortfall in resources, and increasing requests from countries for GDF assistance have prompted the Secretariat and the Board to take appropriate action. Plans include marketing the GDF as a drugs-procurement service for grantees of the GFATM, increasing GDF presence at country level through drug management and direct procurement, and fundraising strategies. Ongoing work includes production of an integrated information package, incorporation of communication activities into GDF country missions, and an expert consultation in 2004 to examine revising the GDF's five-year strategic plan.

The GPSTB provided cost estimates, shown below, for all TB control initiatives totalling US$ 9.1 billion for the five-year period from 2001 to 2005. The plan also provided an estimate of current resources – from TB high-burden countries and from external sources – and a projected five-year gap (US$ 3.8 billion), based on the assumption that resources dedicated to TB control in the year 2000 remained in place throughout the five-year period.

GPSTB

Financial summary

Summary costs in the Global Plan to Stop TB, 2001–2005 (US$ millions)

Figures for 114 countries	Costs	Current resources			Gap
		national	external	subtotal	
	(a)	(b)	(c)	(d)=(b)+(c)	(a)–(d)
DOTS expansion	**6225**	**4300**	**359**	**4659**	**1566**
TB programmes in HBCs	1560	3300	250	3550	1010
Health care services [1] in HBCs	3000				
TB programmes in other countries	590	1000		1000	440
Health cares services [1] in other countries	850				
DOTS Expansion Working Group	225		109	109	116
Adapting and improving DOTS	**1728**	**230**	**60**	**290**	**1438**
• TB/HIV	642	30	8	38	604
Country needs	630	30	6	36	594
TB/ HIV Working Group	12		2	2	10
• MDR-TB	1086	200	52	252	834
Country needs	1070	200	50	250	820
MDR-TB Working Group	16		2	2	14
Research and development totals	**1098**	**0**	**390**	**390**	**708**
• New diagnostics	177	0	53	53	124
Research needs	150		47	47	103
New Diagnostics Working Group	27		6	6	21
• New drugs	347	0	136	136	211
Research needs	317		130	130	187
New Drugs Working Group	30		6	6	24
• New vaccines	424	0	96	96	328
Research needs	420		95	95	325
New Vaccines Working Group	4		1	1	3
• Health policy systems research	150	0	105	105	45
Partnership	**75**	**0**	**10**	**10**	**65**
Partnership Secretariat	27	0	10	10	17
Advocacy [2]	20				20
Resource development and financing [2]	13				13
Monitoring [2]	15				15
TOTAL	**9126**	**4530**	**819**	**5349**	**3777**

(1) The annual averages for 2001–2005 are calculated based on the five-year total.
(2) Cost estimates for these items have not been significantly revised for this update.

This GPSTB Progress Report provides revised cost estimates, where they were available, for the separate components of the GPSTB. The original cost estimate over five years was US$ 9.1 billion, an average of roughly US$ 1.8 billion for each year. The re-estimated costs for 2004 and 2005 in this update are generally similar or higher, as expected, because of the planned increase in activities over time. The main exception is DOTS-Plus treatment of MDR-TB, for which costs have been revised downwards. The net difference between comparable categories amounts to US$ 415 million per annum. The explanation of the 2004–2005 cost estimates for the separate components of the GPSTB is provided in the sections that follow.

Comparison of annual average cost estimates and net change (US$ millions)

	GPSTB update: Annual average for 2004 and 2005 only	**GPSTB:** Annual average for 2001–2005 [1]	Net change
DOTS expansion	**1760.4**	**1245.0**	**515.4**
High-burden country needs	1425.0	912	513
TB care in other countries	288	288	0
DOTS Expansion Working Group	47.4	45	2.4
Adapting and improving DOTS	**220.1**	**345.6**	**–125.5**
• TB/ HIV	128.8	128.4	0.4
Country needs [2]	126	126	0
TB/ HIV Working Group	2.8	2.4	0.4
• MDR-TB	91.3	217.2	–125.9
Country needs	88	214	–126
MDR-TB Working Group	3.3	3.2	0.1
Research and development totals	**248.3**	**219.6**	**28.7**
• New diagnostics	38.6	35.4	3.2
Research needs [2]	30	30	0
New Diagnostics Working Group	8.6	5.4	3.2
• New drugs	78.6	69.4	9.2
Research needs [2]	63.4	63.4	0
New Drugs Working Group	15.2	6	9.2
• New vaccines	101.1	84.8	16.3
Research needs [2]	100	84	16
New Vaccines Working Group	1.1	0.8	0.3
• Health policy systems research [2]	30	30	0
Partnership	**10.3**	**13.6**	**–3.3**
Governance, support and innovation	3.2	5.4	–2.2
Advocacy	2.9	4	–1.1
Resource mobilization and financial management [2]	1	2.6	–1.6
Global Drug Facility [2]	3.2	1.6	1.6
Total	**2239.1**	**1823.8**	**415.3**

(1) The annual averages for 2001–2005 are calculated based on the five-year total.
(2) Cost estimates for these items have not been significantly revised for this update.
(3) These GDF estimates cover only the technical, logistical and management costs. TB drug costs are included in DOTS expansion cost estimates.

