Global Plan to Stop TB

Phase 1: 2001 to 2005

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Francis Adatu-Engwau
Dennis Ahlburg
Dong Il Ahn
Sandra Anderson
Olivier Appaix
Ruri Arnadottir
Dirgh Singh Bam
Frank Bansu
Steve Barid
Enis Baris
Ivan Bastian
Jaime Bayona
Mercedes Becerra
Marijke Becx-Bleumink
Richard Berlin
Nils Billo
Leopold Blanc
Daniel Bleed
Amy Bloom
Barry Bloom
Paola Bollini
Angela Bone
Martien Borgdorff
Maarten Bosman
Fadila Boulahbal
Michael Brennan
Joel Brenner
Jaap Broekmans
Adrienne Brown
Richard Bumgarner
Arachu Castro
Ken Castro
Dick Chaisson
Daniel Chin
Gavin Churchyard
John Crofton
Rodrigo Cruz
Louis Currat
Kevin de Cock
Christopher Dye
Gijs Elzinga
Don Enarson
Sarah England
Guus Eskens
Marcos Espinal
Anne Fanning
Paul Farmer
Paul Fine
Katherine Floyd
John Foulds
Thomas Frieden
Ulli Fruth
Paula Fujiwara
Ann Ginsberg
Peter Godfrey-Fausset
Peter Gondrie
Andrea Gori
Rajesh Gupta
Zuhair Hallaj
Christy Hanson
Anthony Harries
Alan Hinman
Phillip Hopewell
Nobatsu Ishikawa
Akramul Islam
Dean Jamison
Enamul Karim
Tom Kenyon
Javaid Ahmed Khan
GR Khatri
Daniel Kibuga
Jim Yong Kim
Sang Jae Kim
Rudolf Knippenberg
Arata Kochi
Afriano Kritski
Jacob Kumaresan
Richard Laing
Kitty Lambregts-van Weezenbeek
Heidi Larson
Adalbert Laszlo
JW Lee
Fabio Luelmo
Tunde Madaras
Eddie Maganu
Dermot Maher
Giovanni Battista Migliori
Joyce V. Millen
Bess Miller
Jamie Moore
Carlos Morel
Toru Mori
Maria Luisa Moro
Joia Mukherjee
Kolluri Murthy
Alwyn Mwinga
Carol Nacy
Jai Narain
Edward Nardell
Aryeh Neier
James Newell
Jintana Ngamvithayapong-Yanai
Pierre-Yves Norval
Paul Nunn
Richard O'Brien
James Orbinski
Saleh Ottmani
Ariel Pablos-Méndez
Vikram Pathania
Mikhail Perelman
Mark Perkins
Jos Perriens
Peter Piot
Françoise Portaels
Rajeswori Ramachandran
Vulimiri Ramalingaswami
Mario Raviglione
Lee Reichman
Hans Remme
Hans Rieder
Leen Rigouts
Alastair Robb
Wiwat Rojanapithayakorn
Giorgio Roscigno
Mark Rosenberg
Max Salfinger
Jeanette Sanchez
Holger Sawert
Eric Sawyer
Fabio Scano
Nina Schwalbe
Carl Schieffelbein
Akihiro Seita
Aaron Shakow
Richard Skolnik

Ian Smith
Sergio Spinaci
Pedro Guillermo Suárez
Hamadou Traore
Mukund Uplekar
Jeroen van Gorkom
Eric van Praag
Jaap Veen
Bill Walch
John Walley
Ros Walley
Diana Weil
Charles Wells
Karin Weyer
Richard Zaleskis
Zhao Fen Zeng
Fabio Zicker
Paul Zintl

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In 1999, the Open Society Institute and Harvard Medical School published a groundbreaking report, The Global Impact of Drug Resistant Tuberculosis, which sparked considerable public interest and concern about the threat of TB. To build on this momentum for TB control, the Open Society Institute made a further grant to both Partners in Health and the Stop TB Partnership for the development of this plan.

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We are extraordinarily grateful for the support of these institutions. Their generosity and foresight made this Global Plan to Stop TB possible, and their commitment to TB control provides ongoing inspiration and support for our work on this plan.

List of Acronyms

AFRO	WHO Regional Office for Africa
AIDS	Acquired Immunodeficiency Syndrome
ARV	Antiretroviral
AZT	Zidovudine
BCG	Bacille Calmette Guérin
CB	Coordinating Board
CDC	Centers for Disease Control and Prevention
DFID	Department for International Development
DST	Drug Susceptibility Testing
ECHO	Humanitarian Aid Office of the European Union
GATB	Global Alliance for TB Drug Development
GAVI	Global Alliance for Vaccines and Immunization
GDEP	Global DOTS Expansion Plan
GDF	Global TB Drug Facility
GDP	Gross Domestic Product
GLC	Green Light Committee
GMP	Good Manufacturing Practice
GNP	Gross National Product
GPSTB	Global Plan to Stop TB
GTRI	Global TB Research Initiative
HAART	Highly Active Antiretroviral Therapy
HBC	High-Burden Countries
HIV	Human Immunodeficiency Virus
HMS	Harvard Medical School
HPSSR	Health Policy, Systems and Services Research
IEC	Information, Education and Communication
IMMYC	WHO Steering Committee on Immunology and Mycobacteria
INRUD	International Network for the Rational Use of Drugs
IPT	Isoniazid Preventive Therapy
IUATLD	International Union Against Tuberculosis and Lung Disease
IVR	Initiative for Vaccine Research
KNCV	Royal Netherlands Tuberculosis Association
MDR-TB	Multidrug-Resistant Tuberculosis
MSLI	Massachusetts State Laboratory Institute
NGO	Non-Governmental Organization
NIAID	National Institute of Allergy and Infectious Disease
NIH	National Institutes of Health
NRL	National Reference Laboratory
NTP	National Tuberculosis Control Programme

OECD	Organization for Economic Cooperation and Development
PIH	Partners In Health
R&D	Research and Development
RBM	Roll Back Malaria
RMB	Resource Mobilization
SBIR	Small Business Innovative Research
SCC	Short Course Chemotherapy
SEARO	WHO Regional Office for South-East Asia
SRL	Supranational Reference Laboratory
STI	Sexually Transmitted Infection
SWAP	Sector Wide Approach
TASO	The AIDS Support Organization
TB	Tuberculosis
TBVIAC	Tuberculosis Vaccine Initiative Advisory Committee
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

Foreword by Desmond Tutu

When I was only fifteen years old, I was struck down with tuberculosis and had to spend nearly two years in hospital. I had always wanted to be a physician, and when I contracted tuberculosis, this intention was strengthened. I was filled with a remarkable zeal to undertake the quest for a cure to end this scourge that had afflicted me. Although I did not fulfil my wish to become a doctor, I have since been inspired by many others who did. They are the ones who, imbued with a similar passion, devote all their professional energy to ridding the world of this malady, which was the leading infectious killer in the world until it was recently overtaken by HIV/AIDS.

I want to pay tribute to the outstanding team of scientists, doctors, health workers, and ordinary citizens who have dedicated themselves to the task of providing the world with an affordable cure to one of the world's leading killers. Tuberculosis has long undermined efforts to promote sustainable development in many of the countries of the so-called Third World, hindering the provision of health care, education, housing, clean water, adequate food, and a secure environment in which children may grow up in a healthier environment, free of TB and other diseases.

In the space of little more than a year, a marvellous international team of experts has given of its time, energy, and skills to develop this *Global Plan to Stop TB*. For the first time in human history, we have a truly global, comprehensive plan and budget that will be immensely helpful in bringing together the people and resources necessary to effectively attack tuberculosis. It has been especially heartening to witness the scale of consensus achieved by this diverse group of international experts, making this Global Plan a persuasive and powerful instrument.

What a splendid gift TB elimination will be for humanity's Third Millennium.

I commend this *Global Plan to Stop TB* with all the eloquence I can muster, and urge all advocates to be captured—indeed "infected"— with the zeal and passion of those who are committed to this campaign to eliminate TB as a public health concern. May you all be passionate zealots. What a splendid gift TB elimination will be for humanity's Third Millennium.

God bless you all richly as you help bring wholeness to so many of God's children debilitated by something we have the capacity to treat.

Desmond M. Tutu
Archbishop Emeritus of Cape Town
South Africa

Foreword by George Soros

My involvement in tuberculosis began in 1998 with a grant for work on infectious disease in the Russian prison system. I soon realized that my contribution of $12.5 million could not begin to solve what proved to be an epidemic of global proportions. With more than ten percent of the civilian population and twenty-five percent of the prison population infected with MDR-TB, and the number of HIV cases in Russia soaring every year, the scope of the problem was staggering.

When Stop TB approached my foundation asking for assistance with funding and fund-raising, I told them that as a seasoned financier, I needed a sound business plan to be an advocate for this cause. What the Stop TB Partnership has achieved is more than a business plan—it is also an action plan. Together we have achieved a consensus of over 150 TB advocates, including donors, scientists, high-burden country representatives, and NGOs. We have demonstrated how public-private partnerships can succeed through such mechanisms as using collective buying to lower drug prices for the treatment of MDR-TB.

The plan clearly demonstrates that with an investment of $9.1 billion over the next five years, TB can be controlled, averting hundreds of thousands of deaths each year. With over half that sum already raised, the financial targets are within reach.

I am proud to be a sponsor and catalyst of the *Global Plan to Stop TB*. By supporting the development of this model plan, the Open Society Institute advances its vision of promoting equity and global public good.

If we follow this plan and reach the global targets, four million additional people will be cured of the disease, and we will have developed effective responses to the dual pandemics of TB and HIV. As a businessman, I strongly endorse this plan as a sound investment. As a philanthropist, I urge you to support it as a starting point towards a world free of TB.

George Soros
Chairman
Open Society Institute

Foreword by Gro Brundtland

Investing in global health—a Stop TB Partnership responsibility

Investing in the *Global Plan to Stop TB* makes sense! This Plan outlines how the next generation can see tuberculosis eliminated as a public health problem. It also confidently states that the Global Partnership to Stop TB has the mechanisms in place to control tuberculosis within the coming years.

Recently the Commission on Macroeconomics and Health showed how disease is a drain on development, and how investments in health will make a tangible and significant contribution to economic development. The Commissioners argue for a comprehensive, global approach to sustainable development: one with concrete goals and specific time-frames. They propose new investments in health that will bring manifold returns, both in terms of lives saved and economic growth.

To achieve the millennium development goals of the UN, the Partnership is working to ensure that tuberculosis prevalence and mortality will be halved by 2010. WHO has set targets by 2005 to reach out to 70 percent of TB patients under DOTS (WHO-recommended TB-control strategy) and successfully cure 85 percent of these patients. Today only just over a quarter of new TB patients are enrolled in DOTS programmes. The gap between reality and targets is large. This calls for a fundamental change in the way all those fighting TB work together. We must create shared agendas, new partnerships, funding mechanisms, and ways to monitor progress.

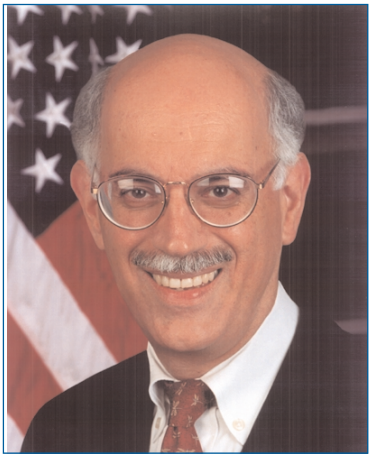
The Stop TB Partnership has taken on this challenge. The Global Plan presented in these pages describes the strategies and resources needed over the next five years to do so. It shows how to create the conditions that will allow more equitable access to high quality services and medicines that have the potential to transform people's lives.

Like all plans, the Global Plan is only as good as the action it produces. If it is successful, the *Global Plan to Stop TB* will accelerate efforts and increase investments in TB control. It must, therefore, be a work in progress. The implementation of the Global Plan is now a priority. As the Global Plan outlines, DOTS needs to be expanded, adapted, and improved, and partnerships need to be strengthened. We will have to increase our monitoring efforts on an annual basis.

This Plan has a clear strategy to tackle tuberculosis to improve the health of many millions around the world, and in so doing, brings the world one step closer to a TB-free world.

Dr. Gro Harlem Brundtland
Director-General
World Health Organization

Foreword by Andrew Natsios



In 1998, the United States Congress first appropriated funds for global tuberculosis control as part of a broader global infectious disease initiative. As the lead U.S. government agency for this initiative, the U.S. Agency for International Development, (USAID), developed a four point strategy to address the global TB problem. Ensuring collaboration among the agencies and organizations concerned with the international TB crisis was the first component. Other components including strengthening country capacity to address TB, accelerating the development of new tools to diagnose and treat TB, and improving TB surveillance and monitoring techniques and capacity. For the first component, it was envisioned that partners from different regions and countries, international organizations and NGOs, donors, and the research community would contribute to the plan to delineate control strategies, training, research, and advocacy activities. This plan would become the basis for coordinated action against TB and for building political consensus and support.

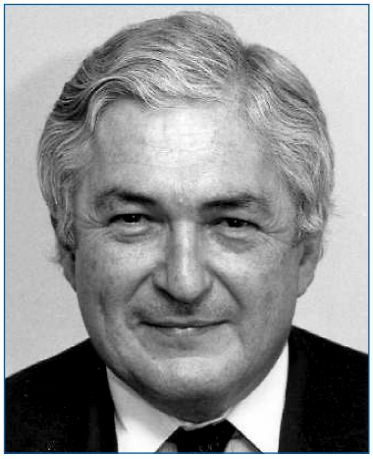
USAID is extremely pleased that the idea for a comprehensive plan has been realized as the "Global Plan to Stop TB". This Plan is an essential, overarching companion to (1) new plans developed by the high-burden countries, and (2) strategies developed by the Stop TB Partnership working groups. It is also a roadmap to reach the goals set forth by the international TB community of ensuring every TB patient access to TB treatment and cure, protection of vulnerable populations from TB, and a reduction in the social and economic toll of TB on families, communities, and nations.

We believe that implementation of the Global Plan is critical to global TB control and prevention. We encourage organizations, governments, and institutions to join our partnership to achieve this most important of goals.

Andrew Natsios
Administrator
United States Agency for International Development

Foreword by James Wolfensohn

In recent years, our global community, and especially poor developing countries, have faced new challenges and opportunities. Economic and political crises have helped to slow or reverse progress in some regions. The global epidemics of HIV/AIDS, tuberculosis, and malaria continue to spread. Yet, there is a growing recognition of the vulnerability faced by poor and marginalized communities, and of the impact such vulnerability has on global stability and growth. We know now, more than ever, that there is no wall between the wealthy and poor nations of the world.



The World Bank's mission is to fight poverty and enable development. Today we welcome new public and private partners in development and new resources to enable action at local and global levels. We value partnerships, such as Stop TB, which help us organize and expedite our collective efforts.

The United Nations Member States have recently defined the Millennium Development Goals, to make our international community accountable for progress in poverty reduction and human development over the next 15 years. Controlling HIV/AIDS, malaria, and tuberculosis are prominent among these goals. This *Global Plan to Stop TB* serves as one of the world's road maps to scale up response and achieve these goals.

This first five-year strategic plan to stop TB, explained in depth in this publication, is a pathfinder in its ambition, in its detail, and in its realistic assessment of the tools and strategies at our command and of the resource gaps that must be filled. When this plan was initially launched last October at the First Stop TB Partners' Forum, it was gratifying to see the commitment of so many governments, agencies, and NGOs to take it forward.

At the World Bank, we intend to use our institutional strengths to help implement this Plan. We intend to link the Plan to the Poverty Reduction Strategy Paper (PRSP) framework and enable country-level dialogue on how TB control is integrated and funded as a result of the PRSP process. We aim to further expand our portfolio of credits and loans that finance TB control and ensure efficient use of these resources alongside other existing and new funding. Such new sources include expanded budgets deriving from debt relief, or from the Global Fund to Fight AIDS, Tuberculosis and Malaria. Along with our partners, we will pursue analysis to overcome financing, institutional, or operational constraints. We also will seek to enable high-level dialogue on how to address the new threats of HIV-associated TB, drug-resistant disease, and on stimulating research investment. We look forward to working in partnership to redouble our efforts to stop this ancient killer.

James Wolfensohn
President
World Bank

Introduction

1. THE PURPOSE OF THE GLOBAL PLAN

Eliminate tuberculosis (TB) as a public health problem. That and nothing less is the goal of the Global Partnership to Stop TB. We, the members of the Partnership, know it will not happen overnight with a disease that has cast a centuries-long shadow; still, that is our aim—and we can achieve it.

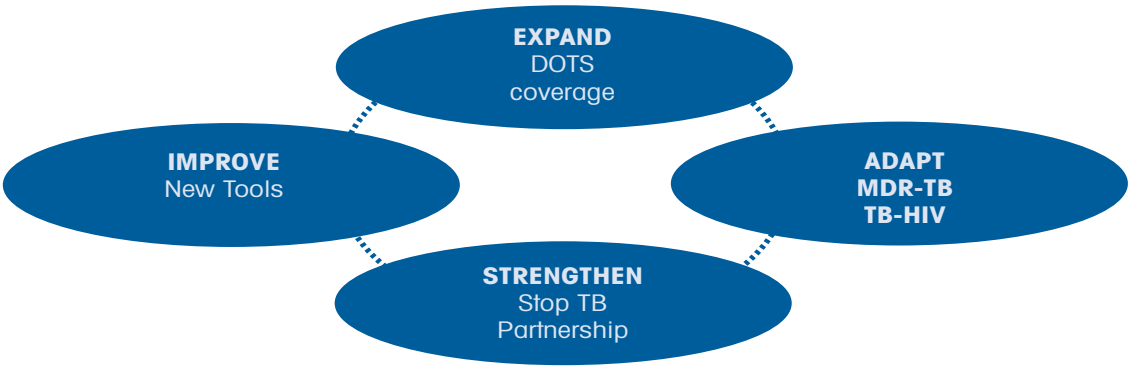
The *Global Plan to Stop TB* (GPSTB) assesses the threat of TB based on the most current global evidence. At the same time, the plan shows why we are confident TB can be controlled and, eventually, eliminated. The Global Plan describes mechanisms and activities that are already in place, as well as resources urgently needed over the course of the next five years to accelerate our efforts to meet the new global TB-control targets.

We can control TB. In contrast to some other modern plagues, with TB we know what must be done, we know how to do it, and we know how much it will cost. If we effectively apply proven, cost-effective strategies for TB control—adapting and improving them to meet the challenges described in this document over the next five years—we will have taken a giant step towards eliminating tuberculosis as a threat to future generations.

2. THE OBJECTIVES

The Global Plan to Stop TB has four 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.



These objectives guide and prioritise our work as Stop TB Partners. They provide a framework through which Stop TB Partners and donors can assess progress and redirect their efforts as needed. They are also meant to attract and energize new partners who will be catalysed by "the zeal and passion," in Archbishop Tutu's words. These partners should see how the day-to-day progress towards shared objectives demonstrates that ***this deadly disease can be vanquished***. Our intention in drafting this plan and subsequent updates is to continually highlight progress and gaps. As our campaign gains momentum, we hope new partners will readily fill those gaps.

One current gap is the lack of adequate programmes to deal with TB-HIV co-infection. We urgently need prevention and treatment of both diseases. The *Global Plan to Stop TB* makes a start on plans to integrate care for these closely linked epidemics. It will be updated as we work with ministries of health and colleagues involved in HIV/AIDS control to enhance understanding and effective action.

A plan is only as good as the effective action it generates. If successful, the *Global Plan to Stop TB* will both **accelerate efforts** and **increase investments** in TB control. It must, therefore, be a work in progress. It will be revisited and updated to keep it current in a rapidly changing world. In practical terms, this means that the estimates of disease burden and the impact of interventions will be regularly updated, and cost estimates consistently revised, to reflect new investments and/or new developments in policy, strategy, and research.

3. PLAN STRUCTURE

The Global Plan to Stop TB is divided into two parts.

Part 1 describes the state of the world's TB epidemic and calls for urgent action to address it.

- Chapter 1 gives an overview of the global TB epidemic and its profound impact on individuals, families, communities, and nations.
- Chapter 2 describes DOTS—the internationally recommended TB-control strategy—and provides estimates of the investments needed to reach the global TB-control targets by 2005.
- Chapter 3 describes the rapidly emerging co-epidemic of HIV-related TB, which is destroying communities in sub-Saharan Africa. An urgent and effective response to this epidemic is needed.

- Chapter 4 addresses the growing problem of multidrug-resistant TB (MDR-TB), which poses a significant threat to TB control.
- Chapter 5 provides an overview of the action and investments needed in research to accelerate development of new TB-control tools, including diagnostics, drugs, and vaccines.

Part 2 describes how the *Global Partnership to Stop TB* plans to respond to the challenges described in Part 1.

- Chapter 6 introduces the structure that has been put in place to coordinate efforts to control and eventually eliminate TB—the Global Partnership to Stop TB—and the objectives that must be fulfilled over the next five years.
- Chapter 7 provides details of the plans of action of the six working groups established by the Stop TB Partnership to ensure that the objectives are reached.
- Chapter 8 describes additional elements being put into place to support implementation of the *Global Plan to Stop TB*, including mechanisms and plans for partnership building, advocacy, financing, priority setting, and monitoring.

4. PLAN COSTS

Effective TB control cannot be imposed from above. It is a fundamental premise of the *Global Plan to Stop TB* that national governments and local communities take responsibility for planning and implementing their TB-prevention and treatment programmes. In assembling the cost estimates for the Global Plan, we respected this premise by calculating cost estimates on the basis of national TB-control plans prepared by the 22 TB high-burden countries that account for 80 percent of the global TB disease burden. The estimates are based on data available in late 2001.

Effective TB control in the next five years will cost an estimated $9.1 billion[1]. Most of this amount will be spent treating patients suffering from TB, including multidrug-resistant TB and TB in patients co-infected with HIV. A significant amount ($1.1 billion) is projected to be spent on research and development of new diagnostic tools, new drugs and new TB vaccines. The Stop TB Secretariat has projected partnership costs of $75 million for its activities in advocacy, resource development, and TB-control monitoring. In addition, there are six Stop TB working groups that will plan and coordinate the TB-control efforts of national governments, donors, and other Stop TB Partners. Their projected costs ($314 million in total) are included in Table 1 within the cost estimates for TB-control programmes and for research activities.

[1] All cost figures included in this plan are in U.S. dollars, unless otherwise noted.

Table 1: *Global Plan to Stop TB* ***Financial Summary (five-year costs, in $ millions)*** [2]

Programme Costs - TB, MDR-TB & TB-HIV	7,953	(87%)
New diagnostics, drugs and vaccines	1,098	(12%)
Stop TB Partnership Activities – advocacy, resource development and monitoring	75	(1%)
Total Plan Costs	**9,126**	
Current Resources	5,349	
Resource Gap	**3,777**	

Table 2 provides each component of the projected $9.1 billion five-year cost for TB control, the resources available, and the resulting resource gap. A draft of this *Global Plan to Stop TB*, presented in October 2000 at the Stop TB Partners' Forum, showed total plan costs of $9.3 billion, nearly $200 million more than this final plan estimate. Revisions since October result principally from improved estimates of DOTS expansion costs and of the capacity of health systems in certain high-burden countries to support it.

At current commitment levels, TB-burdened nations will provide $4.5 billion (85%) of the approximately $5.3 billion in resources projected to be committed for TB control. The projected external resources committed to TB control are based on estimates of resources committed in the year 2000. All projections of five-year committed resources rely on one extremely important assumption—that resources currently committed will remain committed for the five years at current levels. If these existing commitments are not renewed at current levels, the resource gap will increase accordingly.

[2] The total estimated plan costs shown in this table exceed the estimate of resources required for global TB control in a recent analysis conducted by WHO (see K. Floyd, L. Blanc, M. Raviglione and J.W. Lee, "Resources Required for Global Tuberculosis Control" Science 2002, in press). This is because the latter focuses on the costs for DOTS implementation, and does not include an assessment of resources needed for MDR-TB, TB/HIV, new diagnostics, drugs and vaccines, and partnership activities. Estimates for DOTS implementation in both publications are similar. In the analysis undertaken by WHO, it is estimated that $6 billion is required for DOTS implementation in the 22 HBC and in the low- and lower-middle income countries outside the 22 HBC during the period 2001-5 ($225 million less than is projected in this plan), and that the resource gap is about $1.5 billion (compared to $1.6 billion in this plan). The differences arise because the two studies were conducted independently and used slightly different methods to project cases to be treated, costs, and available resources. However, the fact that the two studies are broadly consistent strengthens the validity of both estimates. The main difference lies in the cost estimates for low- and lower-middle income countries outside the 22 HBC. This is to be expected given the limited data and the need for more assumptions in estimating costs for these countries. Both sets of estimates will be updated as more data become available.

Table 2: Summary Costs of the Global Plan to Stop TB, 2001–2005 ($ millions)

Figures for 114 countries	Costs	Current Resources			Gap
		National	External	Subtotal	
	(a)	(b)	(c)	(d)=(b)+(c)	(a)-(d)
DOTS Expansion[3]	**6,225**	**4,300**	**359**	**4,659**	**1,566**
Country needs[4] – high-burden countries	4,560	3,300	250	3,550	1,010
Country needs – other countries	1,440	1,000	0	1,000	440
DOTS expansion working group	225	0	109	109	116
Adapting and Improving DOTS	**1,728**	**230**	**60**	**290**	**1,438**
TB-HIV	642	30	8	38	604
Country needs	630	30	6	36	594
TB-HIV working group	12	0	2	2	10
MDR TB	1,086	200	52	252	834
Country needs	1,070	200	50	250	820
MDR-TB working group	16	0	2	2	14
Research and Development (totals)	**1,098**	**0**	**390**	**390**	**708**
New diagnostics	177	0	53	53	124
Research needs	150	0	47	47	103
New diagnostics working group	27	0	6	6	21
New drugs	347	0	136	136	211
Research needs	317	0	130	130	187
New drugs working group	30	0	6	6	24
New vaccines	424	0	96	96	328
Research needs	420	0	95	95	325
New vaccines working group	4	0	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 [5]	20	0	0	0	20
Resource development and financing [5]	13	0	0	0	13
Monitoring [5]	15	0	0	0	15
TOTALS	**9,126**	**4,530**	**819**	**5,349**	**3,777**

[3] See the preceding footnote regarding the separate analysis of DOTS expansion costs, which estimated substantially similar costs using somewhat different methodologies

[4] "Country needs" includes estimates of costs for TB-control programmes, as well as estimates of the economic burden that TB places on the health care system of the country, beyond those specifically identified for TB control.

[5] Plans of partnership task forces for these initiatives are still being reviewed. Figures provided are rough cost estimates and are not yet supported by detailed budgets. See Chapter 8.

What follows is a brief explanation of how cost estimates were derived for each major component of the plan—DOTS Expansion, Adapting and Improving DOTS, Research and Development, and Partnership Activities. The Stop TB Partnership coordinates TB-control work principally through working groups and through the Stop TB Partnership Secretariat. Working groups focus on a specific area of activity, such as DOTS expansion or development of new diagnostics. The plans and budgets of these working groups are summarized in the following sections. More detail on the working groups is provided in Chapter 7 and working group budgets are shown in Annex 2.

The Economic Annex to the Global Plan to Stop TB is being published separately and provides complete detail of the methodology and results of GPSTB cost estimates and epidemiological projections. Annex 1 provides a summary of this Economic Annex.

DOTS EXPANSION

DOTS is the WHO-recommended strategy for TB control that has been adopted in 119 countries. DOTS is highly effective—its treatment success is 81 percent on average in high-burden countries—and cost-effective. The strategy has five critical components, discussed in Chapter 2, which are essential to the success of TB control. Expanding DOTS programmes will account for two-thirds of the projected TB-control cost ($6.2 billion) and nearly half of the $3.5 billion resource gap.

The estimate of TB-control costs for DOTS expansion is built from national TB-control plans from the majority of the 22 TB high-burden countries (HBC).[6] Data from these plans was used to construct an economic model to estimate likely costs of TB-control expansion in 114 low- and lower-middle income countries (with annual per capita GDP less than $3,000).[7] The model estimates specific costs for expanding TB-control programmes (training, anti-TB drugs, administrative costs, etc.) and also for the costs—in facilities, personnel, equipment, etc. —to general health-care systems that would be incurred in expanding TB control.

The World Health Organization has set TB-control goals for 2005. These goals are to detect 70 percent of all new infectious TB cases worldwide, and to successfully treat 85 percent of all cases detected. Expanding DOTS to meet these goals will require adding an additional 850,000 new cases per year to DOTS programmes, of which 350,000 will be infectious, sputum-smear positive (SS+) cases.[8] This increased volume will come in part from newly detected cases, and in part from diverting patients being treated in non-DOTS programmes into DOTS programmes. The expansion will be substantial, and is the major cost item in TB control. Table 3 shows the detail of this expansion, and Annex 1 provides a more complete discussion of these projections.

The *Working Group on DOTS Expansion* ensures that countries receive needed technical assistance for DOTS expansion; supports and coordinates this assistance throughout the world; monitors its progress; and advocates for resources to implement it. The Working Group has a

6 Countries defined as "high-burden" are those countries with the highest estimated number of new TB cases. The 22 high-burden countries account for some 80 percent of all new TB cases. The list of high-burden countries is provided in Annex 3.

7 A list of the 114 low- and lower-middle income countries is provided in Annex 3.

8 For comparison, in the Global Tuberculosis Control Report 2002, WHO estimates that an extra 330,000 SS+ cases will need to be treated each year if control targets are to be met. The fact that the two figures are very similar strengthens the validity of both estimates.

Table 3: TB-Control Projections for 2001–2005 for the 22 HBC and for 114 Other Low- and Lower-Middle Income Countries (cases in millions)

	Current Level of TB Control		Stop TB Goals	
	All Cases	SS+ Cases	All Cases	SS+ Cases
Number of New Cases (Incidence)	42.9	18.9	42.9	18.9
Cases Detected and Treated	19.1	7.7	26.0	11.3
– Cases Treated under DOTS	8.7	4.7	21.5	10.0
– Cases Treated, non-DOTS	10.4	3.0	4.5	1.3

five-year budget of $225 million. This amount captures the cost of significant technical assistance and capacity building that will be required to rapidly expand DOTS programmes in high-burden countries. Chapter 7 summarizes the Working Group's plans and presents a summary of its five-year budget. Annex 2 describes how this budget will be allocated year-by-year.

ADAPTING AND IMPROVING DOTS

TB-HIV. The overlapping epidemics of TB and HIV/AIDS are the subject of Chapter 3. The GPSTB projects country needs of roughly $630 million over the five-year period for counselling, identifying TB-HIV co-infected people, and for therapy to prevent the onset of active TB in these patients. This projection is likely to be revised because Stop TB Partners and their colleagues in HIV/AIDS-control programmes are still working to plan and implement the most effective approaches to TB-HIV co-infection. Furthermore, epidemiological estimates of TB-HIV co-infection are more uncertain than estimates of TB burdens. The cost estimates, which are quite preliminary, are based on early results from a number of promising pilot projects in several sub-Saharan countries.

Plans envision voluntary counselling and HIV testing for large numbers of people in high HIV-prevalence areas, TB testing for HIV-positive patients and providing a six-month isoniazid (INH) prophylactic treatment (IPT) to prevent the onset of active TB in co-infected patients. Included with the costs for this intervention are projected costs for anticipated secondary effects of the treatment, which can be expected in a fraction of the patient population. The plan assumes that some 28 million people will be tested for HIV, that 3.3 million of these people will be HIV-positive patients and will be then tested for TB, and that roughly 1.6 million co-infected patients will be treated with INH. Details are provided in Chapter 3 and in Annex 1. It is important to note that there will be other important costs, such as those for treating opportunistic infections in HIV-positive TB patients, which cannot yet be estimated but will have to be considered at a later date.

The *Working Group on TB-HIV* provides a forum for the coordination of activities aimed at promoting interventions to decrease the dual burden of TB and HIV. Under the overall umbrella of the Working Group, Stop TB Partners take the lead in developing and disseminating policies, developing innovative approaches, scaling up proven, cost-effective interventions, and developing, producing, and disseminating training materials and a manual for clinical care. The Working Group has a five-year budget of $12.3 million. Chapter 7 summarizes the Working Group's plans. Annex 2 provides the Working Group's budget.

MDR-TB. Chapter 4 is devoted to the growing threat of multidrug-resistant TB (MDR-TB). Country needs for treating MDR-TB have been estimated at $1,070 million over the five-year period. This cost was projected using a high-end estimate (4.6 percent) of the proportion of all TB cases that are MDR. The plan projects that half a million of these cases will be treated under DOTS-Plus programmes, in part through diversion into DOTS-Plus programmes of patients who would otherwise be inappropriately treated.

Table 4: MDR-TB-Control Projections for 2001–2005 in Low- and Lower-Middle Income Countries (cases in millions)

	Current Level of TB Control	Stop TB Goals
Number of New Cases (Incidence)	1.9	1.9
Cases Detected and Treated	0.9	1.2
– Covered by DOTS-Plus	0.0 [9]	0.5
– Not Appropriately Treated	0.9	0.7

The cost estimates for treating these patients and for scaling up DOTS-Plus programmes have been derived from very limited data, mostly from Peru. While drug costs have been greatly reduced, they are still high in comparison to first-line TB drugs, and account for 60 percent of the aggregate cost estimate. Further decreases in drug prices would reduce the aggregate estimate significantly but, in any event, these estimates will need to be revised as further data emerges on the cost of large-scale initiatives to treat patients with MDR-TB.

The *Working Group on MDR-TB* was established in 1999. Its aims are to approve, conduct, and oversee pilot projects to treat MDR-TB. The Working Group has a scientific panel, which has prepared guidelines for pilot projects designed to treat MDR-TB. In addition, the Working Group has established the Green Light Committee (GLC), which strives to improve access to second-line anti-TB drugs for DOTS-Plus pilot projects. The group approves, conducts, and oversees pilot projects based on scientific guidelines prepared by the scientific committee. The Working Group has a five-year budget of $16 million. Chapter 7 summarizes the Working Group's plans. Annex 2 provides the Working Group's budget.

RESEARCH AND DEVELOPMENT

Research and development costs are projected in this plan at nearly $1.1 billion for new diagnostic tools ($177 million); new TB drugs ($347 million); a new TB vaccine ($424 million); and for health policy, systems, and services research ($150 million).

The objectives of **TB diagnostics** research are improving the detection of infectious TB, latent TB, and drug resistance. A rough estimate of the investment required to develop significantly improved diagnostic tests for TB comes to $150 million for the 2001–2005 period. The objectives and strategies of diagnostic research are described in Chapter 5, and the activities of the *Working Group on TB Diagnostics* are described in Chapter 7. The Working Group has set a budget of $27 million, which is provided in Annex 2.

[9] There are now roughly 7,000 patients worldwide being treated for MDR-TB under approved DOTS-Plus programmes.

The objectives of new **TB drug development** research are the development of drugs to shorten and/or simplify TB treatment, more effectively treat MDR-TB, and treat latent infection. The *Global Alliance for TB Drug Development* has set a goal of having at least one new TB drug registered by 2010, and available in high-burden settings two years later. The costs of developing one or more new drugs by 2010, including the cost of failures, are estimated to be up to $240 million. The cost estimate in this GPSTB ($317 million) represents a projected five-year research cost for developing one or more new drugs for TB treatment, of a different class than those currently known, by 2010, plus a $30 million cost estimate for the Working Group on Drug Development. The objectives of TB drug development are described in more detail in Chapter 5. The activities of the Working Group are provided in Chapter 7 and its budget is provided in Annex 2.

The objective of the **TB vaccine** effort is to have a safe, effective, and reasonably priced TB vaccine licensed for global distribution by 2015, and to have it widely used in high-burden countries five years later. Chapter 5 describes the considerable challenges of developing a TB vaccine and explains that it is unlikely to be achieved for less than $1 billion. Costs are likely to be $700 million over ten years for developing better animal models, expanding testing facilities, increasing knowledge of pathogenesis, and developing correlates of protection. Clinical trials through 2005 are likely to require $10 million per year. The $420 million estimate in this plan for vaccine research represents an amount that could be invested in the first five years of this effort. It is unavoidably imprecise, but is roughly half the ten-year projection of known costs, adjusted for some likely front-loading of investment. The *Working Group on TB Vaccine Development* began its work in 2001. It has set a budget of $4.5 million. A summary of the Working Group's activities is included in Chapter 7 and year-by-year budget estimates are provided in Annex 2.

While we await the discovery of new TB diagnostics, drugs, and vaccines, research into **health policy, systems, and service** delivery promises significant gains in TB control—in far less time and at far lower cost. There are a range of challenges in adopting and adapting DOTS to the economic, institutional, social, and epidemiological profiles of diverse countries, and in moving beyond DOTS to cope with the challenges of HIV and/or MDR-TB in particular countries. Low-cost research has historically made an important difference in the success of disease control. Chapter 5 discusses the objectives and the rationale for this research and provides examples of what this research has already achieved. The plan projects that it would cost $110 million over five years for national TB programmes in each of the high-burden countries to establish these research initiatives, and an additional $100 million to establish parallel programmes in other countries with a high incidence of TB. Of this $210 million that would be spent in TB-burdened countries, $180 million has been budgeted as a cost of DOTS expansion. The remaining $30 million is a component of the $150 million of health policy systems research expense in this plan. The balance of the health policy systems research cost ($120 million) is the projected investment in international technical assistance to countries that will be required to scale up operational research.

PARTNERSHIP ACTIVITIES

The **Stop TB Secretariat** coordinates and supports the work of the more than 200 Stop TB Partners under the guidance of a Stop TB Coordinating Board. The Secretariat builds the Partnership, communicates with partners, tracks the progress of TB control and of other

partnership goals, manages the Global TB Drug Facility, and is responsible for coordinating advocacy and resource mobilization. The Secretariat has a five-year budget of $27.5 million, excluding Global Drug Facility costs that are included as part of DOTS expansion.

Chapter 8 describes the Secretariat's four important objectives in carrying out the *Global Plan to Stop TB*—Partnership Building, Information and Communication, Advocacy, and Resource Mobilization. The *Global Plan to Stop TB* envisions a tremendous expansion of TB-control activity, advocacy, and resource mobilisation, without which the plan goals cannot be achieved. The Stop TB Secretariat has organised task forces to plan the Partnership's supplemental work in each of these areas in the coming years, and summaries of those draft plans are provided in Chapter 8. However, these plans are still being reviewed and have not yet been approved by the Stop TB Coordinating Board. Rough estimates by the task forces of likely supplemental costs totalling $48 million have been built into this plan for advocacy ($20 million), resource development ($13 million), and monitoring ($15 million). Because these plans and budgets have not yet been finalized or approved, no details on these estimates have been provided.

5. WHAT WILL BE ACCOMPLISHED?

This plan lays out what must be done over the 2001–2005 period if we are to control TB and eventually eliminate it as a public health problem. It describes the strategies and the mechanisms to achieve our goals and what these accomplishments will cost.

What will have been accomplished if we meet the goals of this plan?

- The 22 high-burden countries that account for 80 percent of the world's TB burden will have rapidly expanded DOTS and met control targets—detecting 70 percent of people with infectious TB, and successfully treating 85 percent of those detected.
- Some 3.4 million deaths from TB will be averted, and millions more people will be cured of their tuberculosis—through detection and treatment in newly expanded DOTS programmes. If DOTS programmes are not expanded, these patients will not be treated for their disease. They will suffer and die, and will infect numerous close contacts and family members.
- Some 12.8 million additional people will have been treated for TB at a projected cost of just over $238 per person, and 3.5 million lives saved for about $485 each.
- We will have defined, adopted, and implemented effective strategies to address HIV-related TB.
- We will have incorporated DOTS-Plus protocols for MDR-TB into the DOTS strategy.
- We will have an improved TB diagnostic test for use in high-burden countries.
- Five new anti-TB drug candidates will have completed pre-clinical trials.
- There will be at least one TB-vaccine candidate in clinical trials to test efficacy.

These are enormous accomplishments, planned to counter an enormous threat to the health, well-being, and development of communities throughout the world. We can control TB. With this Global Plan, Stop TB Partners around the world are on the way to doing so. But we need your help. Come join us in delivering this "splendid gift" to the generations of the Third Millennium.

Part 1:
State of the World's TB Epidemic

World Health Organization

Children playing outside the Medical College Hospital in Khulna, Bangladesh.

The appalling global burden of tuberculosis at the turn of the millennium, despite the availability of effective control measures, is a blot on the conscience of humankind. For developing countries, the situation has become desperate and the "cursed" duet of tuberculosis and AIDS is having a devastating impact on large sections of the global community. The vital question is, can despair be turned to hope early in the next millennium?

-J. Grange and A. Zumla
"Paradox of the Global Emergency of Tuberculosis," 1999

GLOBAL TB CONTROL

The Challenge Before Us

1. The Tragedy of TB

Granville Cemetery, the largest in Zimbabwe, is a 250-acre plot on the outskirts of Harare. Two years ago, it was expected to provide sufficient space for 40 years; now, officials project that HIV will cause the cemetery to fill within 15 years.[1] And the proximate cause of death for most of those laid to rest in Granville will be tuberculosis.

Dr. Anachu Castro, Partners in Health

In rural Haiti, death and mourning are part of daily life.

In Zimbabwe, the terrible synergy between these two diseases takes as many as 3,000 lives a week.[2] A quarter of that country's six million adults are believed to be infected with HIV, and 60 percent of those suffering from active TB are also HIV-infected.[3] In Botswana over the last decade, average male life expectancy has dropped from 63.3 years to 39.5 years mainly as a result of HIV infection, exacerbated by TB co-infection.[4]

Most co-infected patients do not receive treatment for TB. Many may not be aware they have the disease. Even if they know, they may not realize TB can be cured; they may not have access to drugs, and may fear a dual stigma if their TB-HIV status becomes known. When they do seek help, the response is often inadequate, leaving patients chronically ill and their

TB contagious to others. What these patients often do not know is that TB treatment is as effective for HIV-positive patients as for HIV-negative ones. Indeed, prompt treatment would increase the length and quality of their lives, thus benefiting their families and communities.

The HIV/AIDS epidemic has become the greatest public health threat of the last 500 years. To combat it, effective global strategies must be tightly linked to TB-control strategies. The WHO-recommended DOTS TB-control strategy must be made available to all, and so must comprehensive HIV-prevention, -care, and -support programmes. Moreover, these regimens must include advanced treatment paradigms, such as Highly Active Antiretroviral Therapy (HAART), in order to both prolong lives and, by boosting immune systems, to help prevent dramatic increases in new TB cases.