4a. DOTS expansion (*1*)

As shown above, the estimated GPSTB costs for DOTS expansion in the HBCs alone was US$ 4.5 billion over the five-year period, or some US$ 910 million per year. HBCs spent somewhat less than that in 2002 – roughly US$ 850 million – and less than WHO's current estimate (US$ 976 million) of what was required to reach the 70% case detection goal by the year 2005. Planned TB control spending for 2003 in these countries was estimated to have increased to US$ 1 billion; data on actual expenditures are not yet available. In both years, TB control funding came primarily from governments and to a lesser extent from grants. The funding shortfall reported by the HBC governments was only about 4% of the total need.

However, these aggregate statistics conceal a diversity of financial needs among the countries that carry the largest burdens of TB. The *Global tuberculosis control report 2004* analysis of budgets and expenditures classifies the 22 HBCs broadly into three groups. The first group contains 10 countries (*2*) – including the four countries with the highest number of TB cases – that have planned to increase spending significantly from 2003 onwards, in order to meet the global targets for case detection and treatment success by 2005. All of these countries will need some external assistance to put their plans into action; some of this external assistance will come through grants from the GFATM.

A second group of countries (*3*) is not expected to require large budget increases to meet TB control targets, and their funding gaps are low or non-existent. The remaining eight countries constitute a third group, where the NTPs are not yet close to reaching targets, and apparently have neither plans nor budgets that will get them to the targets by 2005. Some of these countries provided no data for either 2002 or 2003; for others, the planned increase in costs was small. Knowing the genuine obstacles to TB control in HBCs, well-considered plans and large, well-justified budgets will be necessary if TB control targets are to be met in these countries. As a result, the real aggregate funding gap in the HBCs was certainly greater than 4% in 2002 and 2003, and will be significant for 2004 and 2005 as well. But it is the plans, budgets, and funding gaps in each of the HBCs that are the revealing and important variables for success of TB control, and these are discussed in detail in the *Global tuberculosis control report 2004*.

For 2004 and 2005, spending of roughly US$ 1.35 and US$ 1.5 billion respectively will be required in 21 of the 22 HBCs in order to achieve the targets.(*4*) Roughly 70% of this need will likely be filled by government resources and a further 10% by external assistance, such as grants from the GFATM. This leaves a likely funding gap of roughly 20% of the total need, approximately US$ 200 million per year.

In general, the governments of richer countries pay a larger fraction of the costs of TB control. For the poorer countries that have identified greater needs, progress in TB control will be closely linked to the flow of funds from grants, especially those recently awarded by the GFATM. The GFATM has rapidly become a major donor for TB control. However, analysis of HBC TB control plans and budgets raises difficulties of two kinds. Firstly, payments from the GFATM have so far been small compared with the size of grants awarded. During 2003, only 16% of the total approved for TB and TB/HIV activities in the first two years was paid to countries. Secondly, it is questionable whether large influxes of new money can immediately be used effectively in countries that have little experience of rapidly scaling up health interventions, as well as weaker capacity to develop effective plans. As external donors contribute more to TB control to fill the current shortfalls in budgets, attention must also be paid to increasing the absorptive capacity of the poorest countries.

The DOTS Expansion Working Group has projected a budget of roughly US$ 47 million for each of the next two years (*Annex 6*), roughly US$ 1 million more per annum than the original GPSTB projections.

4b. TB/HIV

The cost estimates in the GPSTB for TB/HIV were quite limited in scope. The estimates (US$ 630 million in-country) were built on preliminary cost data from pilot projects and studies. The GPSTB applied these figures to project the cost of offering HIV voluntary counselling and testing (VCT) to 28 million people in 12 sub-Saharan countries and offering therapy to prevent the onset of TB in patients co-infected with HIV. These cost estimates are still valid; however, plans to test and treat patients in countries with high burdens of TB and HIV have expanded far beyond what was anticipated in the GPSTB.

The recently announced WHO "3 by 5" Initiative covers 34 countries with high burdens of HIV, many of which are also high-burden TB countries. The success of this new initiative will require considerably greater coordination and, where appropriate, joint implementation of prevention and treatment initiatives.

Most countries with high burdens of TB neither routinely test TB patients for HIV nor actively look for TB among people with HIV, and most do not have national surveillance systems for assessing the scale of the TB/HIV problem. The twin goals of testing TB patients for HIV infection and testing HIV-infected persons for TB have been achieved on a limited scale in Brazil, Cambodia, China, India, Indonesia, Myanmar, the Russian Federation, and South Africa. Most of the HBCs do not yet monitor and evaluate collaborative TB/HIV activities, offer isoniazid preventive therapy, or routinely provide TB patients with the means to prevent HIV infection. The majority also do not provide antiretroviral therapy, or offer little additional care and support for TB patients infected with HIV.

These complementary testing, prevention and treatment initiatives will be planned and implemented over the next two years, based on what has been learned to date from existing pilot projects and using data consistent with the GPSTB's TB/HIV cost projections. These estimates were accurate at the time of our initial projections; however, cost estimates will need to be revised considerably in light of the new commitment and scope of efforts to confront these twin epidemics in the HBCs. This revision is currently under way.

The Working Group on TB/HIV has projected a budget of US$ 5.5 million for 2004–2005 (*Annex 7*).