1.1 THE RISE OF "EBOLA WITH WINGS"

In June 1994, Hawaii's State Health Department notified the U.S. Centers for Disease Control and Prevention (CDC) that a 32-year-old woman from Korea had died of complications from pulmonary TB. Prior to her diagnosis, the woman had flown from Honolulu to Chicago, from Chicago to Baltimore, and then back to Honolulu. The CDC conducted an investigation of the woman's contacts on those flights and discovered six fellow passengers whom the woman might have infected.[5]

As of February 1996, all six passengers remained free of signs and symptoms of active tuberculosis.[6] But this story becomes even more frightening: the deceased woman's TB strain was found to be resistant to five of the strongest antimicrobials used to cure the disease. Quite possibly, the six passengers in question acquired the same strain. Today, drug-resistant strains of tuberculosis, and even of multidrug-resistant tuberculosis (MDR-TB), are spreading quietly, insidiously—within families, institutions, and communities, and across national borders as well.

HIV/AIDS has become the greatest public health threat in the last 500 years. To combat it, effective global strategies must be tightly linked to TB-control strategies.

These prospects are so alarming that the mainstream press has given MDR-TB the singular epithet, "Ebola with wings".[7] Ebola is a deadly haemorrhagic fever, first diagnosed in 1976 in several hundred people in Sudan and the former Zaire. Untreated TB, like Ebola, has a high fatality rate. But unlike Ebola, TB is spread by sharing the air we all breathe. "Once MDR-TB is unleashed, we may never be able to stop it", warned the World Health Organization (WHO) in 1997.[8] But MDR-TB has already been unleashed.

In one sense, the Korean passenger's journey is a cautionary tale about our "global village", where travellers can arrive from anywhere, carrying microbial hitchhikers. More importantly, the rise of MDR-TB speaks to dangerous global disparities in health-care services that affect rich and poor countries alike. For countries like the Ukraine, economic and political upheaval has weakened the health-care system and compromised the treatment of thousands of TB patients. Incomplete treatment has led to the development of microbial resistance to the most

common and effective anti-TB drugs, and thus lowered TB cure rates. The resulting MDR-TB is a clear and present danger to global TB control.

Due to poverty, complacency, and neglect, TB remains a paradox at the very heart of our modern age: in an era of unprecedented wealth and scientific advancement, millions are dying each year from a disease for which there is a proven, cost-effective treatment, and hundreds of thousands are becoming infected with resistant strains that are more expensive to treat.

2. TB: The Ubiquitous Enemy

The "Red Death" had long devastated the country. No pestilence had ever been so fatal, or so hideous. [. . .] But the Prince Prospero was happy and dauntless. When his dominions were half depopulated, he summoned to his presence a thousand hale and light-hearted friends from among the knights and dames of his court, and with these retired to the deep seclusion of one of his castellated abbeys. With such precautions the courtiers might bid defiance to contagion. The external world could take care of itself.

- Edgar Allan Poe
"The Masque of the Red Death," 1842

Tuberculosis is an ancient malady. Evidence of the skeletal form of the disease has been identified in the mummified remains of an Egyptian priest who died around 3,400 B.C.[9] Yet more people died last year of TB than in any previous year in history. Fully one-third of the world's population is already infected with *M. tuberculosis*, with the greatest burden of disease and infection borne by people in developing countries.[10]

The most current estimates confirm that 50 years after the introduction of effective chemotherapy, TB remains—along with AIDS—the leading infectious cause of adult mortality in the world, causing up to 2 million deaths each year.[11] The number of new TB cases climbed 6 percent each year between 1997 and 1999, from 8 million to 8.4 million worldwide.[12] This increase was the result of a 20 percent rise in incidence among people living in sub-Saharan African countries, the region most affected by the epidemic of HIV/AIDS.[13]

Projections of the future toll of the global TB pandemic are even more frightening. Currently, it is estimated that less than half of all TB cases worldwide are diagnosed, and fewer than 60 percent of diagnosed cases are cured.[14] Without unprecedented efforts to improve TB control in regions hardest hit by the disease, incidence is expected to climb steadily.[15] Tuberculosis will remain one of the world's top ten causes of adult mortality in the year 2020; HIV is the only other infectious pathogen slated to remain on that list.[16]

In 1993, WHO declared TB a global emergency. Yet that same year, the World Bank's World Development Report revealed that TB control using the WHO-recommended strategy, at an estimated cost of between $0.90 and $3.10 per year of life saved, was one of the most cost-effective of all health interventions.[17] The WHO strategy, called DOTS, has produced cure rates more than twice those of alternative treatment programmes. Indeed, DOTS may be one of the soundest interventions of any kind for countries struggling to pull themselves out of poverty.[18]

Still, eight years after TB was declared a global emergency—and after about 16 million preventable TB deaths—residents of some of the world's poorest regions where TB incidence is highest have yet to see the benefits of the proven DOTS remedy. Today, only 27 percent of people diagnosed with TB receive DOTS treatment.[19] Intensified implementation and expansion of existing control strategies are needed if TB trends are to be deflected from their present trajectory.[20]

TB is a disease that causes millions of deaths, infects one-third of the world's population, profoundly damages households and national economies and yet can be cured with drugs that cost as little as $10 per patient.

Even if we achieve our goals for DOTS expansion, in the best-case scenario an estimated 171 million new cases and 60 million deaths due to TB will occur between 1998 and 2030. In the worst-case scenario, 249 million new cases and 90 million deaths will occur.[21] HIV already poses a major threat to TB control, increasing TB case rates—and thus the patient caseloads on already overburdened services.[22] While the elimination of TB in some countries has been discussed,[23] its recrudescence in areas affected by HIV would seem to dim such hopes at the global level. Drug-resistant forms of TB, the deterioration of public health infrastructure, and economic and political crises also present significant challenges to many national TB-control programms.[24] *Only unprecedented investment in, and expansion of, DOTS-based strategies, including the development of new vaccines and drugs, has the potential to curb this epidemic.*

Tuberculosis has taken on both new menace and new meaning. The disease's persistence, particularly among the poor, constitutes a global humanitarian crisis and an affront to the notion of scientific progress. No other disease plays such a malignant role in the history of human communities, yet has been almost entirely forgotten in wealthy countries. Tuberculosis is a disease that causes millions of deaths, infects one-third of the world's population, profoundly damages households and national economies, and yet can be cured with drugs that cost as little as $10 per patient.

How will the developed world respond to the humanitarian crises caused by increased TB incidence? Will affluent nations simply close their borders and hope to save themselves in this way? In Poe's story, Prince Prospero's self-imposed quarantine was no match for the Red Death, which imposed its "illimitable dominion over all". As this report makes clear, at the dawn of the new millennium, the Prince's approach is still both potentially disastrous, and wholly unnecessary.[25]

3. The Socio-Economic Impact of TB

Tuberculosis is a social disease, and presents problems that transcend the conventional medical approach. [. . .] *Its understanding demands that the impact of social and economic factors on the individual be considered as much as the mechanism by which tubercle bacilli cause damage to the human body.*

-René and Jean Dubos,
The White Plague: Tuberculosis, Man, and Society, 1992

Haikin, a 26-year-old street vendor from a town in Northern Sulawesi, Indonesia, had been coughing for about three years, visiting private doctors who prescribed a variety of medicines. He spent a great deal of money on this treatment, borrowing substantial sums that he could not repay. His cash and credit resources exhausted, he finally went to a state health centre, where he was diagnosed with TB. After a six-month regimen of short-course chemotherapy (DOTS), he was declared cured.

But Haikin was not the only one with TB. His mother had died of the disease five years before. His pregnant sister, Sari, with whom Haikin shares a home and who supervised his daily intake of the drugs, now complains of a productive cough. Sari was treated by a private doctor with rifampicin, isoniazid, and ethambutol, but was forced to stop her therapy after three months, when she ran out of money. She knows she can obtain TB diagnosis and treatment free-of-charge at the health centre, but is reluctant to do so, because of her pregnancy (a common misconception, perpetuated even by doctors, is that pregnant women should not take antibiotics, including anti-TB drugs).

World Health Organization

Women and children at a rural clinic in Khulna, Bangladesh.

The story of Haikin and his sister reveals how closely infectious diseases are intertwined with social and economic development. People who become ill with TB are often not only unable to work and earn money; they also expend dwindling resources to pay for health care, and often must rely on under-financed public health-care systems. The result is a vicious circle: TB retards development, as surely as lack of development encourages the spread of TB.

3.1 TB AND DEVELOPMENT

Health and economic development are inextricably linked. An overwhelming 98 percent of the 2 million annual TB deaths—and 95 percent of the 8.4 million new TB cases—occur in

developing countries. On average, TB causes three to four months of lost work time and lost earnings of 20 to 30 percent of household income. In addition, for families of persons who die from the disease, about 15 years of income is lost, due to the premature death of the TB sufferer.[26] In developing countries, TB generally afflicts the most economically active segment of the population. Of the 2 million people dying annually from TB, 75 percent are between the ages of 15 and 54.

As economic difficulties put pressure on state health budgets, the social cost of lost productivity is compounded. In Thailand, out-of-pocket expenditure for the diagnosis and treatment of TB in the private sector accounts for over 15 percent of annual income for households already below the poverty line.[27] In Uganda, 70 percent of the cost of treatment is borne by patients or their families.[28] Entire economies suffer as workforces are reduced and productivity falls. Meanwhile, public budgets and health-care expenditures shrink along with the tax revenue.[29]

3.2 TB AND THE POOR

Together, poverty and the tubercle bacillus create a second vicious circle. Poor people, plagued by hunger and crowded into close, non-hygienic quarters, are easy victims in an environment where TB flourishes. Once taken ill with TB, people's capacity to work is diminished, even as treatment expenses spiral, exacerbating poor people's poverty. Meanwhile, the poor receive inadequate health care, which often inhibits the detection of TB in the first place. Treatment is often inconsistent or incomplete, to non-existent. The poor are less likely to seek and receive proper care when ill, exacerbating the impact of the disease. In addition, some studies suggest that the poor are two to three times more likely than other income groups to self-medicate.[30] Self-medication and partial treatment encourage the emergence of drug-resistant TB strains, further increasing the impact of TB on the poor and the risks to others in society.

3.3 TB AND WOMEN

The social cost of tuberculosis is further increased by the toll the disease takes on women.[31] Approximately 3.5 million women develop active TB every year. While men are more likely to have latent TB infection, women are more likely to progress from infection to active disease and, in some settings, less likely to receive diagnostic and treatment services.[32]

World Health Organization

Women waiting for treatment in Khulna, Bangladesh.

Besides contributing to the higher TB mortality rates among women of childbearing age, differential access to treatment has implications for the success of TB-control programmes. Because TB control depends upon

high levels of detection and successful treatment, women's lower likelihood of treatment undermines TB-control strategies.

3.4 TB AND CHILDREN

Vaccination has been the primary TB prevention method in children. In fact, Bacille Calmette Guérin (BCG) is the most widely used vaccine in the world. Although it is relatively ineffective in preventing infectious forms of TB, the vaccine does prevent more serious forms of TB disease in children. Nevertheless, a quarter of a million children still develop TB every year: particularly vulnerable to infection from household contacts, many of these children have been infected in their own homes, by parents or other relatives with active, infectious TB. Diagnosis of TB in children is notoriously difficult, as early symptoms and signs are easily missed. Most national TB-control programmes have little in the way of services for children. Tuberculosis in the family also has serious impact on children. In India alone, 300,000 children are taken out of school every year to care for a parent ill with TB.[33]

Young patient in rural Haiti.

Dr. Anacha Castro, Partners in Health

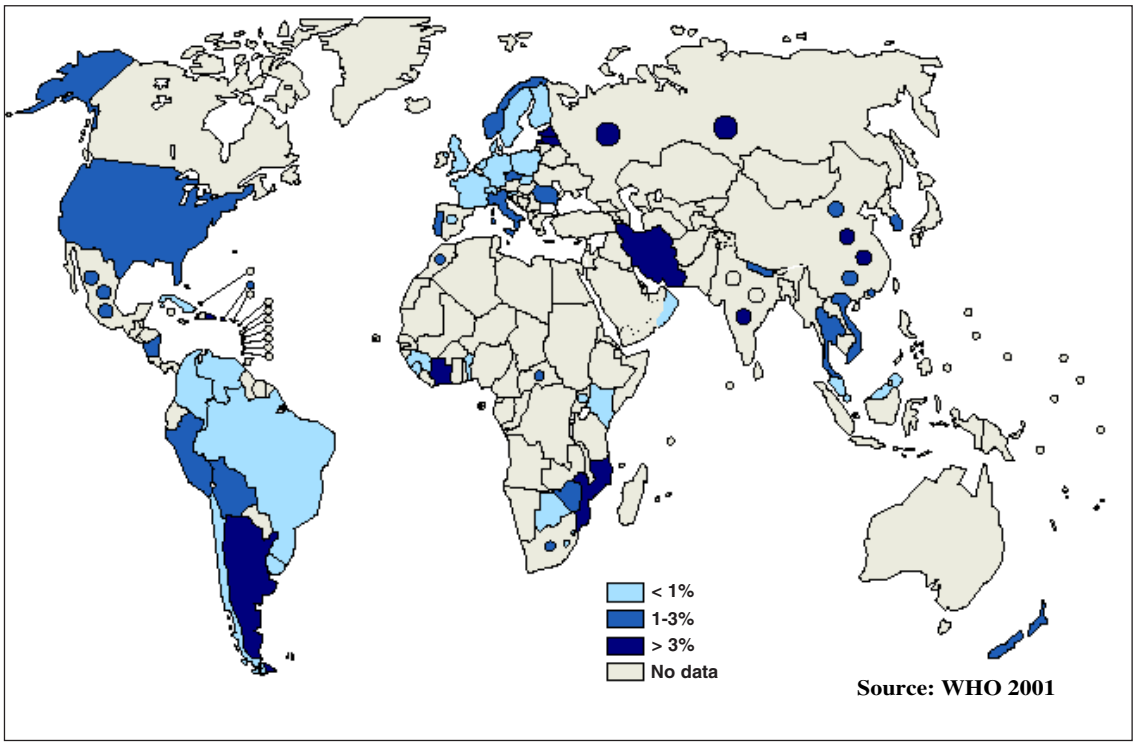
3.5 THREATS TO EFFECTIVE TB CONTROL ARE THREATS TO GLOBAL HEALTH

Important data on drug-resistant TB emerged in a 1997 global survey conducted by WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD). The report showed that drug-resistant TB was present in all 35 countries surveyed, and that MDR-TB was present in all but one.[34] Although MDR-TB cases accounted for 3.2 to 4.6 percent of all TB cases,[35] the contribution of those cases to overall case rates was high in certain settings, termed "hot spots". (A hot spot is a setting where at least 3 percent of all TB cases identified are MDR-TB.) Furthermore, the proportions reported in the survey are likely to be underestimates. As the authors of the study noted, countries most likely to participate in the study were those with more effective TB-control programmes.[36]

The recently released follow-up to the 1997 report has identified several new hot spots, among them Iran and Henan province in China. A strong correlation between the overall quality of TB control and the use of standardized short-course chemotherapy with low levels of resistance was observed. But MDR-TB was found on five continents, and in some settings reached levels as high as 30 percent of the overall TB incidence.[37]

New, targeted interventions to control MDR-TB are necessary, and pilot programmes to verify the clinical efficacy of interventions must be launched.[38] Where MDR-TB is a problem, the short-course chemotherapy employed in DOTS is rendered ineffective, due to high rates of resistance to the two best drugs commonly used in that standardized regimen—rifampicin and isoniazid. Multidrug-resistant tuberculosis demands much lengthier treatment than drug-susceptible disease (usually 18–24 months for the former as compared to only six months for the latter.) Furthermore, many antimicrobials used to treat MDR-TB

MDR-TB Hotspots



were long ago abandoned because of their side effects and their relatively low clinical efficacy.

The cost of curing MDR-TB can be staggering. In the United States, expenditures for drugs and hospitalisation alone have driven up the cost of treating a patient with MDR-TB to as much as $150,000, compared with treatment costs of approximately $2,000 per patient for drug-susceptible TB.[39]

The danger of increasing drug resistance is especially great, given the lack of activity in TB drug development. In the last 34 years, not a single new class of TB drugs has been developed. Clearly, market-based solutions to global TB treatment have failed. Essential medicines are more than just commercial commodities. Ensuring access to new anti-TB drugs means that such drugs must be regarded as public property to which all are entitled, for the sake of the global public good.

Multidrug-resistant tuberculosis, a relatively new disease, is a man-made phenomenon. It results from inappropriate, incomplete, or erratic TB therapy, which encourages the spread of spontaneous mutations rendering the TB bacillus resistant to isoniazid and rifampicin, the two most powerful anti-TB drugs.[40] If TB-control efforts had been well organized decades ago, the dimensions of this problem—which by 1999 had been reported in over 100 countries or territories—would today likely be significantly smaller.[41] The introduction of systematic and effective TB control is not only our best weapon against the generation of drug-resistant TB, it is also our shared moral, social, and economic responsibility.

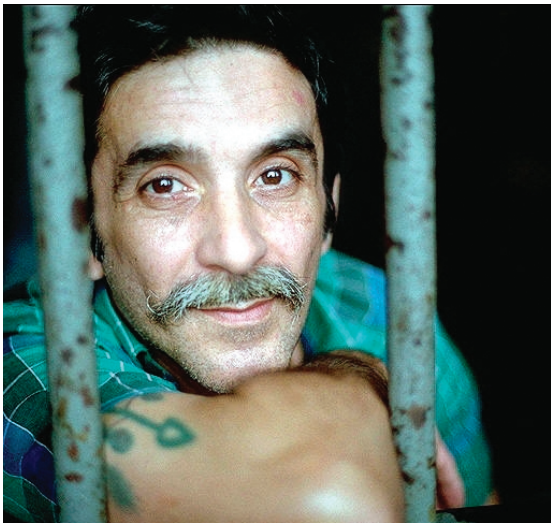
3.6 TUBERCULOSIS IN VULNERABLE POPULATION GROUPS

In Russia, young men incarcerated for relatively minor property crimes are forced to live in close quarters with other prisoners who have active TB—often MDR-TB. In this setting, even petty crimes, such as stealing a loaf of bread, can carry a death penalty in countries where prisons are MDR-TB proliferation sites. MDR-TB is currently untreated in all but a few prison settings. Infection with HIV is also disproportionately prevalent among prisoners, greatly accelerating the cycle of TB propagation. To make matters worse, inmates are often moved from facility to facility for security reasons, contributing to a wider dissemination of TB, including drug-resistant strains. When released, the sick ex-prisoners become vectors of infection for the rest of the population.

But Russian prisons are only one of several "open spigots", where the problem of TB is compounded by exceptionally harsh or confining conditions. Shelters for the homeless in urban centres around the world pose similar risks. Worker hostels, mines, military barracks, congregate living centres, refugee camps, and acute and chronic health-care facilities are also important sites of TB transmission. Early TB detection and treatment in congregate settings and the community act synergistically to control the disease. Conversely, inadequate control in one setting results in increased cases in the other.

The relative contribution of each of these spigots varies from site to site, but each constitutes a direct threat—not only to existing TB-control efforts, but also to entire health-care systems and economies. In these settings, the natural history of TB is perfectly consonant with the man-made reality of confinement. Those who live in such settings are more likely to be infected, more likely to develop active, infectious disease, and more likely to develop secondary drug resistance through inadequate treatment.[42] Finally, these populations spread disease to the general population. Any TB-control strategy that does not include attention to prisons, shelters, and other settings of especially high-disease burden is doomed to failure.

In the New York State Prison System, during the peak of the 1985–1992 TB resurgence, MDR-TB was spread to prisoners and guards throughout the state—as well as to hospitalised patients and health-care workers outside the prison system—when inmates were admitted to acute-care hospitals.[43] While earlier diagnosis and better TB treatment in prisons is essential, penal reform is an even more important means of preventing unnecessary exposure to TB, and of reducing the crowding that greatly facilitates transmission. Moreover, because most inmates are ultimately released, control of TB in prisons and suitable follow-up care are essential to TB control in the community.[44]



World Health Organization

TB patient in prison.

An epidemiological catastrophe is now unfolding inside Russia's prisons—and in

many other prisons throughout the former Soviet Union. In the Russian Federation, more than one million people out of an overall population of 146 million are in prison.[45] One in every ten of these Russian prisoners is now estimated to have active TB—approximately 100,000 prisoners in total. These rates are fifty times higher than in the general population.[46]

Worse, strains of non-resistant TB are being transformed into drug-resistant "superbugs" as the result of inadequate treatment regimens, and prisoners who have developed MDR-TB are infecting others. In some prisons, up to one-quarter of the prisoners with active TB are sick with MDR-TB. No epidemic of drug-resistant disease on this scale has ever before been documented. The Russian MDR-TB epidemic is already so widespread that no single country—and certainly not one in the midst of economic collapse—could ever hope to assume total financial and technical responsibility for its control. If the global spread of MDR-TB is to be contained, direct aid to Russia is essential.

Another population group at disproportionate risk for developing TB is the homeless, including those in developed countries. Immuno-compromised because of poverty and exposure, the TB-infected homeless find shelter in crowded missions, where the risk of disease transmission is extreme.[47] Furthermore, homelessness, substance abuse, and HIV infection are often highly correlated, putting those infected with HIV at further risk of developing active and transmissible TB. The homeless—especially the mentally ill—are also difficult to supervise in their treatment regimens, raising the spectre of interrupted chemotherapy and the development of resistance to anti-TB drugs.[48]

3.7 TUBERCULOSIS IN COMPLEX HUMANITARIAN EMERGENCIES

Wherever catastrophe strikes—in the wake of natural disaster, war, or famine—the spectre of TB rears its lethal head.[49] Relief efforts are often stymied by inadequate or interrupted transportation, political arguments, or continued hostilities. Lack of sanitation, malnutrition, and crowding—the great incubators of TB—bring together people who under normal circumstances might never come in contact with one another. Therefore, TB diagnosis and intervention must be added to relief efforts seeking to deal with the basic food and shelter needs of such population groups, lest acute emergencies evolve into chronic ones.