4c. DOTS-Plus for MDR-TB

The GPSTB estimated a need of US$ 1.1 billion over five years to treat patients with MDR-TB, based on the assumption that 494 000 patients with MDR-TB, representing 40% of the likely new cases, would be treated over five years. This projection of patient enrolment and cost was a function of the alarming numbers of patients developing MDR-TB and an evaluation of how rapidly DOTS-Plus treatment programmes would be established and scaled up. Establishment and scale up of the programmes is dependent both on available financial support and on sufficient technical and programmatic resources.

Fourteen DOTS-Plus pilot projects have been established, as discussed in Chapter 1, and the GLC approved more than 4500 patients for treatment. Meanwhile, there are an estimated 273 000 new MDR-TB cases each year worldwide. As a result, the need for support of DOTS-Plus treatment projects will remain large. Drug costs have continued to come down, and programme costs are expected to fall as patients are diagnosed and enrolled in appropriate treatment before additional resistance develops.

The pace of patient enrolment is likely to pick up during 2004–2005, now that so many DOTS-Plus treatment programmes have been established, yet logistic constraints will limit growth and make it unlikely that more than 10% of all MDR-TB patients will be enrolled in each of the next two years, even with adequate financial support. As a result, the revised projected costs in this GPSTB update for MDR-TB control are significantly lower.

Using data from established DOTS-Plus projects, the revised cost estimates assume per patient costs of US$ 3 262 and an enrolment of 54 000 in 2004 and 2005 (roughly 10% of new cases each year). These assumptions generate an estimated cost of US$ 176.1 million. The DOTS-Plus Working Group for MDR-TB has projected a budget of US$ 4 million for 2004 and a smaller budget of US$ 2.65 million for 2005 *(Annex 8)*.

4d. New diagnostics

The GPSTB estimated a need of roughly US$ 150 million in research and development costs over five years for the development of new diagnostic tools. The estimates for the cost of this research have not been re-evaluated in detail for this progress report, but this aggregate estimate – of some US$ 30 million per annum in 2004 and 2005 – is probably still accurate.

The establishment of FIND brings an infusion of new resources to support key activities and projects. It also strengthens opportunities to mobilize additional resources, including in-kind and other contributions from the private sector.

The Working Group on TB Diagnostics has a budget for 2004 and 2005 of US$ 17.2 million. This will support, among other initiatives, facilitation of commercial tool development (US$ 4.9 million) and oversight and evaluation work, including Phase III clinical trials (US$ 6.7 million). The details of this budget are provided in *Annex 9*.

4e. New drug development

In the GPSTB, the Working Group on TB Drug Development estimated the costs of TB drug development activities over five years to be US$ 347 million, as the first phase of a decade-long undertaking with the aim of registering one new TB drug by 2010. To accomplish its objectives, the Working Group plans to have at least five drug candidates through preclinical development by 2005.

The US$ 347 million figure for five years covers R&D costs (US$ 317 million), priority coordination and development activities (US$ 27.3 million), advocacy and information (US$ 2 million), and support of the Working Group activities (US$ 0.4 million). Of this five-year total, the cost estimates for 2004 and 2005 amount to US$ 206 million, and are presented in more detail in the table in *Annex 10*.

To date, the Working Group has secured nearly US$ 235 million to meet its five-year budget estimate of US$ 347 million, leaving a gap of US$ 112 million for 2004 and 2005.

4f. TB vaccine development

In the GPSTB, the Working Group on TB Vaccine Development projected US$ 420 million for TB vaccine R&D costs and US$ 4 million for Working Group activities over the five-year period. The estimates for the cost of this research have not been re-evaluated in detail for this progress report, but the cost for vaccine development activity in 2004 and 2005 is roughly estimated at US$ 100 million per year. These costs include roughly US$ 40 million each year to maintain current levels of preclinical research and a similar amount to support Phases I and II trials for five candidate vaccines. The remaining US$ 20 million per year is required to build capacity for Phase III trials on successful vaccine candidates.

The recent award of US$ 82.9 million to the Aeras Global TB Vaccine Foundation represents an estimated doubling in the funding for vaccine development and will make a substantial contribution to progress toward the GPSTB goals.

The budget for Working Group activities is approximately US$ 2 million (*Annex 11*).

4g. Stop TB Partnership Secretariat

The Stop TB Partnership Secretariat provides operational support to the Stop TB Coordinating Board and supports Partnership activities by mobilizing and coordinating partners and working groups and by disseminating information. The Secretariat also manages the Global Drug Facility. The Secretariat has a small staff, housed in WHO and headed by an Executive Secretary.

The GPSTB provided only rough cost estimates for the Secretariat's work over the five-year period and these estimates were not yet supported by detailed budgets. In 2003, the Stop TB Coordinating Board commissioned an independent evaluation of the Partnership and specific work plans and budgets emerged from that evaluation and the related strategy deliberations. Cost estimates for the Secretariat work plans for 2004 and 2005, totalling US$ 9.1 million per year, are provided in *Annex 12*. The initiatives are categorized into three broad areas of work – support and innovations (US$ 5.4 million/year); management and implementation of GDF activities (US$ 2.7 million/year); and general management and administration (US$ 1 million/year).