3.8 TUBERCULOSIS AMONG HEALTH AND PRISON WORKERS

In some resource-rich countries, TB-control programmes to protect health-care workers receive a great deal of attention. Significant resources are deployed for administrative controls, isolation, air disinfection, personal respirator protection (masks), skin testing, and treatment of latent infection. Although proven to be effective under high-risk conditions, similar resources have simply not been available in poor countries. In addition to effective treatment of TB cases—including MDR cases—in low- and middle-income communities, effective, low-cost strategies to prevent transmission in hospitals and prisons in low- and middle-income countries are badly needed.

3.9 TUBERCULOSIS AND TRANSNATIONAL TRAVEL

What might be the long-term effect of multiple "hot spots" of drug-resistant TB in a world linked by innumerable air and land bridges, in which distance and time have been radically compressed? Transmission of multidrug-resistant strains of TB during commercial air travel has already been documented.[50]

Tuberculosis outbreaks have been shown to be only briefly local, and both pan-susceptible and drug-resistant TB strains have shown the capacity to spread rapidly across regional and national borders.[51] Like influenza, TB and its drug-resistant strains create epidemics that are transnational; indeed, transcontinental.[52]

4. What Can Be Done?

Globalisation has improved many people's living standards, "bringing unprecedented opportunities to billions", but has also plunged some regions deeper into poverty.[53] While undoubtedly enabling the fruits of scientific advance to reach the planet's remotest settings, globalisation has also magnified the scope and range of deadly epidemics. The resurgence of disease in one setting will soon be felt in others linked to it through commerce, tourism, and migration. Immediate and sustained action is needed if the spread of TB within and beyond national boundaries is to be halted. Such action must have several aims:

- Accelerate the worldwide expansion of effective TB control using the DOTS strategy.
- Develop and fund treatment programmes that address the problem of existing drug resistance.
- Implement treatment, care, and support programmes for people co-infected with HIV and TB.
- Expand the search for new pharmaceutical agents with clinical efficacy against TB, as well as the search for new tools to detect the presence of *M. tuberculosis*.
- Expand the search for TB-prevention measures, such as vaccines.
- Intensify efforts to improve existing health-care infrastructures in poor countries through training, investments in personnel and facilities, and other activities.
- Improve the methods, strategies, and alliances through which TB control is funded and implemented.

WHEN WORLDS COLLIDE

The Power and Potential of DOTS

Dr. Anacha Castro, Partners in Health

An 11-year-old Haitian girl suffering from HIV/AIDS and TB.

Between 2:00 and 3:00 p.m. on 28 October 1998, 213 people around the world shared a common death: 211 of them died in developing countries; the other two died in high-income industrialized countries. Few will be remembered by any but their immediate family. Many died in misery, most died in poverty; all of them died of TB.

At about the same time, a small group of people gathered in Washington, D.C. They included international financier George Soros, World Bank President James Wolfensohn, WHO Director-General Gro Harlem Brundtland, U.S. Secretary of Health and Human Services Donna Shalala, and then American First Lady Hillary Rodham Clinton.

The invisible link between these two profoundly different groups was—and is—tuberculosis. Those who died did so because of tuberculosis. Those who gathered in Washington did so with a growing top-level commitment to eliminate this disease from our midst.

Faced with growing awareness that the global TB epidemic was progressing unchecked and that HIV and drug resistance threatened to turn a dangerous epidemic into a global disaster, this small group of people had gathered to call for intensified efforts to stop TB.

The world has begun to respond to their call. Senior government officials from 20 countries with the highest burdens of TB gathered in Amsterdam in March 2000 for a conference on TB and Sustainable Development. There they made an historic declaration and commitment to accelerated action against the disease. Four months later, heads of state of the G8 countries established an international task force to fight TB along with other poverty-related diseases, such as malaria and HIV. In 2001 the U.N. Secretary General Kofi Annan called for a massive increase in resources to fight AIDS and other diseases associated with poverty. The Global Fund to Fight AIDS, TB and Malaria has been established, with nearly $2 billion already pledged.

It is time to act. In the minute it may have taken you to read these words, TB has taken another four lives. Had these victims had DOTS available to them, they might be alive and healthy now—and for many years to come. And so the clock ticks on, cadencing more lives needlessly lost to a disease that is curable. Yes, it is indeed time to act. We have the commitment. We have the tools. The opportunity must not be allowed to pass.

1. What is DOTS?

The principles of DOTS were first developed in the national TB programme in Tanzania, and subsequently expanded to a further six countries in Africa and to Nicaragua, with the assistance of the International Union Against Tuberculosis (IUAT–later to become the International Union Against Tuberculosis and Lung Diseases). The role of Dr Karel Styblo, IUAT Scientific Director, in the development of these innovative programmes cannot be understated. He combined an astonishing knowledge of the epidemiology of TB with a remarkable understanding of the management principles of TB control and a tenacious commitment to excellence in his work. His contribution to TB was immense, and he will go down in history as the father of modern TB control and one of the heroes of public health of the 20th century. The principles developed by him in Africa were later adapted and promoted by WHO as DOTS, and adopted in places as diverse as China, New York, and India.

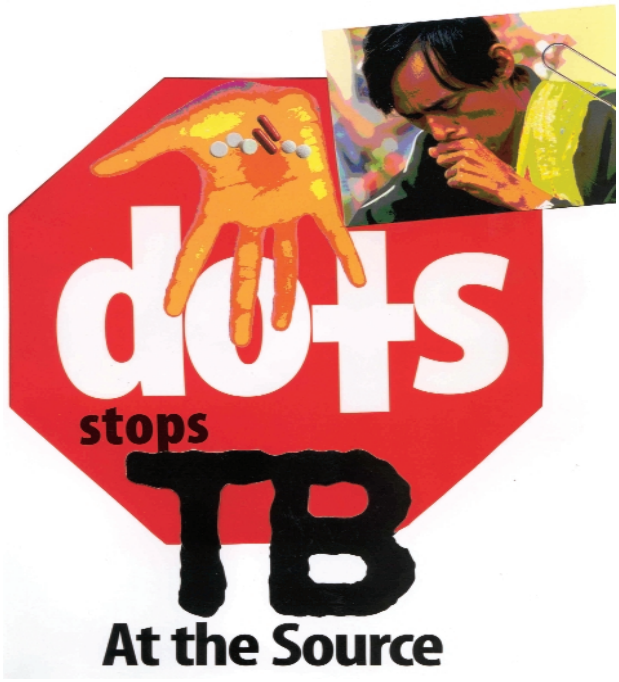
In the early 1990s, when asked to describe the best TB treatment, most TB-control professionals would produce a long list of interventions, including passive case-finding, short-course chemotherapy (SCC), patient compliance with treatment, adequate drug supply, and sound reporting and recording systems. The basic principles of the strategy were not new. The crucial innovation was the addition of the human element—having health-care workers or volunteers form a close bond with their patients to help them successfully complete treatment. In the United States, this approach was known as Directly Observed Therapy, or DOT.

The brand name "DOTS" was born in 1994. Modifying the commonly used DOT acronym to include another key element of the strategy—the Short-course from "SCC"—now gave

meaning to "DOTS". *Stop TB—Use DOTS* became a clarion call for TB-control programmes around the world. Because of its novelty, this health intervention quickly captured the attention of even those outside the international health community.

The five major components of DOTS, as described by WHO, are:

1. **Political commitment and resources** TB control is a public health responsibility, and top-down support is crucial. This component must be the strongest link in the chain.
2. **Microscopy** Accurate diagnosis using sputum-smear microscopy among symptomatic patients is the first step in early detection of active TB infection. It sets the DOTS cure cycle in motion and protects others from infection.
3. **Treatment** Standardized six- to eight-month regimens for all patients with active TB, with directly observed treatment for at least the first two months, is necessary. The success of this phase is contingent upon a sound, functional health-sector infrastructure and trained personnel.
4. **Medicines** Regular, uninterrupted supplies of the four to six most effective anti-TB drugs is essential. Full compliance with the drug regimen results in nine out of ten patients being cured.
5. **Monitoring** A standardized recording and reporting system allows assessment of each patient's treatment and progress. Rigorous overall record-keeping also acts as early warning for emerging disease trends (such as MDR-TB).



2. What's So Special about DOTS?

DOTS cures active TB. It is remarkably effective. Without treatment, seven in ten people with infectious TB will die of the disease, on average within four to five years of onset, even if they are young when they contract the disease.[1] Though non-DOTS TB-control programmes in low- and lower-middle income countries may decrease deaths considerably, such programmes are usually less successful at curing TB. Many sufferers remain chronically ill and continue to unknowingly transmit the disease to family, friends, and even strangers.

Conversely, good DOTS programmes rapidly reduce both death and disease, curing more than 85 percent of patients. In human terms, DOTS gives young people marked for premature TB death a chance to lead full and productive lives, raise children to adulthood, and make contributions to their communities and society. Additionally:

- ***DOTS saves lives.*** Modelling suggests that achievement of WHO's 2005 targets would avert 15.5 million TB deaths during the period 2001–2005, in addition to the 4.2 million lives saved through ongoing DOTS expansion programmes. Even today, in China alone DOTS has prevented 46 percent of deaths that would otherwise have occurred in the provinces in which the programme is being applied. This translates into 30,000 lives saved each year.[2]

- ***DOTS stops the chain reaction of transmission.*** Curing people with TB prevents them from infecting others. For example, introducing DOTS in Peru has accelerated the decline in notified TB incidence to about 7 percent per year.[3]

- ***DOTS prevents treatment failure and the emergence of even more deadly strains of drug-resistant TB.*** For example, the China Tuberculosis Coalition (CTC) reported that the failure rate in previously treated patients fell from 17.6 percent to 6.2 percent following the introduction of DOTS in World Bank-assisted provinces in China.[4]

- ***DOTS reduces TB recurrence rate.*** For example, in the U.S. state of Texas, TB recurrence rates fell from 20.9 percent to 5.5 percent within six years when a DOTS-based TB-control strategy was introduced.[5]

- ***DOTS indirectly alleviates poverty.*** Saving lives, reducing periods of illness, and prevention of new infections means fewer years of productive work lost.

- ***DOTS overcomes TB's stigma.*** Effective treatment, combined with a positive approach, reduces the fear of death and disability that has fuelled the profound stigma often associated with TB. In Nepal, for example, the introduction of DOTS has led to a general awareness that TB is curable. As a result, TB is now less feared, no longer "khapate"—the disease that "dries you up" before you die.

- ***DOTS provides a model for strengthening health services.*** Remarkably successful in promoting the development of peripheral health services, the DOTS strategy can serve as a model for expanded use of HIV antiretrovirals, as proposed in Malawi.[6] If adaptations of the DOTS strategy were shown to be effective in AIDS treatment, networks linked to DOTS TB-treatment programmes could rapidly be set up, given that up to one-third of all AIDS patients ultimately die of tuberculosis.

- ***DOTS saves taxpayers' money—and lives.*** The World Bank has hailed DOTS as "one of the most cost-effective interventions available". Country studies in the early 1990s from Malawi, Mozambique, and Tanzania showed the cost of TB interventions ranging from $19–52 per life saved. But drugs cost up to four times as much at that time. Today, the DOTS drug package can be purchased for as little as $10.[7] This means that investing in TB control will save lives, immediately. Over time, TB control will also "turn a profit" as it reduces the disease burden on society.

Benefits of DOTS

Tackle TB There is really no other choice. The right to disease prevention, diagnosis, treatment, and cure is not only a fundamental human right; it also makes sound economic, social, and public health sense.

The means are there Affordable and effective interventions are available to save lives, prevent drug resistance, and reduce TB transmission.

The targets are clear and consensual Countries have committed to diagnose 70 percent of estimated new active TB patients and to successfully treat 85 percent of those patients by 2005.

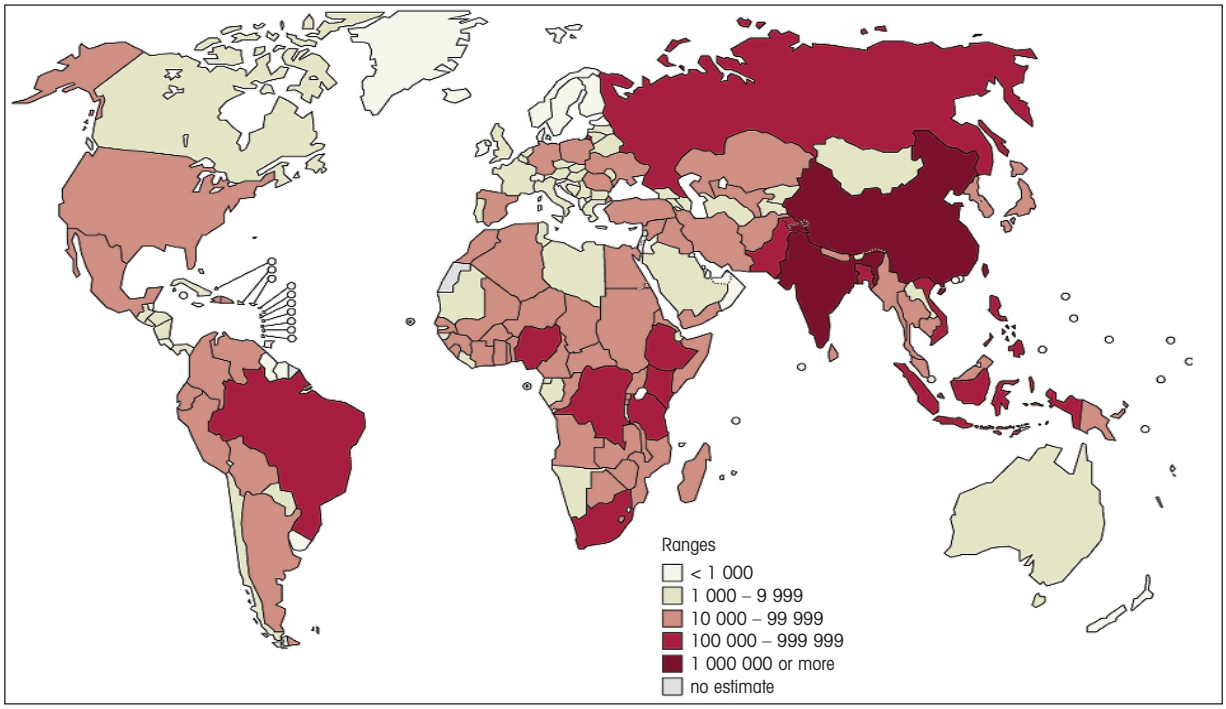
3. Where Do We Stand Now with DOTS?

Choosing as a starting point the 22 TB high-burden countries (HBCs) that together account for 80 percent of the global TB burden, successful DOTS expansion in these countries will clearly make an enormous contribution to global elimination of TB.

Several of the HBC countries have already taken DOTS to scale. For example:

- **China** was one of the first. Its DOTS programmes covered more than half a billion people by 1994, treating more than 110,000 patients a year.[8]
- **India** has also progressed rapidly. Between 1997 and 1999, the Revised National TB Control Programme expanded DOTS coverage from 22 to 135 million people, providing treatment to nearly 150,000 TB patients.[9] Since then, DOTS expansion has continued and now covers a population of 400 million, treating more patients every day than any other DOTS programme in the world.

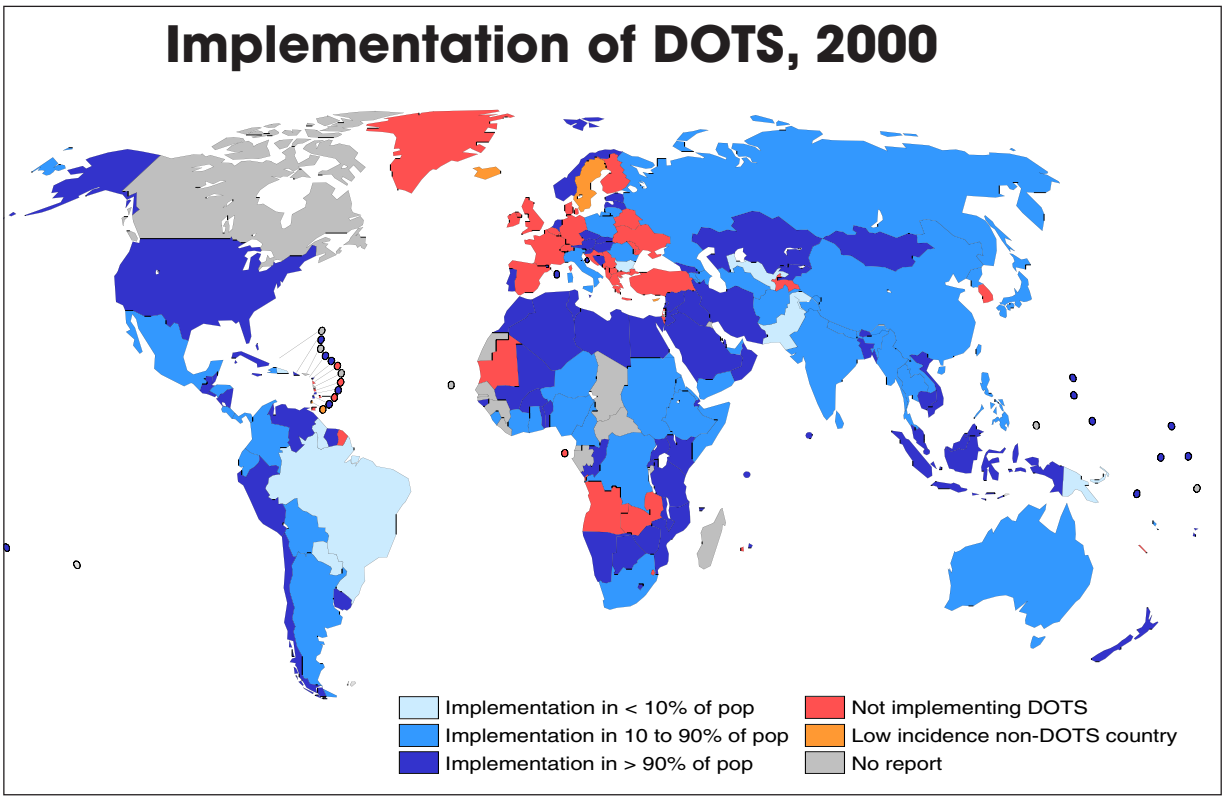
High-burden countries



The World Health Organization monitors the global TB epidemic. According to the WHO annual report (2002) on the state of the world's TB epidemic:[10]

- 148 countries, including all 22 TB high-burden countries, had adopted DOTS. Ninety-five of these countries were already implementing this strategy for over 90 percent of their populations.
- Nearly 2 million patients with TB were treated in DOTS programmes in 1998; 1,021,000 of these patients—27 percent of the cases estimated to have occurred that year—had active infectious (smear-positive) TB.
- Eight out of ten patients treated in DOTS programmes in 1997 were reported to have been successfully treated, compared with less than three out of 10 in non-DOTS programmes.

Numbers of countries implementing DOTS

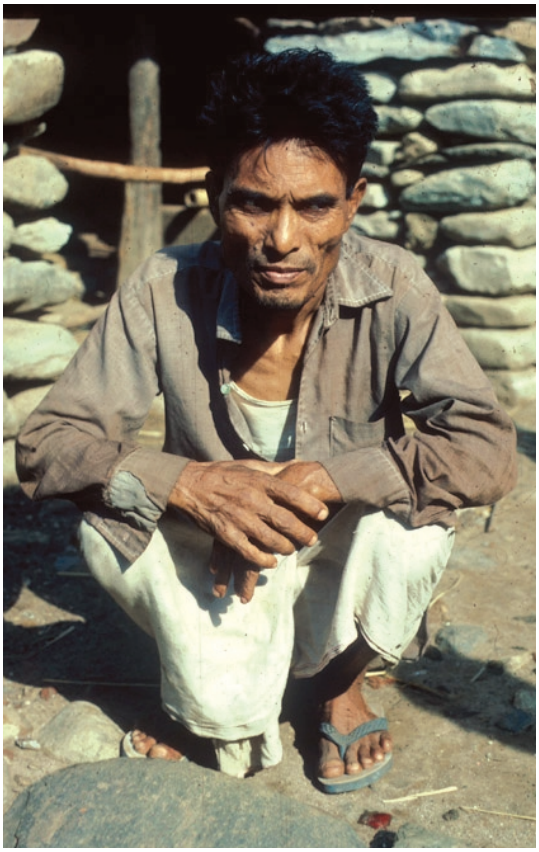


Most of the 95 countries implementing DOTS on a wide scale are relatively small. Progress in large-population countries has generally been slow, with a few notable exceptions as noted above, such as China and India, as well as Viet Nam and Peru. The latter two are the only two large countries to achieve the Stop TB targets for TB control. Worldwide, DOTS programmes will serve an additional 850,000 new cases each year (including 350,000 infectious, sputum-smear positive cases) to reach the Stop TB targets by the year 2005.[11]

Tuberculosis encompasses perhaps the greatest health paradox of our times. Despite the proven effectiveness of a low-cost strategy:

- just one-quarter of all TB patients worldwide receive care in accordance with the international guidelines for diagnosis, treatment, and monitoring;
- many TB patients receive inadequate treatment in poorly organized and insufficiently monitored programmes in the public and private sectors, posing a grave danger by encouraging the development of drug-resistant strains, one of the greatest threats to TB control; and finally,
- some TB patients in fact receive no treatment at all. It is not only paradoxical—but also perverse—that children born in the third millennium, as well as at-risk adults who have inherited this "dark legacy", should continue to be plagued with this entirely treatable disease.

4. Why Don't All TB Sufferers Get DOTS?



World Health Organization

A TB patient in Nepal.

Although today's scene is rapidly changing, the "dark legacy" of obstacles to rapid DOTS expansion has usually included: lack of top-level political commitment; insufficient financial resources; problems with health service organization, management, and human resources; inadequate health-care infrastructure; lack of secure supplies of high-quality, anti-TB drugs; and inadequate public information and awareness.[12] In short, national and organizational access barriers have been mainly political and managerial, while community and individual obstacles have been more geographical, social, and economic in nature.[13]

Geographic obstacles On the one hand, remote, rural areas (such as mountainous Himalayan countries, isolated Pacific island communities, and nomadic East African tribes) pose obvious problems in terms of accessibility of TB treatment. Not only is detection thwarted in such cases; even when diagnosed, patients living in such remote rural communities cannot easily travel to distant health facilities. As a result, the introduction of community-based approaches is necessary.

Access can also be a significant problem in urban areas, today home to half the world's population (up from only 24 percent in 1950). The challenges for TB control in urban areas include: higher rates of TB infection; the prevalence of drug-resistant strains; the growing risk of HIV co-infection; difficulties providing continuity of care to mobile populations and socially disadvantaged groups (such as homeless people and slum dwellers); and the complexities inherent in large-scale and/or problematic settings (such as mega-city private hospitals and clinics; university hospitals; industries; prisons; and the military).

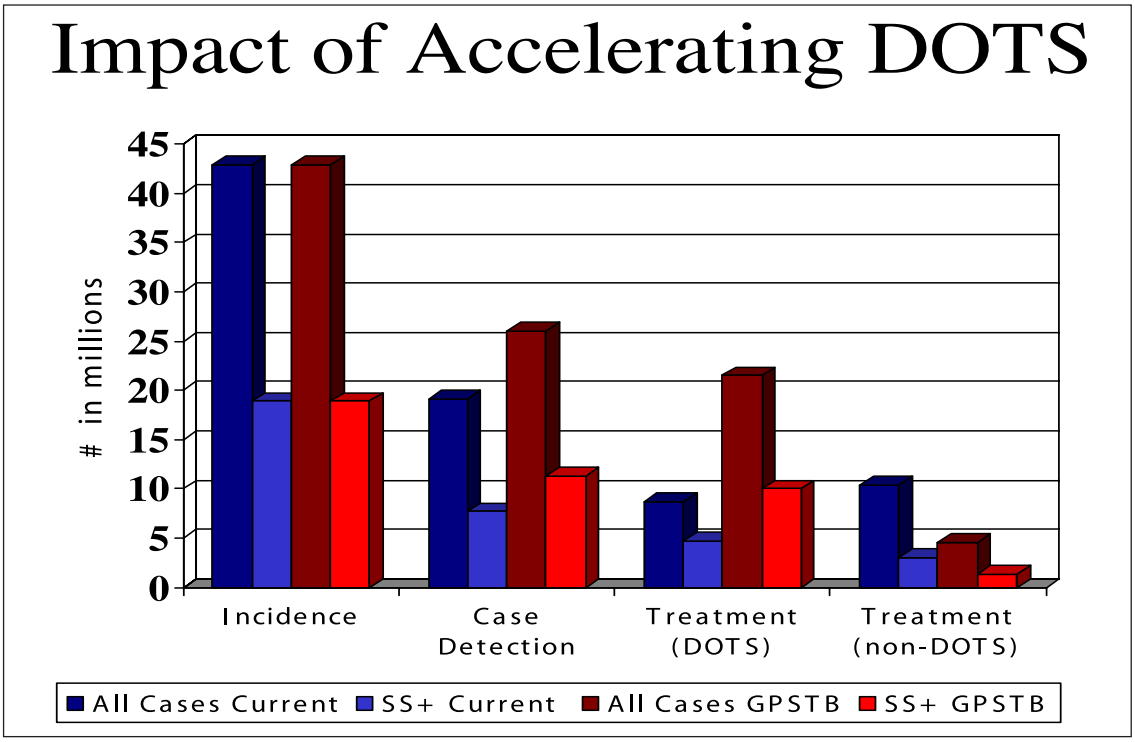
Social obstacles such as the stigma attached to disease remain a problem in many societies, and health systems do not always respond to patients' needs in a supportive manner. The WHO's World Health Report 2000 analysed the level of "responsiveness" of public health services: 15 of the 22 countries with the highest TB burden were in the bottom (less responsive) half of the table.[14]

If we are to reach the four million people with TB who currently lack access to effective treatment, swift and massive global DOTS expansion will need to be set into motion.

5. How Do We Accelerate DOTS Expansion?

To benefit from the full power and potential of DOTS, we must increase access to drug treatment and care, mobilize society, build capacity, and expand DOTS population coverage. The potential impact of accelerating DOTS expansion is dramatically demonstrated in the accompanying graphic. Increasing DOTS coverage to provide effective treatment to just 70 percent of people with active infectious TB by 2005 would save millions of lives and jump-start a decline in TB that could lead to future elimination. Investing in accelerated DOTS expansion can clearly have a profound impact:

- 21 million people can be cured of TB by 2005—5.3 million more than with the current level of TB control.[15]



Momentum for DOTS expansion is already being generated at the highest political levels. As indicated earlier, when ministers and senior officials from 20 of the TB highest-burden countries met for the March 2000 Conference on TB and Sustainable Development, delegates committed their countries to reaching specific, time-bound global targets by 2005, namely:

- expanding DOTS to all countries;
- diagnosing 70 percent of all people with infectious TB; and
- successfully treating 85 percent of those diagnosed.[16]

Reaching these global targets by even as late as 2010 would prevent 48 million cases (23 percent of the predicted total) by 2020.[17] The percentage of deaths averted would be even greater. Indeed, most TB deaths could be prevented **immediately** if all patients took a full course of anti-TB drugs **now**.

Further evidence of political commitment to accelerated action is visible in the outcome of the G8 Summit in July 2000 in Okinawa, Japan. There, the G8 heads of state committed their countries to a massive increase in funding for action against infectious diseases. The goal set was to halve the TB burden—both the number of people living with the disease and the number dying from it—within a decade.[18] The European Union and the U.S. government also pledged to work together "in partnership with the countries concerned" to combat communicable diseases such as HIV/AIDS, malaria, and TB. The world has moved quickly to make the Okinawa commitment more than just words. The Global Fund to Fight AIDS, TB and Malaria was launched in 2001, has pledges of over $1.9 billion—and is about to make the first grants to countries, to assist them in scale-up and effective action to address these diseases.

In addition, low-income countries throughout the world are preparing Poverty Reduction Strategy Papers (PRSPs). PRSPs describe a country's policies and programmes to promote growth and reduce poverty, and define associated financing needs. Over 25 heavily indebted poor countries (HIPC) to date have been granted packages for debt-relief, including four of the TB high-burden countries (Ethiopia, Mozambique, Tanzania, and Uganda), and all 25 are high TB-incidence-rate countries. All provide increased support for social sector expenditures.

PRSPs represent a broad development framework for poverty reduction that is being supported by many donors and other financial partners. Even countries not qualified to receive debt relief are developing PRSPs as poverty reduction is raised as a priority on the development agenda of countries and their partners. Eleven of the twenty-two high-burden countries have developed or are in the process of developing PRSPs. These countries include Cambodia, DR Congo, Ethiopia, Indonesia, Kenya, Mozambique, Nigeria, Pakistan, Tanzania, Uganda and Viet Nam. PRSP collaborators have strongly encouraged inclusion of communicable disease prevention and control as one priority for new investment, yet few countries to date have explicitly mentioned tuberculosis control in their PRSPs or in debt-relief packages. To avoid missing a major opportunity, Stop TB Partners need to engage in the dialogue on poverty reduction plans. The Stop TB Partnership is highlighting the links between TB and poverty in 2002, and this should help advance this agenda, but success will require specific efforts in each country.

Now, concrete follow-up action is needed in three areas to realize DOTS' full potential. The **supply** of funds for DOTS programmes must be increased, as must the **demand** for DOTS programmes, and the **capacity** for implementing DOTS. These activities must be advocacy-driven to ensure high-level political commitment. They need operational research to improve the effectiveness and efficiency of mechanisms for action, and close monitoring and surveillance to demonstrate the impact of the interventions.

5.1 INCREASE ACCESS TO DRUG TREATMENT AND CARE

Increasing access to accurate diagnosis and swift treatment for people with TB can be achieved by:

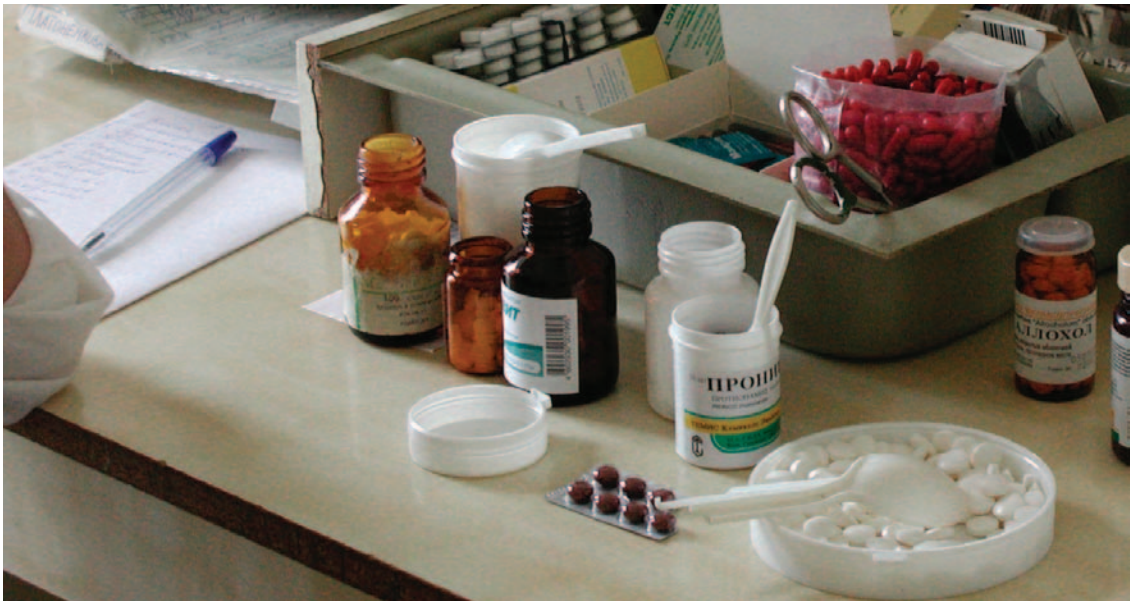
- expanding DOTS coverage through public health services;

- securing sustainable supplies of quality TB drugs for National Tuberculosis Control Programmes (NTPs); and
- involving other health service providers, including the private sector and not-for-profit providers such as non-governmental organizations (NGOs).

DOTS Most TB high-burden countries have gained considerable experience in introducing DOTS, but may face difficulties in reaching 100 percent population coverage. These differences may be specific to certain national TB-control programmes (for example, human and financial resource constraints) or more applicable to health services in general (such as providing services to "hard to reach" population groups). In addition, in some instances much-needed health sector reforms have been introduced without ensuring maintenance of an effective TB-control programme, with catastrophic results for patients.[19]

The key to successful TB control is "broader, better, and bolder" use of drugs to ensure that all TB sufferers in all countries have uninterrupted access to effective treatment. However, frequent interruptions in the TB drug supply are common in many countries.

Drugs Participants in the Amsterdam Conference 2000 called for a global facility to increase access to high-quality TB drugs. In response, the Global TB Drug Facility (GDF) was inaugurated on World TB Day 2001 by the Global Partnership to Stop TB. The GDF provides free drugs for people in the poorest countries and emergency supplies to assist countries facing stock-outs.[20]



Dr. Anchu Castro, Partners in Health

Dispensing TB drugs in a Siberian prison.

Managed by the Stop TB Partnership Secretariat in WHO, the GDF has received initial funding of $10 million from the Canadian government, and, within less than a year after its creation, had already awarded grants in kind of TB drugs to 12 countries in Africa, Asia, and Eastern Europe. The GDF is living proof of just how quickly and effectively Stop TB Partners can work together to respond to an urgent need faced by many countries. However, the GDF will require a substantial increase in funding to meet its goal of supplying drugs to an additional 10 million patients over the next five years.

In most countries where TB is common, its diagnosis and treatment are not restricted to public health services. Non-governmental organizations and private medical practitioners often provide a substantial proportion of care. Successful DOTS expansion will require close collaboration between these different health-care service providers to ensure all patients get access to effective and affordable care. Models of public–private sector collaboration in health service delivery are being developed in many countries, but need to be rapidly scaled up.[21]

5.2 MOBILIZE SOCIETY

Community awareness and involvement in care and education is crucial to sustainable activities to eliminate disease and promote health. DOTS expansion has been hindered by a lack of community awareness concerning TB, by social barriers against access to care (for example, stigmas—particularly for women), and by traditional models of health-care delivery based primarily on health service institutions.

Polio—Learning from experience. Mobilizing society has been key to increasing the rates of immunization against several diseases, an effort that has saved millions of young lives. Smallpox has been eradicated, and polio eradication will be the first public health triumph of the new millennium. Similar social mobilization efforts must now be made against TB to raise community awareness regarding prevention, diagnosis, and treatment, and to create an increased demand for services.

Peru—Learning from success. Peru has been singularly successful in addressing the problem of TB. Today it has what is widely regarded as the best national TB programme in the world. The story began in the early 1990s, with a spontaneous street demonstration by TB patients calling for access to effective drugs. Their protests led to high-level commitment and action, as the president of Peru made TB control a high priority. Funding for TB control subsequently increased, and the central unit of the NTP was strengthened with the appointment of a dynamic manager.

The programme has gone through a series of developmental stages since its beginnings. In 1990–1991, the emphasis was on laying a foundation for good TB control, with programme restructuring and development of standardized policies. These improvements were further modified in 1992–1993, based on the DOTS strategy, and the programme rapidly expanded. The period 1994–1997 was one of consolidation, with emphasis on strengthening technical and social management and the development of a national research agenda.

Based on WHO estimates and national reports, today Peru is detecting over 90 percent of estimated infectious cases, with 90 percent of people successfully completing treatment. Most recently, the programme has demonstrated a sustained decline in TB incidence[22] and is developing an effective approach to address the serious problem of MDR-TB.

From Peru's acclaimed success, we can learn of the crucial importance of:

1. ***Political commitment and social mobilization*** A fully mobilized community demanding services, high-level political commitment, and effective leadership creates an enabling environment for effective TB control.

2. ***Technical excellence and standardized but flexible policies*** In 1991, the NTP used a single anti-TB treatment scheme for all patients, irrespective of their previous treatment history. Since 1996, differentiated treatment regimens were introduced for new and previously treated patients, with direct observation of treatment. As a result, the cure rate for new patients increased from 50 percent in 1990 to 93 percent in 1999.
3. ***A well-developed primary health-care infrastructure*** Peru expanded primary health-care staffing and infrastructure and thereby allowed for free and supervised TB treatment in all health-service settings.
4. ***Patient incentives*** The programme provides support in the form of meals and other incentives to TB patients, encouraging adherence to treatment, and improving nutrition.

Increasing community mobilization worldwide means introducing specific initiatives to develop:

- broader models to increase access to care, including community-based approaches;
- better national strategies to educate communities and better national and regional NGO networks working to reduce TB; and
- bolder, more inclusive self-help groups for people with TB.

5.3 BUILD INSTITUTIONAL CAPACITY

Capacity building must take place concurrently with community mobilization efforts. Improving supply and increasing demand will not add value unless health services can cope with the influx of more drugs and more patients. Indeed, "dumping" drugs on an ill-prepared, inadequate health service would be disastrous, because epidemics of drug-resistant TB could easily occur in the wake of improper use.

5.4 EXPAND GLOBAL DOTS POPULATION COVERAGE

The 20 TB high-burden countries attending the Amsterdam Conference in March 2000 also called for assistance in developing their national TB-control plans. Over the course of the last year, WHO, along with other Stop TB Partners, has worked closely with these high-burden countries to do just that.

These plans have now been consolidated into a Global DOTS Expansion Plan (GDEP). It specifically sets out the action and resources needed to assist high-burden countries in meeting the global TB-control targets by 2005, estimating the magnitude of the resource gaps in these and other countries.[23] It also provides the first assessment of the status of TB-control financing worldwide, together with an explanation of the involvement and commitment of international agencies, both technical and financial, in country assistance.

6. Conclusions

For TB, the times are changing, at least in much of the developed world. The epidemics of "galloping consumption" that ravaged Europe and North America in the nineteenth century have passed, as treatment with highly effective drugs accelerates the decline of TB in many industrialized countries. Sadly, the same cannot be said for the rest of the world.

We are accountable, both to ourselves and to future generations. The question history may well ask us is less "What did you do about TB?" than "Why did you not do more when the means to defeat TB were at your fingertips?"

This question is all the more pressing as we witness the window of opportunity for effective action against TB closing before our very eyes. Two situations threaten the effectiveness of DOTS to halt the spread of TB. The first is the emergence of MDR-TB that occurs with inadequate or interrupted TB treatment. High levels of drug resistance mean that the standard DOTS treatment regimens fail at unacceptably high rates, when compared to regular TB strains.[24] As for HIV, it greatly increases the risk that an infected individual will develop active TB, thus causing the number of active TB cases to increase rapidly. Some sub-Saharan African countries have witnessed a fourfold increase in TB cases over the last 10–15 years.

Under such ominous circumstances, the rapid and sustained expansion of DOTS is that much more urgent to keep the window of opportunity open. Chapters 3 and 4 describe these challenges in greater detail and identify the actions necessary to meet them.

7. Economic and Financial Overview

Table 2.1: Estimated costs of DOTS implementation—National TB-Control Programmes and DOTS expansion in low- and middle-income countries, 2001–2005 ($ millions) (1)

Component	5-Year Cost	Current Resources			Financing Gap
		Government	External	Subtotal	
22 High-Burden Countries – TB programmes (2) – Health-care services (3)	4,560 *1,560* *3,000*	3,300	250	3,550	1,010
Other low- and middle-income countries – TB programmes – Health-care services	1,440 *590* *850*	1,000	0	1,000	440
DOTS Expansion Working Group	225	0	109	109	116
Total	**6,225**	**4,300**	**359**	**4,659**	**1,566**

Notes

1. The total estimated plan costs shown in this table exceed the estimate of resources required for global TB control in a recent analysis conducted by WHO (see K. Floyd, L. Blanc, M. Raviglione and J.W. Lee, "Resources Required for Global Tuberculosis Control" Science 2002, in press). This is because the latter focuses on the costs for DOTS implementation, and does not include an assessment of resources needed for MDR-TB, TB/HIV, new diagnostics, drugs and vaccines, and partnership activities. Estimates for DOTS implementation in both publications are similar. In the analysis undertaken by WHO, it is estimated that $6 billion is required for DOTS implementation in the 22 HBC and in the low- and lower-middle income countries outside the 22 HBC during the period 2001-5 ($225 million less than is projected in this plan), and that the resource gap is about $1.5 billion (compared to $1.6 billion in this plan). The differences arise because the two studies were conducted independently and used slightly different methods to project cases to be treated, costs, and available resources. However, the fact that the two studies are broadly consistent strengthens the validity of both estimates. The main difference lies in the cost estimates for low- and lower-middle income countries outside the 22 HBC. This is to be expected given the limited data and the need for more assumptions in estimating costs for these countries. Both sets of estimates will be updated as more data become available.
2. TB programmes cover: equipment for laboratories, drugs, diagnostic supplies, training, administration of the programme and salaries and expenses, supervision, monitoring, incentives to support treatment compliance and increased case detection, operational research, and surveillance. Total projected cost of first-line drugs and re-treatment drugs is $780 million for all 114 countries.
3. Health-care services cover patient ambulatory care (visits to health centres or TB dispensaries) and in-patient care (in hospitals or sanatoria).

Further detail on programme costs is provided in the *Economic Annex to the Global Plan to Stop TB*, published separately.

TB and HIV/AIDS: Overlapping Epidemics, Complementary Responses

ENNA: FIGHTING AN UPHILL BATTLE

At twenty-six years of age, Enna has already borne six children, five of whom are living. Her life has not been easy. Born to an impoverished family in Savanette in Haiti's Central Plateau, at ten she was sent to Port-au-Prince as a restavék—a child servant. "I used to mop the floor and cook. I also used to baby-sit", she says. She was not paid except "they gave me food to eat". At 14, Enna was raped. "The man, a friend of the family where I was staying, raped me. He waited until no one was home, then he jumped on me. I was just a child. I didn't know what was happening. This happened four times. Then I was pregnant. The family sent me away".

Enna returned to Savanette, where she almost died in childbirth. After she recovered, for a time she sold fruit in the regional markets and in Port-au-Prince. At 18, while sleeping in a communal depot in a Port-au-Prince market, Enna was raped again, this time by three men. "I didn't see them, so what could I tell the police? Besides, I was afraid of the police". Enna regards her entire life as "a disaster". She says, "I had three children from two different men, but neither of them would help me [financially]".

In 1997, sapped by recurrent fevers and chronic diarrhoea, she was diagnosed with TB, co-infected with HIV. Treated successfully for TB in the local DOTS programme, she gained weight—but later developed an opportunistic illness indicative of advancing HIV disease. She lost weight again and complained of intermittent diarrhoea. Enna received AZT during her sixth pregnancy, but lost her newborn. When her post-pregnancy weight then fell precipitously, she was started on a combination antiretroviral regimen. Within six months, she had gained nine pounds, was asymptomatic and had resumed working. The lifesaving medicines were delivered to her by the same community health-care workers who had helped her through her earlier TB treatment.