Annexes

Epidemiological update of the 22 TB high-burden countries

Countries	DOTS coverage (%) [1]		Case detection under DOTS (%) [2]		DOTS treatment success (%) [3]		NICC-TB	GFATM funding
	2001	2002	2001	2002	2001	2002		
AFRO								
DR Congo	70	70	67	68	78	77	Yes	Round 2
Ethiopia	70	95	35	36	80	76	Yes	Round 1
Kenya	100	100	49	47	80	80	Yes	Round 2
Mozambique	100	45	45	45	75	77	No	Round 2
Nigeria	55	55	16	16	79	80	Yes	Round 2
South Africa	77	98	84	108	66	65	No	Rounds 1&2
Uganda	100	100	47	49	63	56	Yes	Round 2
UR Tanzania	100	100	46	42	78	81	Yes	Round 3
Zimbabwe	100	100	47	47	69	71	Yes	
AMRO								
Brazil	32	25	8	9	73	62	Yes	
EMRO								
Afghanistan	12	38	14	19	86	84	Yes	Round 2
Pakistan	24	45	6	15	74	77	Yes	Round 2
EURO								
Russian Federation	16	25	5	6	68	68	Yes	
SEARO								
Bangladesh	95	100	25	29	83	84	Yes	Round 3
India	45	52	24	31	84	85	Yes	Round 1
Indonesia	98	100	20	28	87	86	Yes	Round 1
Myanmar	84	88	57	66	82	81	(Yes)	Round 2
Thailand	82	100	74	60	69	75	NR	Round 1
WPRO								
Cambodia	100	100	42	48	91	92	Yes	Round 2
China	68	77.6	29	28	95	96	Yes	Round 1
Philippines		98	58	63	88	88	Yes	Round 2
Viet Nam	99.8	99.9	86	90	92	93	Yes	Round 1

(1) DOTS population coverage (%)
(2) DOTS detection rate (new sputum smear-positive cases, (%)
(3) DOTS treatment success rate (new sputum smear-positive cases, (%)
NR: Not required

DOTS Expansion Working Group: summary of activities and accomplishments in 2002

Partnership component	Progress indicators	2002 target	2002 results
Technical assistance			
Capacity building and human resources development for DOTS implementation	International training courses, including training of consultants	Checklist of competencies for TB consultants developed	Activities implemented
	Training materials, coordination of training	Training of consultants in Europe under way	
	In-service training	International training in all six regions	
		WHO training modules revised	
		New training material for peripheral health workers developed	
		TBCTA task force training established	
		Medium-term plans developed for all 22 HBCs	
		DOTS detection rate reaches 35% at the end of 2001 (data reported in 2002)	
Provision of direct NTP assistance, advisers, missions, and tools	Medium-term plans including budget	Medium-term plans developed for all 22 HBCs	Medium-term plans developed for all 22 HBCs except Mozambique
	DOTS detection rate	DOTS detection rate reaches 35% at the end of 2001 (data reported in 2002)	DOTS detection rate reached 31% at the end of 2001
Support and coordination			
Formulate action plans for endemic countries	Action plans as guiding principles for DOTS expansion	Action plans developed for all 22 HBCs	Action plans developed for all 22 HBCs except Mozambique
Regional coordination and partnerships	RICCs and regional advisory groups formed	RICCs established in all 6 regions	Activity implemented
Update plans, strategies and acheivements in DOTS expansion	Global TB Control Report	2002 and 2003 reports published	Activity implemented
National coordination and partnerships	Functional NICCs	TB-NICCs established in all HBCs	TB-NICCs established in 18 of 22 HBCs
Monitoring and reporting	Annual DOTS Expansion WG meetings DOTS Expansion reports	Annual meeting in Montreal, October 2002 Report of the 2001 DEWG Paris meeting published; report of the 2002 DEWG meeting in preparation	Activities implemented

TB/HIV Working Group: summary of activities and accomplishments in 2002

Partnership component	Progress indicators	2002 target	2002 results
Decreasing the burden of TB/HIV	Formulation of strategic framework	Strategic framework published and disseminated	Activity completed
Collaborative TB/HIV programme activities	Formulation of guidelines for phased implementation of activities (PIA)	Guidelines published and disseminated	Activity completed
Expand ProTEST through phased implementation of joint TB/HIV activities (PIA)	Ongoing expansion of ProTEST and initiation of PIA	Expansion completed in two countries	Contracts signed with four countries and proposals under development or expected from three countries
Modelling of impact	Impact models of different interventions developed	Modelling completed	Activity completed
TB & HIV epidemiology	Worldwide analysis of HIV implication for TB control in different settings under way	Analysis completed	Activity completed

DOTS-Plus Working Group on MDR-TB: summary of activities and accomplishments in 2002