1. TB and HIV/AIDS: More than a Double Burden

Together, TB and HIV/AIDS encompass a humanitarian catastrophe of unprecedented global proportions. The magnitude of today's HIV/AIDS crisis is such that many predictions termed "alarmist" just a decade ago now seem naïve.[1] HIV/AIDS mortality rates are outstripping those of all other infectious diseases. In 2000, HIV overtook TB as the single leading infectious cause of adult deaths in the world. HIV has, in fact, recently overtaken the great influenza epidemic of 1918 as the most devastating communicable cause of adult death since the bubonic plague of the fourteenth century.[2]

The socio-cultural and political-economic impact of HIV has been particularly severe in Africa, where HIV/AIDS has created an estimated 14 million AIDS orphans. If current trends continue, 40 million African children will be orphaned by 2010.[3, 4] Because HIV flourishes in conditions of poverty and social inequality, the full extent of the spread of HIV in India and other parts of Asia remains to be seen.[5]

However, concurrent with these grim prospects now facing victims in poor countries, HIV mortality in affluent countries has dropped precipitously, in large part because of people's access to highly active antiretroviral therapy (HAART).[6, 7, 8] The outcome gap in HIV deaths and disease is now well known throughout the world: in the absence of an extraordinary response, the disparities between rich and poor will likely become more pronounced in coming years. A critical determinant worsening these outcome differentials is the interaction between TB and HIV/AIDS.

Young mother in rural Haiti.

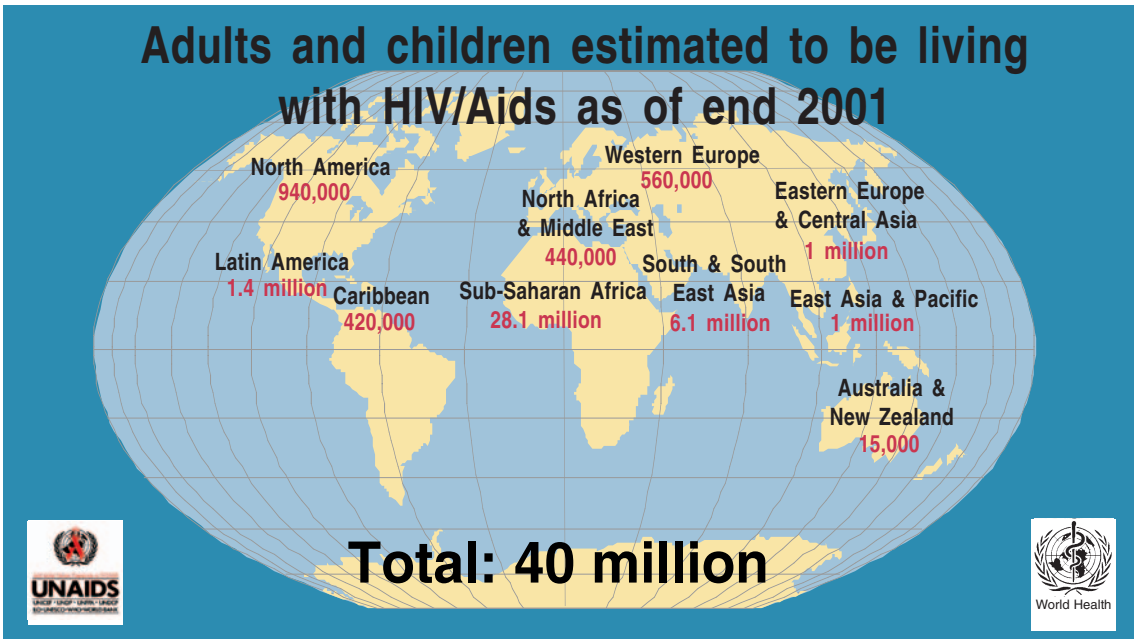
Dr. Anchu Castro, Partners in Health

HIV promotes TB's progression from latent infection to active tuberculosis. While non-HIV-infected persons have only a five to ten percent lifetime risk of activating latent TB, HIV-positive persons have a five to ten percent per year likelihood of progressing to the active disease. Infection with HIV is the most potent risk factor for the conversion of latent tuberculosis into active tuberculosis. Tuberculosis has become the leading cause of death among people with HIV infection,

accounting for about one-third of AIDS deaths worldwide. The more people in a community with active tuberculosis, the greater the likelihood TB will be transmitted to both HIV-infected and uninfected persons.

2. HIV: Fuelling the TB Epidemic

At the beginning of the new millennium, WHO and UNAIDS estimated that worldwide, 40 million adults and children were living with HIV.[9] The vast majority—95 percent—were living in the developing world. During 1999, some 5 million people became newly infected with HIV, while 3 million people died of AIDS-related causes.

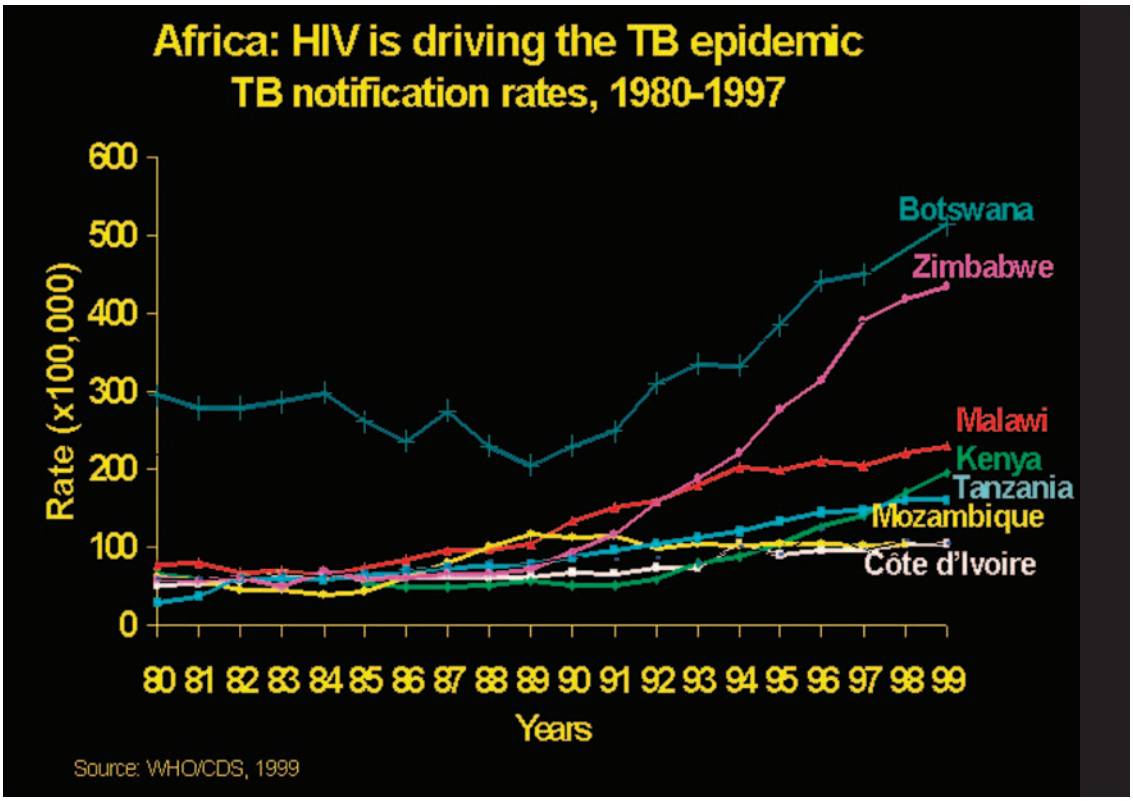


HIV increases the risk of developing active TB by weakening the immune system. Similarly, the presence of other infections, including TB, can result in more rapid progression of HIV infection to AIDS. In 1999, about one-third of the 34 million HIV-infected people worldwide were also infected with *Mycobacterium tuberculosis*, which means that about 6 million HIV-positive persons will develop active TB. The World Health Organization estimated that in the year 2000, at least 12 percent of the global TB burden was associated with HIV infection, up from 4 percent in 1995[10]—a tripling of the rate in the short space of five years.

As of 2000, sub-Saharan Africa bore the heaviest burden of HIV/AIDS, with close to 70 percent of the world's HIV-positive people. Without effective therapy, 20 million Africans are likely to die of AIDS in the next ten years, on top of the 13.7 million lives the epidemic has already claimed in Africa alone. AIDS has devastated families and crippled prospects for development, and it has contributed mightily to the steady rise of TB in sub-Saharan Africa since the late 1980s.[11]

Sub-Saharan Africa had the highest observed TB-incidence rate of any region in the world in 1997: 259 afflicted persons per 100,000 population. TB in Botswana, Namibia, South Africa, Zambia, and Zimbabwe—all of which have incidence rates of approximately 400 per 100,000 persons—contribute to this high regional incidence rate.[12] Sub-Saharan Africa also had by far the highest proportion of persons co-infected with TB and HIV. Projected changes in TB incidence from 1995–2005 show that, by 2005, sub-Saharan Africa may contribute more than 3 million cases to the global burden of TB-HIV co-infection.[13]

With a population of 43 million, South Africa is burdened by one of the worst TB epidemics in the world. It is also one of the countries most severely affected by HIV/AIDS.[14] Since 1996, South Africa has made concerted efforts to implement the DOTS strategy. DOTS programmes now cover 60 percent of the population, and DOTS-Plus programmes have been established in all nine provinces. These programmes have led to significantly greater cure rates. In one rural district, a community-based DOTS programme that utilizes community members to administer directly observed treatment achieved cure rates similar to programmes administered by health-care workers.[15]



However, despite these advances in DOTS coverage and cure rates, TB-incidence rates have continued to rise, and remain of deep concern, particularly in the face of the HIV epidemic. Elsewhere in the world, the characteristics of this TB-HIV synergy are less apocalyptic—but no less disturbing. *HIV and TB co-infection represent an unprecedented global public health crisis.*

Central and Eastern Europe/Newly Independent States: The world's fastest-growing HIV epidemic is now unfolding in the newly independent states of the former Soviet Union, where the proportion of the population living with HIV doubled between the end of 1997 and the

end of 1999.[16] In the larger region encompassing the former U.S.S.R., as well as in the remainder of Central and Eastern Europe, the number of new infections has been doubling annually since 1998. Political instability and social disintegration following the 1991 collapse of the Soviet Union fuelled soaring unemployment and a concomitant rise in alcoholism and drug use, believed to be the main risk factor in the burgeoning HIV epidemic in the region. In Ukraine, one percent of the adult population is HIV-infected, and in Eastern Europe, UNAIDS estimates that over one million people carry the virus.[17]

Asia: Given their sheer size, India and China inevitably dominate Asia's HIV assessments. Because these countries have very large populations, even small percentage changes in estimates of national infection rates reflect large changes in the absolute numbers of people infected.

In **India**, for example, a rise of just 0.1 percent HIV prevalence among adults would add more than half a million people to the national total of adults living with HIV. In some states, principally in southern and western India, HIV has invaded the urban population. There, more than one in 50 pregnant women currently tests positive for HIV. In the northeast, HIV infection is surging among networks of drug-injecting men who spread the infection to their sexual partners. Work-driven migration among economically stressed populations has proved a significant risk factor in India, as in other poor countries. While TB-HIV co-infection rates are highest in Africa, the absolute number of co-infected people is greater in India (1.7 million in 1997) than in any other country.[18]

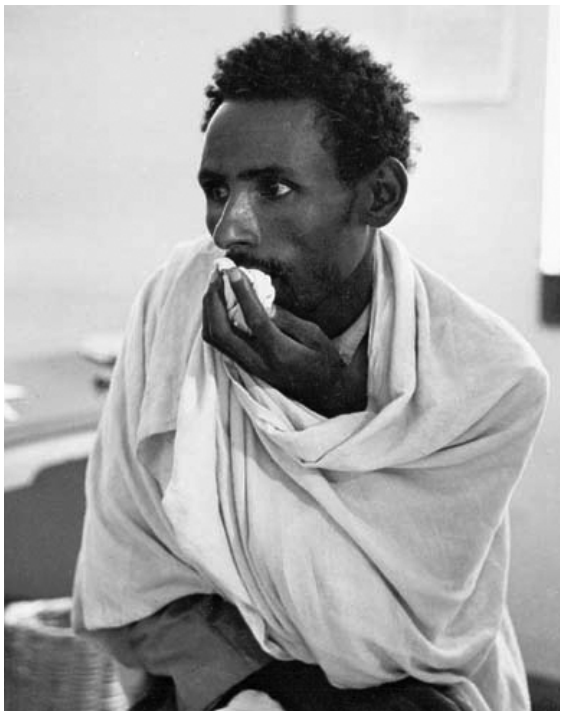
In **China**, HIV-infection rates—once thought to be very low—are now rapidly escalating. Current reports conservatively estimate that half a million of China's more than one billion people are HIV-positive. The Chinese government maintains that most of the new infections are concentrated among intravenous drug users.[19]

3. Complementary Interventions for TB and HIV/AIDS

In Africa during the last decade, the rapid spread of HIV/AIDS in Africa has fuelled the TB epidemic across the continent. Yet very few countries in sub-Saharan Africa have strengthened collaboration between TB and HIV/AIDS control programmes. The control of HIV/AIDS continues to focus on HIV prevention—through advocacy; information, education and communication (IEC); condom promotion; and behavioural changes. Most of these programmes mistakenly polarise prevention and treatment. They often place little or no emphasis on the treatment of serious HIV-related diseases—TB being the most prevalent, deadly, and easily treatable one.

Tuberculosis programmes, meanwhile, have focused on implementing the DOTS strategy without regard to escalating HIV infections, which call for more intensive TB case finding, more widespread preventive treatment of people with latent TB infection, and better links between HIV testing and access to TB prevention and care.

Gradually, however, perceptions are changing. HIV/AIDS and TB are increasingly being recognized as devastating overlapping epidemics, which together are undermining the social and economic development of much of Africa. Autopsy studies have shown that TB accounts for up to one-third of AIDS deaths,[20] which has led to the understanding that programmes and organizations addressing HIV/AIDS should strengthen their contributions toward effective diagnosis and treatment of TB.



A co-infected patient in Africa.

World Health Organization

Similarly, because HIV clearly fuels the TB epidemic and many TB patients live with HIV, TB programmes and organizations must also join the fight against HIV/AIDS. Preventing new HIV infections will simultaneously prevent additional TB cases. More importantly, intensified case finding, rigorous diagnosis, and effective treatment of TB in HIV-infected patients will prolong the patients' lives and decrease the further spread of TB. Therefore, both programmes should be keen to cultivate opportunities for collaboration.

At the national level, committees derived from relevant ministries and sectors may be best equipped to facilitate such a coordinated approach to TB-HIV prevention, care, and treatment. Every approach should strive to deliver universal, equitable, high-quality care for TB and HIV/AIDS. Care and support are key to reducing stigma and denial in society and to breaking the cycle of cynicism and despair. A common agenda should guide TB-HIV activities in such areas as advocacy, health education, policy formulation, training, service provision, social support, community mobilization, surveillance, monitoring and evaluation, supply logistics, operational research, and treatment.

4. TB And HIV/AIDS: Undermining Health and Development

The health catastrophe in sub-Saharan Africa is further exacerbating the continent's dire economic situation. Both industrial and agricultural production are declining in many countries while drastic declines in life expectancy of between 10 and 20 years in those countries most badly affected by HIV/AIDS are now negating hard-won economic and health gains achieved over the course of the last several decades. An additional barrier to economic development is the rapidly increasing child mortality rate—the result of increasing mother-to-child transmission of HIV/AIDS and excess mortality of non-infected children born to parents sick with HIV. Approximately 3 million children have died of AIDS since the

beginning of the epidemic. In 1999, an estimated 570,000 children became newly infected with HIV, 90 percent of them in sub-Saharan Africa.

Household surveys reveal that families whose breadwinners contract HIV/AIDS and/or TB suffer dramatic decreases in income. In Thailand, one-third of rural families affected by AIDS saw agricultural output halved and their basic food security threatened. As a result, 15 percent of those families had to take their children out of school, while 57 percent of elderly family members were left to fend for themselves.[21]

In AIDS-affected families in urban areas of Côte D'Ivoire, school education outlays were halved; food consumption decreased 41 percent per capita; and expenditures on health care increased by more than 400 percent.[22] Studies have repeatedly shown the tragic strength of family ties: indeed, families may fall into impoverishment to provide treatment, relief, and comfort for sick relatives. In Thailand, AIDS-affected families spend, on average, 60 percent of their savings on AIDS care. And, of course, individuals who become ill with TB are not only often unable to work; they are also forced to expend scarce resources on health care. Other studies show that on average, a TB sufferer loses three to four months of work a year and 20 to 30 percent of annual household income. Also, on average, when a family breadwinner dies prematurely—no matter the cause—the family unit is denied an additional 15 years of income.[23]

Labour-intensive industries such as industrial production, mining, and agriculture are most seriously affected by the overlapping epidemics of TB and HIV/AIDS. When measured in terms of population dependency, agriculture is one of Africa's key sectors. Although it generates only 20 percent of the continent's income, it sustains up to 80 percent of the continent's population. Therefore, when someone (especially an active worker) in a farming family falls ill and dies, agricultural output plummets: typical decreases include a 61 percent drop in the production of maize; a 47 percent drop in the production of cotton; a 49 percent drop in the production of vegetables; and a 29 percent drop in number of cattle owned.[24] HIV/AIDS not only kills people; it also stunts economic growth. For a developing country such as Kenya, where the loss in gross domestic product (GDP) between 1995 and 2005 is estimated to be as high as 14.5 percent, social development will surely be compromised.[25] Because of AIDS in Namibia, the Human Development Index—which combines life expectancy at birth, adult literacy rate, and GDP—is predicted to decrease by 10 percent by 2006; in South Africa, the index is predicted to decrease by 15 percent by 2010.[26]

The overlapping epidemics of TB and HIV take a large share of the blame for this devastation. Tuberculosis accelerates the development of other HIV-related diseases, exacerbating the social and economic impact of this already costly disease.

4.1 TB-HIV: BURDENING HEALTH SYSTEMS

The increased demand for services from people with HIV/AIDS threatens already overburdened and under-financed public health systems. In Zimbabwe, for instance, half of hospital in-patients have HIV/AIDS-related illnesses.[27] Public health workers and clinicians are also becoming ill and dying of HIV/AIDS. The overall result is a rise in the cost of health care and increasing personnel, drug, and equipment shortages. The work capacity and quality

of staff suffer. Health-care workers in many African countries probably experience the same HIV-seroprevalence rates as the general adult population. Thus, their capacity to deliver effective care is increasingly undercut by high absentee rates, caused by illness or the workers' attendance at funerals, and high death rates within their own ranks.

The spiralling demand for services from people with HIV/AIDS stretches public health systems, which are already sorely overburdened and under-financed.

The incidence of TB has increased significantly in high HIV-prevalence countries. Between 1997 and 1999, TB incidence increased by at least 25 percent in South Africa and 40 percent in Botswana.[28] For every TB patient registered, there are at least four or five people who are suspected to have TB.

Dr. Ayacho Castro, Partners in Health

Patient co-infected with TB and HIV.

5. TB: Treatable and Curable—Even in People Living with HIV/AIDS

Grace is a 27-year-old Zambian mother of three small children. She recounts, "I was married at 16 but I left my husband after our second child because he was a heavy drinker. I was afraid of him so I came to stay with my mom. Life was hard and I had no other way of making money than by selling sex".

When her second child was only four months old, Grace came down with a cough. She had headaches, fever, and chest pains. She was taken to the hospital, where she was diagnosed with TB. She returned home to Zambia's Copperbelt, where she received treatment as part of a home-care health plan involving health workers, volunteers, and comprehensive services for people living with HIV/AIDS and TB.

After nurses from the home-care health plan counselled Grace about HIV, she agreed to be tested, and was found to be HIV-positive. Even though she was told she might as well forgo her TB treatment because she was going to die of AIDS anyway, Grace completed her treatment and made a full recovery. "I even put on weight", she says. More than four years after being diagnosed with HIV, she is still leading a full and active life. The moral of the story is that, even though TB deaths are more likely in HIV-positive patients, a high proportion of co-infected patients nevertheless can be cured and live relatively healthy lives before their HIV progresses to AIDS.

Studies conclusively show that short-course chemotherapy regimens utilizing isoniazid and rifampicin, supplemented by pyrazinamide and ethambutol (or streptomycin), are effective in treating TB in HIV-infected patients.[29] In one large Malawi study, 69 percent of HIV-positive patients newly infected with TB completed short-course chemotherapy. Although they had only normal access to the health-care system, 56 percent of them were alive almost three years later. Most of these patients were well and employed, although without treatment almost all of them would have probably died, in the meantime infecting others. Moreover, it seems certain that the Malawi outcomes can be improved upon by achieving earlier diagnosis, better care, and interventions to prevent other opportunistic infections.

5.1 TREATING LATENT TB HELPS

At least one in every three HIV-positive adults worldwide is latently infected with the TB bacillus, but not actively sick with TB, and not infectious to others. TB-preventive therapy is aimed at preventing progression from latent disease to active TB. The World Health Organization supports the introduction of TB-preventive therapy—specifically, six months of isoniazid daily for the benefit of people co-infected with HIV and the TB bacillus—in countries where national HIV/AIDS programmes are able to supply adequate HIV counselling and testing facilities, and those that have a well-functioning DOTS programme.