Partnership component	Progress indicators	2002 target	2002–2003 results
Establish new pilot projects	Report on pilot projects	First three projects established.	Nine new projects established
Support to projects	Progress reports	Continued support	Activity implemented
Technical assistance for developing applications	Technical assistance and training activities	Training session at WG meeting and in-country training for two countries conducted	Six training sessions conducted [1]; Technical assistance provided to 11 countries for the development of GLC applications
Training in clinical MDR-TB management	Number of training sessions	Training in two countries conducted	Implemented at four sites [2]
Collection and analysis of data	Data collection and publication	Research clearinghouse at WHO established	Research agenda and internet-based database complete; standardized data collected from DOTS-Plus pilot projects
Monitoring and evaluation	Monitoring and evaluation reports	Monitoring visits to three projects conducted; report on drug procurement produced	Implemented [3] and complete
Advocacy activities	Production and dissemination of press releases, newsletters; release of documentary, "The Return of TB"	Publications widely disseminated; documentary distributed to 20 countries.	Stop TB newsletter, CD-ROM produced and distributed
Diagnostic/clinical tools	Progress reports from projects filed	Pilot projects implemented	TDR Peru study produced
Operational research	Developing protocols	Protocols established.	Activity implemented [4]
Annual meetings	Annual Working Group meeting	Meeting of the WG held in Estonia, April 2002	Annual meeting held in Estonia (2002) and Paris (2003)
Production of monograph	Preparation and publication of monograph	Monograph published and disseminated	Scheduled for completion in 2005
Policy document	Policy document developed	WHO Executive Board and WHA	Scheduled for completion in 2005
Production of guidelines on drug susceptibility Testing of second-line drugs	Guidelines developed		New version scheduled for 2005

(1) Training sessions conducted in Algeria, Bolivia, Costa Rica, and Mexico at meetings in Cairo/Montreal.
(2) Clinical training conducted in Bolivia, Costa Rica, and Mexico at Cairo Conference.
(3) In Estonia, Latvia, Peru, Philippines, and Russian Federation (Tomsk and Kemerovo Oblasts).
(4) Research protocols established and studies underway in Estonia, Peru, Philippines, Russian Federation, and Viet Nam.

TB Drug Development Working Group: summary of activities and accomplishments in 2002–2003

Partnership component	Progress indicators and 2005 target	2002–2003 results
Research and development		
Establish a pipeline of new drug candidates to maximize the chances of delivering a new drug by 2010	Have at least five drug candidates through preclinical testing by 2005	• Three drugs in clinical trials stages for first line treatment (including moxifloxacin and gatifloxacin) • Two compounds in advanced preclinical development stages, including PA 824 • Quinolones, nitroimidazopyrans, isoniazid analogs, ethambutol analogues, rifalazil derivatives and other compounds in lead optimization stages • Several other families in lead identification stages • Other projects at various stages [1]
Platform technology investments & facilitation		
Invest in shared platform technologies to support TB drug research and development	Map activities in TB Drug R&D	• Two RFPs completed by TB Alliance between 2001 and 2003 • First Working Group Mapping exercise completed in 2003
	Establish partnerships with industry	• Chiron Licence of PA-824 to TB Alliance • Agreement with Bayer for moxifloxacin clinical trials (CDC, with TB Alliance support) • Novartis pledge of royalty-free lead compounds • Action TB folded but GSK established dedicated centre in Spain • AstraZeneca and Novartis dedicated centres are in place in India and Singapore • Other industry discussions advancing collaborative developments
	Undertake studies to define surrogate markers	• Some studies initiated by TBTC, TBRU, Action TB [2] and through other projects funded by NIAID
	Develop endemic countries clinical capacity	• IUATLD building capacity with TB Alliance support in Africa, Asia and South America • South African TB Trials Consortium supported by CDC five-year funding • EDCTP established and poised to initiate support to the first projects by 2004
	Harmonize regulatory requirements and promote surrogate markers	• Public-private working groups designed in late 2003 and starting enrollment in early 2004

(1) Confidentiality constraints do not allow mention of several specific compounds in lead optimization and preclinical stages. Those openly mentioned here have been or are the objects of publicly announced agreements.
(2) Action TB support ended in 2003.

DOTS Expansion Working Group: budget requirements (US$)

Activities	2004	2005	Total
1. Technical assistance [1]			
1.1 Technical assistance to countries	35 000 000	35 000 000	70 000 000
1.2 Capacity building on HR development	10 000 000	10 000 000	20 000 000
1.3 Updating country needs and gaps	1 000 000	1 000 000	2 000 000
Subtotal	**46 000 000**	**46 000 000**	**92 000 000**
2. Monitoring and reporting			
2.1 Annual meeting DOTS Expansion Working Group	350 000	350 000	700 000
2.2 DOTS expansion report	20 000	20 000	40 000
Subtotal	**370 000**	**370 000**	**740 000**
3. Monitoring and reporting (subgroups)			
3.1 DOTS Expansion Working Group Core Team	10 000	10 000	20 000
3.2 PPM subgroup	400 000	400 000	800 000
3.3 Laboratory strengthening subgroup	300 000	300 000	600 000
3.4 Additional subgroups	200 000	200 000	400 000
Subtotal	**910 000**	**910 000**	**1 820 000**
4. Advocacy and communications			
4.1 Advocacy and communcations	100 000	100 000	200 000
Subtotal	**100 000**	**100 000**	**200 000**
Total for DOTS Expansion Working Group	**47 380 000**	**47 380 000**	**94 760 000**

(1) Additional technical assistance to HBCs is expected for the next several years for preparation of GFATM grant applications and the implementation of GFATM funded projects.

TB/HIV Working Group: budget requirements (US$)

Activities	2004	2005	Total
1. Analysis, policy, guidelines			
1.1 Regional workshops for country-specific policy development in Africa	115 000	—	115 000
1.2 Development and/or revision of data-collection tools and evaluation instruments	25 000	20 000	45 000
1.3 Modeling, field testing and piloting of guidelines	95 000	15 000	110 000
1.4 Development, translation and dissemination of policies, strategic frameworks and ARV delivery guidelines	120 000	—	120 000
1.5 Cost-effectiveness	80 000	80 000	160 000
1.6 Operational research	50 000	50 000	100 000
1.7 Short-term staff	280 000	280 000	560 000
Subtotal	**765 000**	**445 000**	**1 210 000**
2. Interagency collaboration and partnership			
2.1 TB/HIV Working and core group meetings and production of reports	250 000	250 000	500 000
2.2 Participation in the International AIDS Society Conference	20 000	20 000	40 000
2.3 Contribution to the "3 by 5" goal	50 000	50 000	100 000
2.4 Community TB/HIV meetings and initiatives; national conference sponsorship	75 000	75 000	150 000
2.5 Short-term staff	167 500	167 500	335 000
Subtotal	**562 500**	**562 500**	**1 125 000**
3. Implementation of activities in countries			
3.1 Technical assistance to WHO Regions and countries	155 000	155 000	310 000
3.2 Malawi, Kenya, Mozambique, Nigeria, and Ethiopia support for TB/HIV activities in South Africa, UR Tanzania, Uganda, Zambia	599 000	559 000	1 158 000
3.3 Support for TB/HIV activities in Eastern Europe and Francophone countries	142 000	182 000	324 000
3.4 Consultancies: pilot districts to provide ARV through NTP	80 000	80 000	160 000
3.5 Support for TB/HIV "3 by 5" goal in countries out of Africa	35 000	35 000	70 000
3.6 Continuation of prevention of mother-to-child transmission project in Zambia	53 000	—	53 000
3.7 Training	50 000	100 000	150 000
3.8 Short-term staff	350 000	350 000	700 000
Subtotal	**1 464 000**	**1 461 000**	**2 925 000**
4. Communication and advocacy			
4.1 APW for development of TB/HIV advocacy strategy	75 000	75 000	150 000
4.2 Support for activists groups in target countries	50 000	50 000	100 000
4.3 Bangkok meeting/Ukraine conference advocacy and support	40 000	—	40 000
Subtotal	**165 000**	**125 000**	**290 000**
Total for TB/HIV Working Group	**2 956 500**	**2 593 500**	**5 550 000**

DOTS-Plus Working Group: budget requirements (US$)

	Activities	2004	2005	Total
1.	**Working group coordination**			
	1.1 Annual Working Group meeting	100 000	100 000	200 000
	1.2 Advocacy and resource development [1]	100 000	100 000	200 000
	1.3 Subgroup meetings (including GLC)	150 000	150 000	300 000
	1.4 Secretariat support	350 000	350 000	700 000
	Subtotal	**700 000**	**700 000**	**1 400 000**
2.	**Operations**			
	2.1 Pilot projects	—	—	—
	2.2 Training and technical assistance	1 500 000	1500 000	3 000 000
	Subtotal	**1 500 000**	**1500 000**	**3 000 000**
3.	**Access system**			
	3.1 GLC applications and monitoring [2]	300 000	300 000	600 000
	Subtotal	**300 000**	**300 000**	**600 000**
4.	**Monitoring and policy development**			
	4.1 Data collection and analysis [3]			
	4.2 Operational research			
	4.3 Policy guidelines and development			
	Subtotal	**1 500 000**	**150 000**	**1 650 000**
	Total for DOTS-Plus for MDR-TB Working Group	**4 000 000**	**2 650 000**	**6 650 000**

(1) Because of the collaboration with the GFATM and the convergence with the GDF, increased advocacy will be required for the GLC.
(2) Following the establishment of the GFATM and the mandated relationship between the GLC and GFATM, additional assistance in preparation of GLC applications and monitoring of GLC projects will be required.
(3) Due to the increased number of projects to be monitored via the GFATM, more time and resources will be required to gather and analyse data.

New Diagnostics Working Group: budget requirements (US$)