Studies in Malawi, South Africa, Thailand, Uganda, and Zambia have shown that TB-preventive therapy in people with HIV/AIDS does indeed work.[30] A minimum package of

care, including TB-preventive therapy at a voluntary counselling and testing centre, can be an incentive to use such service, thus assisting HIV prevention.

5.2 PREVENTING AND TREATING HIV TO CONTROL TB

On a global scale, antiretroviral combination therapy is at present a rare commodity. With few exceptions, such therapy is available to people with HIV/AIDS in industrialized countries only. This inequity is attributable to the high—albeit declining—cost of treatment and the poor public health-care infrastructure in many developing countries.

Even in **Latin America**, where the adult HIV-prevalence rate is relatively low, providing antiretrovirals places a heavy burden on health budgets. Yet, the indirect costs of the illness are also large, and without antiretroviral therapy, many more HIV-positive people will develop opportunistic infections associated with a compromised immune system.

In middle-income countries such as **Brazil**, the government provides funds to purchase the necessary drugs. Estimates indicate that between 1997 and 1999, Brazil thus averted approximately $422 million in hospital admission and treatment costs for people with HIV, suggesting that antiretroviral therapy can be cost-effective.[31] In **Argentina**, too, antiretrovirals are provided for HIV-positive patients. The result has been a decrease of over 40 percent in the rate of new AIDS cases reported each year.[32]

The widespread treatment of people with HIV/AIDS with highly active anti-retroviral therapy (HAART) will likely result in a significant decrease in the incidence of TB. Before HAART, patients with HIV and TB often died quickly—typically within 2 years—even when treated for TB.[33, 34] Yet in an innovative programme in Haiti, patients without longstanding HIV when diagnosed respond well to conventional TB treatment, often showing few symptoms of their HIV infection for long periods of time. In such circumstances, treating TB first—or ruling out active TB before enrolling patients in an antiretroviral treatment programme—is recommended.[35]

In **Kenya**, districts with the highest prevalence of TB-HIV co-infection were seen to have rising TB incidence.[36] A recent review of 13 different studies in sub-Saharan Africa shows that TB deaths increase in proportion to growing HIV prevalence in TB patients,[37] as well as with increasing HIV prevalence in the general population. Controlling TB in high HIV-prevalence countries requires full implementation of the DOTS strategy and large-scale HIV prevention and treatment.

Although the cost of HAART has decreased in recent years—from $12,000 per year in 1999 to $1,200 per year and below in 2001—it is still far too high. A country such as **Zimbabwe**, for example, would need to spend as much as 27 percent of its Gross National Product (GNP) to purchase all the drugs needed to treat its citizens living with AIDS. Additional measures, such as financing of drug purchases by developed countries and more cost-effective use of HAART, are therefore needed.

The scale of provision of antiretroviral drugs is presently extremely limited in low- and middle-income countries, although the potential impact on the burden of HIV-related

disease, including TB, is considerable. Operational research is needed to establish the feasibility and effectiveness of antiretroviral (ARV) treatment, and to examine the impact of large-scale use of HAART on the incidence of common HIV-related diseases—including TB—in a high HIV-prevalence population. Possible stigma associated with the use of HAART must also be addressed.

Additionally, a comprehensive research agenda to decrease the burden of HIV-related TB must include:

- epidemiological research to assess the extent of the spread of TB to HIV-negative people;
- mathematical modelling to estimate the potential impact of different interventions on TB-HIV co-infection;
- clinical research to improve the diagnosis of TB in people with HIV;
- evaluation of the effectiveness of prophylaxis in decreasing morbidity and mortality in HIV-infected TB patients, when the prophylaxis are used to ward off common infections; and
- operational research to identify ways to improve coordination and collaboration between HIV/AIDS and TB programmes, and to expand the contribution of all service providers (governments, NGOs and missions, private practitioners, and employers). This research includes the need to develop new policies and financing mechanisms.

5.3 DOTS WORKS IN HIGH HIV-PREVALENCE COUNTRIES

Thailand In the decades following World War II, Thailand experienced a consistent decline in TB cases. Deaths from TB declined tenfold from 1945 to 1997. However, since the beginning of the 1990s, the tide is turning, particularly in the north of the country, where increasing TB case notifications and deaths have paralleled increasing HIV prevalence. Thailand has controlled the spread of HIV with the "100 percent condom campaign", aimed at ensuring that every high-risk sex act is a protected act. The control of HIV is thus likely to translate into decreased TB incidence.

Moreover, within Thailand there appear to be strong correlations between HIV and MDR-TB. A 1997 survey showed an overall national MDR-TB prevalence in previously untreated patients of 2.07 percent, while high HIV-prevalence areas reported much higher MDR-TB levels. During the 1997 survey, the MDR-TB level was 6.6 percent in Chiang Rai, and the Bangkok Chest Hospital reported an increase in the incidence of MDR-TB in HIV-positive cases from 2.7 percent in 1987 to 8.8 percent in 1996.[38]

Thailand is a good example of what vigilance and political will can achieve in the face of TB and HIV.

Thailand has reacted quickly to the emerging TB-HIV epidemic. The DOTS strategy has been implemented since 1996 and, at the beginning of 2000, nearly 60 percent of all districts in the country had adopted the new TB-control policy, with full coverage anticipated soon. Despite treatment supervision, the death rate among TB-HIV co-infected patients remains high, indicating that many of these patients are treated only at advanced stages of HIV infection.

While working towards full DOTS coverage, Thailand is also introducing additional measures specifically targeted at high-risk groups. These measures include improved diagnosis and treatment of MDR-TB cases and preventive treatment in HIV-positive persons. Thailand is a good example of what vigilance and political will can achieve in the face of TB and HIV.

Republic of Tanzania While reasons to be optimistic about the potential of the DOTS strategy to reduce the global TB burden clearly exist, the HIV epidemic presents a severe impediment to health and development in sub-Saharan Africa. Modelling of the TB epidemic in the Republic of Tanzania suggests that a good DOTS programme may slow the increase in TB cases in the early stages of a rapidly growing HIV epidemic.[39] However, on its own, DOTS is unlikely to reverse the upward trend; the estimated TB incidence rate in the Republic of Tanzania has increased roughly in parallel with the HIV-notification rate. Still, projections suggest that TB incidence would have increased more quickly without DOTS. Modelling also predicts that DOTS would have reduced TB notifications, had there been no HIV epidemic.

5.4 THE CORE ROLE OF THE COMMUNITY

DOTS in Zambia: Up Close and Personal

Josephine arrives out of breath at the small, mud-walled house in Ndola, Zambia, where Henry sits on the doorstep. "I'm sorry I'm late", Josephine says. "Have you taken your medicine already?" "No, not yet", replies Henry. "I was just waiting for you". He slowly pulls himself to his feet and shuffles into the house he shares with his mother and six younger brothers and sisters. "How are you feeling today?" asks Josephine. "Oh, just a little bit OK", says Henry.

Josephine knows Henry is only putting on a brave face. She is a volunteer health worker in Nkwazi Township, a low-income neighbourhood on the northern edge of Ndola. She is one of 14 HIV/AIDS home-care visitors who have received special training as DOTS volunteers.

Every morning, at about 7:30, Josephine comes to make sure that Henry takes his TB medication, and to give him encouragement and advice. She will keep visiting Henry every morning for at least two months. Then, if Henry continues to improve, she will reduce the visits to once a week for another six months. "I've seen it so many times before", she says. "At first, the patients are so thin that you think they can't possibly survive. But after the treatment starts to take effect, and with the food they get from the programme, you can see the improvement. They put on weight and usually they recover completely".

Henry is one of the lucky ones. Most people with TB in sub-Saharan Africa do not have access to DOTS. Ndola Catholic Diocese runs the programme that is helping Henry with financial assistance from a consortium of European aid agencies. The Zambian Ministry of Health provides only the TB drugs and laboratory services.

Nkwazi is just one of 23 townships—with a total population of over 400,000—where the Ndola Catholic Diocese promotes DOTS and provides home care for people with AIDS. More than 500 part-time volunteers, mostly women, are the key to this programme's success. The women identify potential new patients in their neighbourhoods, help run community clinics, accompany patients to hospital, and regularly visit them to ensure they complete their treatment.

The principle that TB treatment regimens be fully supervised in various environments—from crowded cities to sparsely populated rural communities—was established in the 1970s. In the pre-HIV era in rural sub-Saharan Africa, patients were often hospitalised for the initial two-month phase of treatment, to ensure regular supervised drug intake in areas where the patient would otherwise have to walk 20 to 30 kilometres to obtain health care.

World Health Organization

Nurse dispensing TB medication.

But in recent years, overcrowded TB wards have led to new approaches involving less time spent in hospital or even full, supervised ambulatory treatment. For example, in KwaZulu-Natal, South Africa, TB treatment has been successfully decentralized to the community, with responsibility for drug supervision entrusted to non-health-care workers such as shopkeepers, teachers, and work colleagues. The choice of supervisor is the patient's, and the emphasis is on convenience for the patient, not that of the TB service. In Ghana, home visits by extension workers encouraging patients to continue treatment have been influential in improving treatment completion rates. In Malawi, patients can choose a guardian to supervise treatment,

typically a member of the immediate family or a close family relative. In response to the challenges of HIV-related TB, the Ugandan Ministry of Health is developing its national strategy, including community care for AIDS and TB patients. In a pilot district, the support of community members has resulted in high rates of TB-treatment completion.

Since 1998, the "Community TB Care in Africa" project, jointly sponsored by WHO, the CDC, and the United States Agency for International Development (USAID), has supported the implementation of eight district-based projects in six countries in sub-Saharan Africa. The initiative has also evaluated the acceptability, effectiveness, cost-effectiveness, and affordability of community contribution to TB care as part of NTP activities. In the case of projects in which the community organization involved is not an HIV/AIDS care organization, preliminary data generally show high rates of treatment success. Focus group discussions have shown that community involvement is acceptable to the patients, their families, and health-care providers. Provisional cost data show that the new strategies involving community contributions to health care are generally lower in cost to patients and families—and more cost-effective—than previous strategies that offered care through health facilities only.

Mixed lessons are to be learned from three of the projects, in which the community organization involved is an HIV/AIDS care organization. So far, two have been successful in providing effective TB care on a small scale. The challenge lies in scaling up. Progress has been slow, however, in incorporating TB care into community HIV/AIDS care, such as that provided through The AIDS Support Organization (TASO) in a high-density population in Kampala, Uganda. The stigma attached to HIV/AIDS has prevented community mobilization from tackling the challenges of TB. More experience with community HIV/AIDS care organizations in different settings is needed to fully understand the challenges of linked TB-HIV/AIDS care.

6. DOTS and Antiretrovirals: Complementary Components

Due to growing attention and political commitment to directly address the global AIDS pandemic, the initiation of antiretroviral therapies in poor countries, including those countries in sub-Saharan Africa, now seems possible. Recent reports suggest that ARV therapy could be managed effectively using the DOTS strategy as a model;[40] pilot projects are currently under way. Close collaboration between TB and HIV programmes in sub-Saharan Africa is essential for the following reasons:

- The recent massive and rapid increase of TB incidence in Africa is largely due to the spread of HIV/AIDS;
- The immediate response to this crisis must be to accelerate DOTS coverage;
- Widespread use must be made of preventive therapy and antiretrovirals; and
- The principles underpinning the DOTS strategy are equally applicable to ARV delivery.

6.1 INTRODUCING HAART IN HAITI

Haiti is the poorest country in the Western Hemisphere and one of the poorest in the world.[41] Per capita GNP is approximately $400. Unemployment exceeds 70 percent; fewer than one in 50 Haitians has steady wage employment.[42] So it is no coincidence that Haiti is also the Western Hemisphere's most heavily HIV-burdened country.[43] In 1999, the Joint United Nations Programme on HIV/AIDS (UNAIDS) reported a national HIV seroprevalence of five percent among Haitian women attending antenatal clinics—and a prevalence twice as high as that in urban slums.[44] HIV is considered the chief contributor to premature adult death in Haiti,[45] and the latest estimates of Haitian life expectancy at birth are 47.5 years for men and 49.2 years for women.

For these reasons, the Boston-based charity Partners In Health (PIH) launched its "HIV Equity Initiative" with its Haitian sister organization. The modest therapeutic efforts that have been initiated in Haiti have been rigorous when compared to clinics in other poor, rural regions of the developing world. Shortly after the publication of the ACTG-076 trial, which for the first time showed that providing the antiretroviral drug zidovudine (AZT) to pregnant women reduced the risk of mother-to-child transmission of HIV,[46] health-care workers in the initiative began offering AZT to pregnant Haitian women in order to prevent mother-to-child transmission. After AZT was made available free of charge, over 90 percent of Haitian

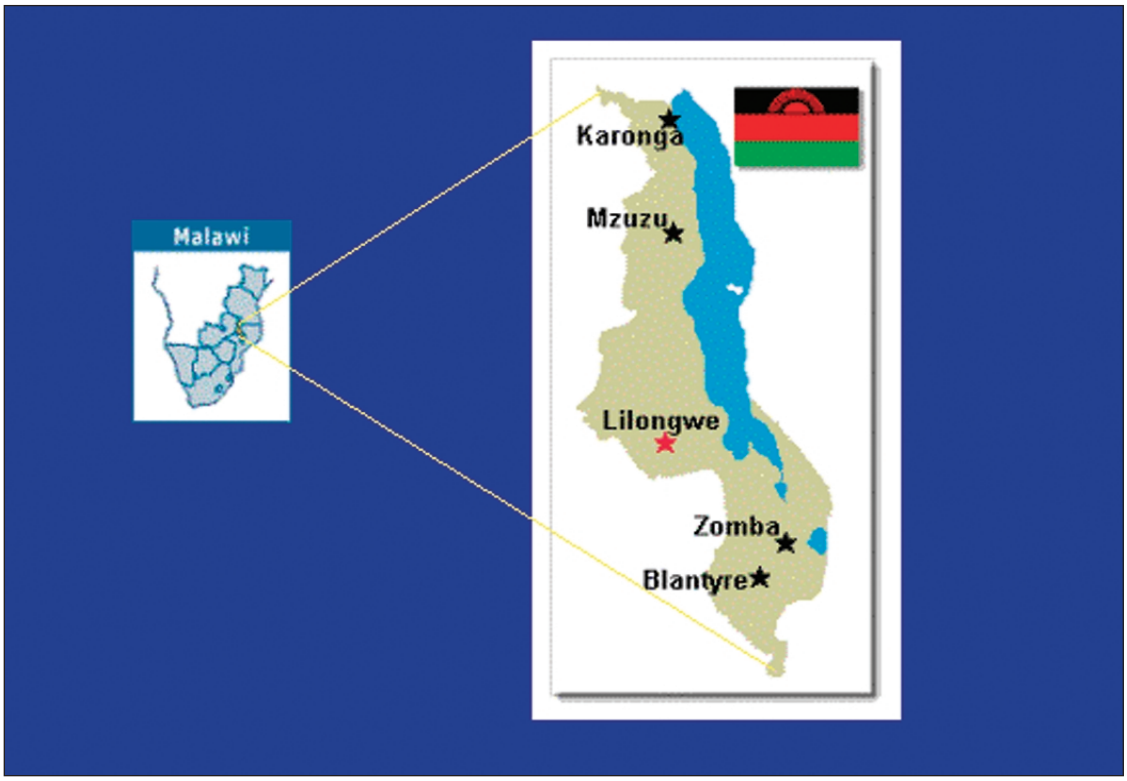
women who were offered HIV testing accepted it. Dramatic declines in vertical HIV transmission ensued.

In 1997, PIH began offering prophylaxis with a three-drug regimen (usually AZT, lamivudine, and efavarenz) post-exposure to Haitian victims of rape or professional injury.[47] Beginning in late 1998, a small number of patients with longstanding HIV who no longer responded to syndromic treatment of opportunistic infections were offered HAART. In all cases in which therapy was offered, health-care workers from the DOTS programme played an integral role in supporting patients through daily visits providing DOT-HAART.[48]

6.2 PLANNING FOR HAART IN MALAWI

In **Malawi**, the National TB Programme was developed with clear objectives to reduce mortality, morbidity, and transmission of TB. The programme's strategy was to provide short-course chemotherapy, at least to all patients with active TB. The Malawi NTP has set targets of a 70 percent case detection rate and 75 percent cure rate for new TB patients. The NTP is based on WHO's recommended DOTS strategy and operates in accordance with WHO's framework for effective TB control.

Map of Malawi



Based on the NTP success, Malawi has developed a plan for piloting HAART as part of the essential package of HIV/AIDS care. The plan includes the following elements:

- increased investment in the NTP structure;
- case detection by intensified passive case finding of HIV-infected persons through voluntary counselling and testing; and
- provision of standardized triple therapy under direct observation to HIV-positive symptomatic patients.

The programme will secure regular supply of drugs, and treatment results will be monitored, recorded, and regularly reported. The goals are to provide lifelong treatment and to ensure over 90 percent drug adherence rates.

7. Developing a Joint TB-HIV Strategy

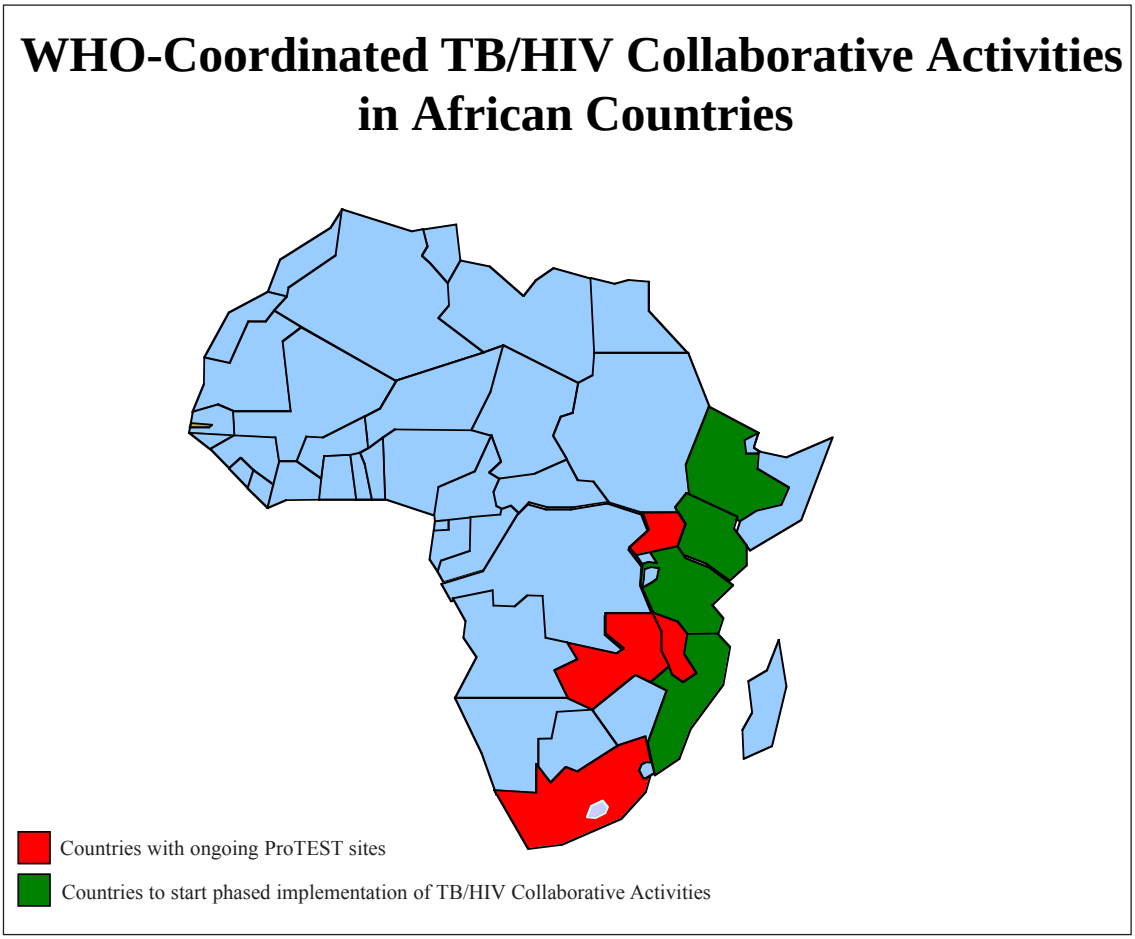
7.1 PROTEST

The World Health Organization is facilitating operational research through the ProTEST initiative, which aims to promote voluntary HIV testing for a more coherent response to TB in high HIV-prevalence settings. In collaboration with UNAIDS, projects are currently underway in South Africa, Zambia, and Malawi. A project has also recently started in Uganda. These projects forge links between different service providers, train staff, and strengthen the provision of services. These services include voluntary counselling and testing (VCT), isoniazid preventative therapy (IPT), and treatment of common HIV-related diseases, including TB.

At least 90 percent of the 28 million people living with HIV in sub-Saharan Africa do not know they are HIV-positive. More people will likely choose to be tested for HIV if, in the case of testing positive, they can access services for the prevention and care of common HIV-related diseases such as TB. Therefore, VCT for HIV can be an entry point for access to a range of HIV/AIDS- and TB-prevention and care interventions.

In **South Africa**, four ProTEST TB-HIV pilot districts were created in 1999. Initial activities included establishing a District HIV/AIDS/Sexually Transmitted Infections/TB Committee; conducting a baseline assessment of services; and training counsellors and health-care workers. The formation of a district committee involving key stakeholders has led to the strengthening of both TB and HIV/AIDS services. The number of people tested for HIV and the proportion of those tested who actually receive test results are increasing with rapid testing. One TB-HIV training district has been established in each of the nine South African provinces in 2001; further expansion is planned to cover all districts in the country by 2005.