Activities	2004	2005	Total
1. Facilitation of commercial tool development			
1.1 Development of *M. tuberculosis* strain bank	250 000	150 000	400 000
1.2 Extension of WHO/TDR specimen bank to Include extrapulmonary TB	—	200 000	200 000
1.3 Longitudinal studies looking for predictors of TB	500 000	500 000	1 000 000
1.4 Ongoing support for WHO/TDR specimen bank	350 000	500 000	850 000
1.5 Enhancing diagnostic trials capacity in selected sites	800 000	800 000	1 600 000
1.6 GCP training/certification	200 000	200 000	400 000
1.7 Laboratory strengthening workshops	100 000	150 000	250 000
1.8 Market analysis of global expenditures on TB diagnostics	200 000	10 000	210 000
Subtotal	**2 400 000**	**2 510 000**	**4 910 000**
2. Oversight and evaluation of new tools			
2.1 Laboratory evaluation of new methods for DST	150 000	150 000	300 000
2.2 Phase III clinical trials of new methods for DST	750 000	750 000	1 500 000
2.3 Demonstration studies of implementing new DST methods	350 000	350 000	700 000
2.4 Laboratory evaluation of new methods for case detection	250 000	250 000	500 000
2.5 Phase III clinical trials of new methods for case detection	1 000 000	1 250 000	2 250 000
2.6 Demonstration studies of implementing new methods for case detection	500 000	750 000	1 250 000
2.7 Developing of instruments for monitoring diagnostic trials	100 000	100 000	200 000
Subtotal	**3 100 000**	**3 600 000**	**6 700 000**
3. Global diagnostics regulatory harmonization			
3.1 Survey of global regulatory requirements for new diagnostics	50 000	—	50 000
3.2 Preparation of regulatory standards for new diagnostics	150 000	—	150 000
Subtotal	**200 000**	—	**200 000**
4. Development of evidence base of appropriate use of TB diagnostics			
4.1 Mathematical models of impact of improved case detection tools	30 000	—	30 000
4.2 Mathmatical models of impact of improved methods for DST	30 000	—	30 000
4.3 Cost of diagnostic delay	180 000	—	180 000
4.4 Kinetics of *M. tuberculosis* and impact of improved case detection on TB control	640 000	940 000	1 580 000
4.5 Longitudinal studies of new LTBI diagnostic methods	1 000 000	1 000 000	2 000 000
4.6 Evaluation of TST and new LTBI diagnostics in ARI surveys	500 000	500 000	1 000 000
Subtotal	**2 380 000**	**2 440 000**	**4 820 000**
5. Communication and advocacy for new diagnostics			
5.1 Develop and implement advocacy strategy for new TB diagnostics	50 000	50 000	100 000
5.2 Create central clearing house for information on TB diagnostics	100 000	100 000	200 000
Subtotal	**150 000**	**150 000**	**300 000**
6. Working Group coordinating activities			
6.1 Annual Working Group meeting	100 000	100 000	200 000
6.2 Regional ad hoc Task Force meetings	50 000	50 000	100 000
Subtotal	**150 000**	**150 000**	**300 000**
Total for New Diagnostics Working Group	**8 380 000**	**8 850 000**	**17 230 000**

TB Drug Development Working Group: budget requirements (US$)

	Activities	2004	2005	Total
1.	**Research and development**			
	1.1 Compound portfolio development costs from lead identification to registration			
	1.2 Supporting discovery, screening, and testing activities			
	1.3 Development of clinical trials capacity			
	Subtotal	**90 000 000**	**100 000 000**	**190 000 000**
2.	**Platform technology investments and facilitation**			
	2.1 Assessment and mapping of technologies and capacities			
	2.2 Establishment of industry partnerships			
	2.3 Additional surrogate markers studies			
	2.4 Controlled clinical trials studies support			
	2.5 Regulatory approval streamline and harmonization projects			
	Subtotal	**7 500 000**	**7 500 000**	**15 000 000**
3.	**Advocacy and information**			
	3.1 Establish drug advocacy task force and develop comprehensive strategy			
	3.2 Develop collaterals for working group communications			
	3.3 Develop white papers for publication			
	3.4 Convene joint media events			
	3.5 Develop web-based projects mapping and map publication			
	Subtotal	**500 000**	**500 000**	**1 000 000**
4.	**Coordination of activities**			
	4.1 Annual meeting of the Working Group			
	4.2 Ad hoc meeting of task forces			
	Subtotal	**100 000**	**100 000**	**200 000**
	Total for TB Drug Development Working Group	**98 100 000**	**108 100 000**	**206 200 000**

Note: This estimate includes the total projected costs for delivering one new drug by the end of the decade. Drug development expenses will rise sharply after 2005 when clinical trials will get underway.

TB Vaccine Development Working Group: budget requirements (US$)

Activities	2004	2005	Total
1. Facilitation			
1.1 Validate primate testing facilities	100 000		100 000
1.2 Build capacity for clinical testing of vaccine candidates	300 000	300 000	600 000
1.3 Develop adult immunization strategy	150 000		150 000
1.4 Coordinate fast-track transition of vaccine candidates from academia to industry	150 000	150 000	300 000
1.5 Identify and support development of needed GMP manufacturing capacity	50 000		50 000
1.6 Build awareness among national TB control staff		100 000	100 000
1.7 Building in-country infrastructure for monitoring and ethical review of clinical trials		200 000	200 000
Subtotal	**750 000**	**750 000**	**1 500 000**
2. Advocacy and information			
2.1 Develop a comprehensive advocacy and information strategy for new TB vaccines	150 000	200 000	350 000
Subtotal	**150 000**	**200 000**	**350 000**
3. Coordination of activities			
3.1 Annual meeting of the Working Groups	N/A	N/A	
3.2 Ad hoc meeting of task forces	N/A	N/A	
Subtotal	**100 000**	**100 000**	**200 000**
Total for TB Vaccine Development Working Group	**1 000 000**	**1 050 000**	**2 050 000**

Stop TB Secretariat proposed budget 2004–2005 (US$)

Activities	2004	2005	Total
1. Support and innovations			
1.1 Governance	771 800	771 800	1 543 600
1.2 Coordination and growth (partnerships)	1 405 675	1 405 675	2 811 350
1.3 Working groups	741 000	741 000	1 482 000
1.4 Communications and advocacy	2 473 525	2 473 525	4 947 050
Subtotal	**5 392 000**	**5 392 000**	**10 784 000**
2. Global Drug Facility			
2.1 Application review and monitoring	1 247 325	1 247 325	2 494 650
2.2 Supply [1]	—	—	—
2.3 Drug management	106 800	106 800	213 600
2.4 General management and support	1 365 900	1 365 900	2 731 800
Subtotal	**2 720 025**	**2 720 025**	**5 440 050**
3. Administration			
3.1 Resource mobilization and financial management	405 075	405 075	810 150
3.2 Information management	291 650	291 650	583 300
3.3 General administration	282 575	282 575	565 150
Subtotal	**979 300**	**979 300**	**1 958 600**
Total for Stop TB Secretariat	**9 091 325**	**9 091 325**	**18 182 650**

(1) The GDF budget estimates costs of US$ 27 million and US$ 40.5 million, in 2004 and 2005 respectively, for drugs supplied to high burden countries.

References

Chapter 1

1. Information in this section is drawn largely from the WHO Report 2004. *Global Tuberculosis Control: Surveillance, Planning, Financing*, Geneva, WHO. WHO/HTM/TB/2004.331.
2. The five components of DOTS are: 1) strong political commitment and sustained resources; 2) accurate diagnosis through smear microscopy; 3) standardized six- to eight-month treatment regimens with directly observed treatment for at least the first two months; 4) a regular, uninterrupted supply of all essential medicines and; 5) standardized monitoring, recording, and reporting systems.
3. The high-burden countries identified in 2003 were: Afghanistan, Bangladesh, Brazil, Cambodia, China, DR Congo, Ethiopia, India, Indonesia, Kenya, Mozambique, Myanmar, Nigeria, Pakistan, Philippines, Russian Federation, South Africa, Thailand, Uganda, UR Tanzania, Viet Nam and Zimbabwe.
4. Evaluation of the Global Drug Facility. Geneva, Mc Kinsey & Co, 2003. (available at: http://www.stoptb.org/GDF/GDF_Report-April2003.pdf.)
5. Kumaresan J et al. The Global Drug Facility: innovative global procurement. *International Journal of Tuberculosis and Lung Disease, 2004.* 8(1): 130-138.
6. The TB Coalition for Technical Assistance is a USAID supported programme that brings together the six leading organizations fighting TB globally: WHO, CDC, KNCV, IUATLD, ALA, and ATS.
7. Report on the meeting of the second ad hoc Committee on the TB Epidemic: recommendations to Stop TB partners. Montreux, Switzerland, 18–19 September 2003. Geneva, World Health Organization, 2004 (WHO/HTM/TB/2004.28)
8. This document is available at: http://www.who.int/3by5/publications/en/ARVGuidelinesRevised2003.pdf.
9. Corbett EJ et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Archives of Internal Medicine,* 163(9): 1009-1021.
10. Additional details including meeting notes and working group membership can be viewed at: www.who.int/gtb/policyrd/DOTSplus.htm
11. Suarez PG et al. Feasibility and cost-effectiveness of standardised second-line drug treatment for chronic tuberculosis patients: a national cohort study in Peru. *Lancet* 8;359(9322): 1980-1989.
12. Mukherjee JS et al. Programmes and principles in treatment of multidrug-resistant tuberculosis. *Lancet*, 2004; 363: 474-481.

Chapter 2

1. *Global Regulation of Medical Devices.* World Health Organization 2002 (internal document).
2. Participating sites are currently in Brazil, Canada, Gambia, South Africa, Spain and Uganda.
3. See, *Economics of TB Drug Development.* Global Alliance for TB Drug Development. October 2001.
4. *Tuberculosis* magazine. April 2001.
5. This document is available on the web site of the Global Alliance for TB Drug Development.

Chapter 3

1. The vision of the GPSTB is to work toward a TB-free world. Its mission is to pursue four goals:
   – ensure every TB patient access to effective diagnostic, treatment and cure;
   – stop the worldwide transmission of TB;
   – reduce the inequitable social and economical toll of TB, and;
   – develop and implement new preventive, diagnostic, and therapeutic tools and strategies to eliminate TB.
2. *Independent External Evaluation of the Global Stop TB Partnership Report.* Institute for Health Sector Development. December 2003. The full evaluation can be viewed at the Stop TB website: http://www.stoptb.org/.
3. Raviglione MC et al. The burden of drug-resistant tuberculosis and mechanisms for its control. *Acad Sci. 2001,* 953: 88–97.
4. *Global Drug Facility: A Global Mechanism to Ensure Uninterrupted Access to Quality TB Drugs for DOTS Implementation.* Geneva.World Health Organisation. 2001 (WHO/CDS/STB/2001.10a).
5. Evaluation of the Global TB Drug Facility. Geneva, McKinsey & Co., 2003 (available at: http://www.stoptb.org/GDF/GDF_Report-April2003.pdf).

Chapter 4

1. Information in this section is drawn largely from *WHO Report 2004. Global Tuberculosis Control: Surveillance, Planning, Financing. Geneva,* WHO(WHO/HTM/TB/2004.331).
2. Bangladesh, Cambodia, China, Ethiopia, India, Indonesia, Kenya, Myanmar, Russian Federation and Uganda.
3. Brazil, Philippines, Thailand and Viet Nam.
4. This excludes an estimate for the Russian Federation.

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