In **Zambia**, the ProTEST project started in October 1999 in an urban health centre in Lusaka. From January to December 2000, 24 percent of the 2,855 people tested were HIV-positive. All of those recruited into the project were screened for TB, and all symptomatic patients were offered IPT. But the IPT adherence rate was low: 30 percent of patients dropped out after the first visit. The main reasons were disclosure of HIV status, inadequate information supplied to the patients, and hunger. Home-based care and household



counselling are currently being used to address these problems. The next stage of the Zambian ProTEST project includes the development of a site attached to a clinic, providing antiretroviral therapy to prevent maternal-to-child-transmission of HIV.

In **Malawi**, two ProTEST voluntary counselling and testing centres were created, helping catalyse collaboration between the National TB Programme and the National Aids Control Programme. In **Uganda**, the ProTEST project began in January 2001 with a pilot programme run by a local NGO (which provides voluntary counselling and testing), by the National TB and Leprosy Programme, and by the CDC. In the first three months of the project, 658 seropositive patients were screened and 9 percent had active TB. Those meeting the criteria now receive isoniazid tablets at enrolment and are asked to return after 30 days. Thereafter, they visit every two months to complete a nine-month course of treatment. Both patients and counsellors report being satisfied with the programme.

7.2 THE GLOBAL AIDS PROGRAMME

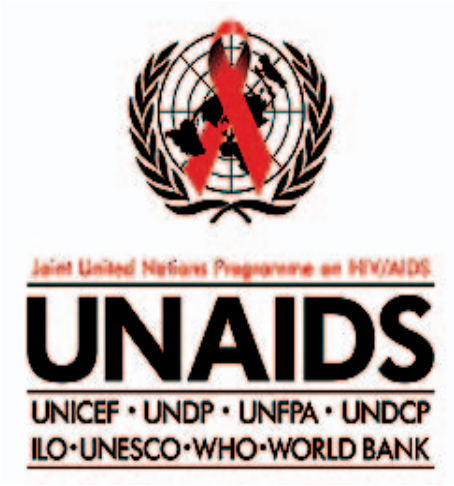
The Global AIDS Programme (GAP), coordinated by USAID, is a collaborative effort formed in 1999 that includes the CDC, the American Red Cross, and the U.S. Health Resources and Services Administration. GAP addresses four key areas:

1. Primary HIV/AIDS prevention, including sexual, mother-to-child and blood-borne transmission;
2. HIV care and support, including community- and home-based care for HIV, sexually transmitted infections (STIs), TB, and other HIV-related infections;
3. Caring for children affected by AIDS; and
4. Surveillance and infrastructure development to support management of National AIDS programmes.

In the future, GAP aims to develop pilot projects in selected countries and to scale up programmes that would include voluntary counselling and testing, isoniazid preventive therapy, and prevention of mother-to-child transmission of HIV in the initial GAP countries.

The HIV prevention and control environment is changing rapidly. The arrival of rapid HIV test kits, which allow accurate determination of HIV antibodies with no need for sophisticated technology, will stimulate a strong demand for HIV care packages, including preventive therapy. Therefore, it is imperative to develop guidelines for National AIDS Programmes, NGOs, and international agencies; these guidelines should include information on prerequisites for implementation, monitoring, evaluation, and training.

7.3 UNAIDS PERSPECTIVES ON TB CONTROL[49]



In 1996, aghast at the havoc being wreaked by the burgeoning HIV/AIDS pandemic, the United Nations created UNAIDS (the Joint United Nations Programme on HIV/AIDS). Today, UNAIDS has seven United Nations co-sponsors: the United Nations Children's Fund (UNICEF), the U.N. Development Programme (UNDP), the U.N. Population Fund (UNFPA), the U.N. Drug Control Programme (UNDCP), the U.N. Education, Science and Culture Organization (UNESCO), WHO, and the World Bank. The global mission of UNAIDS is to lead, strengthen, and support an expanded response to the HIV/AIDS epidemic.

Participants in the first meeting of the Stop TB Global TB-HIV Working Group, which took place in Geneva in April 2001, discussed the development of a strategic framework for addressing TB-HIV co-infection. This framework has been published[50] and reflects principles and conclusions from this first working group meeting:

- overlapping TB and HIV epidemics justify joint TB-HIV programme activities;
- health-service interventions to decrease the burden of TB should be part of the overall response to HIV/AIDS in high HIV-prevalence populations;
- expanded scope of the new strategy for TB control in high HIV-prevalence populations should comprise both interventions against TB (for example, intensified case-finding and cure, and TB-preventive treatment) and interventions against HIV (for example, condoms, STI treatment, safe injecting drug use, and HAART); these latter interventions should also be considered as indirect interventions against TB;

- prioritisation according to rational and explicit criteria is necessary to develop and deliver the essential package of HIV/AIDS care and prevention, including TB care and prevention, even as efforts continue to generate more resources.

8. The Costs of Responding to HIV-Related TB

This plan provides preliminary costs estimates of $642 million over the 2001–2005 period as shown on Table 3.1 below—for voluntary counselling and testing (VCT) for HIV, for TB screening and testing, and for INH preventive therapy for co-infected patients. Table 3.1 also notes various interventions without projecting any associated cost. Costs for these cannot yet be adequately estimated. Yet they are important components of the response to TB and HIV, and they warrant careful assessment in the future.

Dr. Arachu Castro, Partners in Health

A peasant at his home in rural Haiti.

Controlling TB in high HIV-prevalence areas will require, first of all, a highly effective DOTS programme. The DOTS expansion plans include cost estimates for building and sustaining successful programmes in all high-burden countries, including countries with high HIV-infection rates. Once DOTS programmes are well established in high HIV-prevalence countries, they will likely need to be supplemented with active case-finding initiatives for co-infected patients.

More immediately, however, expanding and building on the success of ProTEST projects will mean providing voluntary counselling and HIV testing in high-risk areas, TB testing for HIV-positive patients, and TB-preventive therapy in co-infected patients without active disease. Further, it will mean well-organized support services to enable patients to complete preventive therapy.

Ultimately, it will also mean highly active antiretroviral therapy for patients. Joint TB/HIV planning activities anticipate pilot projects to administer HAART that could begin as early as 2004.

For now, we have only preliminary cost data on some of these interventions and no reliable data on others. Preliminary estimates were used to project costs for this plan, and they will need revision as more cost data is available and as plans are revised based on the results of pilot programmes.

9. Conclusions

The overlapping epidemics of TB and HIV/AIDS have had a severe, adverse impact on the macroeconomic development of high HIV-prevalence countries, particularly in sub-Saharan Africa. Life expectancy has declined, child deaths have increased, and economic growth has been stunted. The co-epidemic places a heavy burden on the public health services.

A comprehensive global AIDS strategy needs to incorporate the prevention and treatment of TB. The expanded scope of the new strategy for TB control in high HIV-prevalence populations comprises interventions against tuberculosis (intensified case-finding and cure, and TB-preventive treatment) and interventions against HIV (and therefore, indirectly, against tuberculosis); these interventions include, for example, condoms, STI treatment, safe-injecting drug use, and highly active antiretroviral therapy.

The provision of effective TB treatment will both prolong the length and improve the quality of the lives of people with HIV-related TB and reduce the spread of TB in the community. Close collaboration between TB and HIV/AIDS programmes is vital to delivering this expanded strategy. Ongoing TB/HIV operational collaboration and projects, such as ProTEST, will inform the design of an effective package of prevention and care for co-infected patients. Phased implementation of these interventions in countries severely hit by these overlapping epidemics offer an opportunity to reverse the grim epidemiological trends of recent years. Successful collaborative projects could then be rapidly scaled up as integral components of the general health service in these countries.

10. Economic and Financial Overview

Table 3.1: Estimated Costs for Management of TB-HIV Co-Infected Patients in Low- and Middle-Income Countries, 2001–2005 ($ millions)

Component	5-Year Cost	Current Resources			Financing Gap
		Government	External	Subtotal	
All Aspects of TB-HIV Control	**630**	**30**	**6**	**36**	**594**
• Voluntary Counselling and HIV Testing (1)	290				
• TB Screening, Testing and Programme Costs (2)	330				
• INH Preventive therapy drug cost (3)	10				
• Cotrimoxazole Preventive Therapy (4)	n.a.				
• Further DOTS expansion to co-infected patients (5)	0				
• Treatment of Opportunistic Infections (6)	n.a.				
• HAART (7)	n.a.				
TB-HIV Working Group	12	0	2	2	10
Total	**642**	**30**	**8**	**38**	**604**

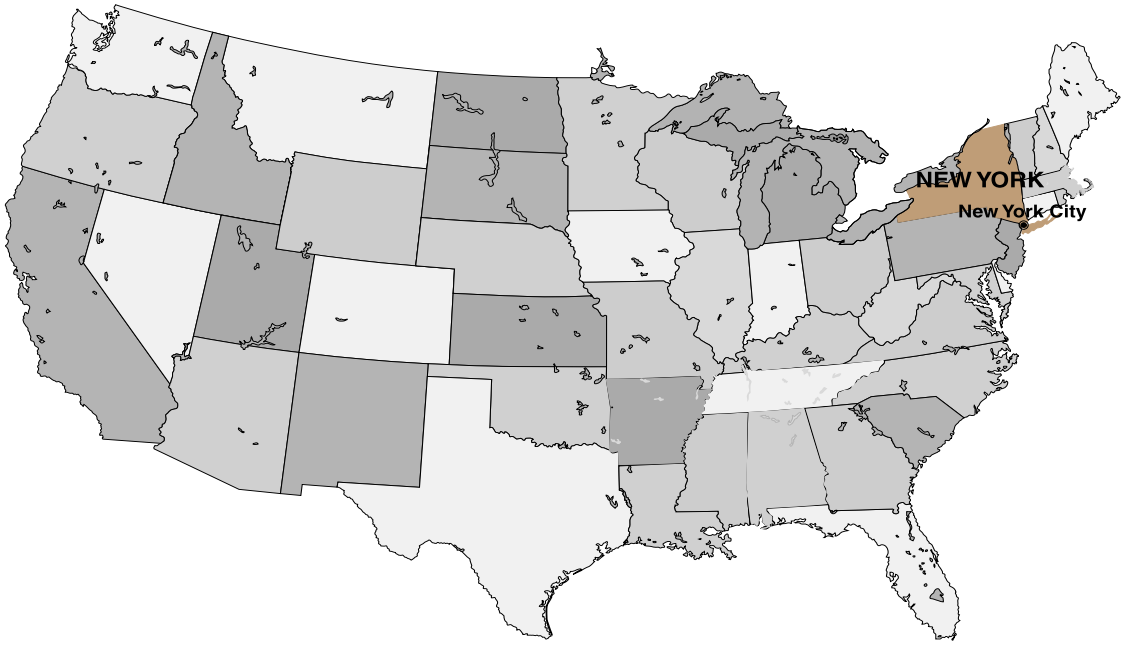
Notes

1. Voluntary Counselling and Testing–This plan projects that TB-HIV initiatives will offer TB testing and screening for roughly 3.3 million HIV-positive patients in 12 sub-Saharan countries – eight countries where ProTEST projects are planned and 4 additional high HIV-prevalence countries. To reach these HIV-positive patients, the programmes will offer voluntary HIV testing and counselling to some 28 million people, of whom roughly 3.3 million will be HIV-positive (12 percent). This cost estimate is just over $10 per person for counselling and HIV testing.
2. TB Testing and Screening–will be offered to a projected 3.3 million HIV-positive patients. The $330 million is an estimate of $100 per patient. This projection assumes that roughly 50% of HIV-positive patients will be co-infected with TB (as evidence from ProTEST projects has shown). These co-infected patients—approximately 1.6 million of them—would then be expected to receive preventive therapy.
3. INH Preventive Therapy–Estimated costs for INH preventive therapy for some 1.6 million co-infected patients in 2001–2005. The projected INH drug costs—roughly $2.20 per patient ($3.5 million total)—are relatively low. Adverse side effects and complications are likely in approximately 6 percent of patients. Treatment and drug costs to deal with adverse side effects are estimated for some at roughly $68 per person for some 96,000 patients.
4. Cotrimoxazole is increasingly being used to prevent bacterial and parasitological complications of HIV. Estimates on its cost and on volumes of patients will be built into future revisions of this plan.

5. DOTS Expansion–must successfully reach and treat co-infected patients. The costs for this expansion are built into the DOTS Expansion portion of this plan. It is noted here because of its importance and because further developments may require expansion in high HIV-prevalence environments beyond what is contemplated in this plan.
6. There is as yet limited data available on the cost of treating opportunistic infections in HIV-positive TB patients.
7. HAART–Noted to highlight the need and for future cost projections, once plans are in place and decisions are made on how to administer these programmes and who will be responsible for them.

Multidrug-Resistant TB: A Growing Threat

1. You Think It Can't Happen Here?



Dateline: New York City, 1991

Surprisingly to many, New York City's TB rates began to rise towards the end of the 1970s,[1] accelerating dramatically in the early 1990s. These two trends were causally linked. The dismantling of the city's TB-control infrastructure had meant that fewer than half of the patients who entered treatment were cured. Many of these inadequately treated individuals were sick with drug-resistant TB strains. Due to inadequate infection control in many of the city's hospital wards,[2] these wards became "hot spots" for MDR-TB transmission—especially for HIV-positive patients. This "inexplicable" TB resurgence in the

midst of affluent New York City was later found to have been catalysed by immigrants from high TB-prevalence countries. They not only fuelled the flame of active cases, they later became the group in which those cases were concentrated.

By 1991, researchers had documented several New York hospital-based TB outbreaks.[3] Their data showed that, compared with 1983, there was a 130 percent rise in the incidence of resistant TB strains among patients never previously treated.[4] Based on this information, governmental support, especially in the form of federal aid for the city's municipal TB-control programme, began to increase. And the focus switched: whereas virtually no TB patients had received DOT in 1992, by 1998, 72 percent of eligible patients had.[5, 6] Intensive TB case management also became an integral part of the strategy. Quarterly meetings between programme directors and staff reviewed every patient's treatment, outcome, and contact investigations results. Everyone—from director to outreach worker—bore the personal responsibility to see to it that patients complied with, and completed, treatment.

Compared with the fewer than 50 percent of New York City's TB patients who completed treatment in the late 1980s, over 90 percent of TB patients do so today.[7] The city used both "the carrot and the stick", even invoking "last resort" penalties as unequivocal as detention in locked hospital wards to ensure that individuals completed treatment. This "all out" approach worked, even among difficult-to-reach patients, including drug users, alcoholics, and homeless.[8] The programme also collaborated with New York State's TB-control authorities to promote CDC TB-control guidelines and provide consultative services. Documented hospital-based outbreaks were monitored closely for adherence to recommended treatment regimens and infection-control practices.

Between 1992 and 1999, an "all out" counterattack brought the number of TB cases in New York City down by 62 percent while MDR-TB plummeted by an astonishing 93 percent.

The results were remarkable. Between 1992 and 1999, the number of TB cases in New York City declined by 62 percent, while the incidence of MDR-TB plummeted by an astonishing 93 percent.[9] Cases of MDR-TB, once almost 12 percent of the total TB cases seen in New York City, dropped to only 2.1 percent of all cases by 1999. Despite this improvement, New York City's case rate still is more than three times the national rate. Most of today's carriers in New York are immigrants born outside the United States, especially those from countries with high TB rates such as China, the Dominican Republic, Haiti, Ecquador, and India.[10]

Although New York City is a model for dramatic turnaround when political will and leadership are brought to bear on pressing public health problems, this tale should also serve as a warning of the dire consequences of abandoning public health infrastructure, even in otherwise affluent settings. Ultimately, there is an important lesson to be learned about the costs of resurgent TB. Especially when multidrug-resistant strains are added to the equation, the costs of containment—and the costs of failure—are staggering, as New York's experience showed. Not only that: epidemics of drug-resistant TB can emerge in a frighteningly short time span.

1.1 MDR-TB: A MAN-MADE HEALTH THREAT

Seen from the scientific perspective, modern medicine's role is to cure disease. It frequently does so by developing drugs that kill microscopic pathogens. However, from the pathogen's point of view, it's all about survival. To paraphrase Nietzsche, whatever does not kill them, makes them stronger. Thus, at the "provocation" of science, pathogens mutate so that they are more resistant to the drugs used to annihilate them. However, if the drugs used are unable to kill all the disease-causing organisms, the patient with the organism—and others the patient may infect—risks becoming incurable. In effect, this resultant strain of the disease is *man-made*.[11]

With the TB bacillus, the risk of producing man-made organisms that do not respond to drugs is particularly high. There are several reasons for this.[12] First, soon after the discovery of anti-TB drug treatment in the 1940s, physicians realized that using only a single drug would actually promote resistant TB strains. So physicians began using several drugs at once. Combination therapy reduced the duration of treatment, but increased the likelihood of flawed or interrupted compliance.

To reduce this risk in India, health workers developed the strategy of directly observed therapy—DOT—in the late 1950s, which required someone to actually observe the patient taking each dose of medication. Some three decades later, WHO announced its DOTS strategy. Their standardized approach simplified drug supply and permitted inexpensive, effective management, even in resource-poor countries where health-care infrastructure was scant or lacking.

Dr. Anuchu Castro, Partners in Health

MDR-TB patient in Siberia receiving his daily medication under nurse supervision.

Because they are inexpensive, reproducible, and relatively easy to supervise on a local level, DOTS programmes allow TB officials to direct their resources efficiently to the areas with the highest caseloads and to maintain high rates of cure. The emergence of national TB-control strategies based on DOTS has provided a crucial tool in slowing the generation of drug-resistant TB.[13]

Still, with increasing frequency over the last 20 years, physicians have been confronted with mutant *M. tuberculosis* strains that do not respond to treatment with the standard combination of drugs. Such strains must be treated with anti-TB drugs that are more toxic, less potent, more expensive, and less well tolerated than rifampicin and isoniazid, the most powerful medications. Administered in higher concentrations and over longer periods of time than first-line drugs, these so-called "second-line" antimicrobials often cause serious side

effects. During the late 1980s and early 1990s, outbreaks of MDR-TB in North America and Europe killed over 80 percent of those who contracted the disease.[14] Although these much-publicized outbreaks were ultimately contained through rigorous and costly public health-care measures, they were only the tip of the iceberg, as is now clear.

During the last ten years, MDR-TB has had a sobering impact on national TB-control programmes. In 1997, a WHO study found drug-resistant strains of TB in all but one of 35 countries surveyed.[15] For some "hot spots", at least 20 percent of all registered TB cases were due to multidrug-resistant strains. Some have estimated that between 185,000 and 415,000 MDR-TB cases might be expected, based on WHO data.[16] Another review found reports of patients with drug-resistant TB in over 100 countries.[17]

In developing countries such as Peru and Viet Nam, DOTS-based programmes have had impressive results. But since the backbone of this therapy is the combination of rifampicin and isoniazid, patients whose TB strains are resistant to this standard combination will not be cured. Without effective treatment, those infected will continue to transmit drug-resistant bacteria, making short-course chemotherapy futile for some proportion of those sick with TB.

Epidemics of MDR-TB can spread swiftly from city to city,[18] country to country,[19] even bridging continents.[20] Thus, success against what is, for now, a relatively small component of the global TB epidemic will require new and effective strategies.

1.2 MDR-TB: A CLEAR AND PRESENT DANGER

There are at least four interrelated reasons why existing reservoirs of MDR-TB present new and worrisome problems for TB-control programmes:

1. Standardized short-course chemotherapy does not yield acceptable cure rates for MDR-TB.
2. Effective therapy for MDR-TB is currently more expensive than short-course chemotherapy for pan-susceptible TB.
3. Without effective treatment, transmission of MDR-TB and drug-resistant TB will continue—indeed, the rates of spreading may increase.
4. Most ominously, MDR-TB threatens the potential salutary impact of DOTS programmes.

1.2.1 STANDARDIZED SHORT-COURSE CHEMOTHERAPY DOES NOT CURE MDR-TB

As observed most recently and dramatically in the former Soviet Union,[21] patients ill with MDR-TB and other polyresistant strains do not respond to short-course chemotherapy, even if the patient is fully supervised to ensure compliance.[22] Another recent six-country study showed conclusively that short-course chemotherapy "is not an adequate treatment for some patients with drug-resistant TB."[23] That review was the first ever conducted under routine programme conditions to assess the impact of anti-TB drug resistance on the outcome of directly observed short-course chemotherapy. Patients with MDR-TB were more likely to fail

treatment and to die than were patients with drug-susceptible TB strains. The greater the number of drugs to which the TB strain was resistant, the higher the risk that treatment would fail.

1.2.2 EFFECTIVE MDR-TB THERAPY COSTS MORE THAN SHORT-COURSE CHEMOTHERAPY

Treatment of patients with MDR-TB takes longer than treatment of patients with drug-susceptible TB. Treatment of MDR-TB is also considerably more complicated, and currently more expensive. However, the absolute cost of any treatment programme is considerably lower in developing-country settings. By way of comparison:

- in 1990, the cost to treat a single New York City patient with drug-susceptible TB was approximately $20,000;[24] while
- in 2000, the total costs of treatment for a patient in China with drug-susceptible TB was less than $200.[25]

Estimates of the cost per patient for MDR-TB therapy in developed countries have been in the tens of thousands.[26] Until recently, in resource-poor countries, such treatment had been deemed "prohibitively expensive."[27]

Because rifampicin and isoniazid are not useful in the treatment of MDR-TB, the standard of care for MDR-TB therapy must be longer—at least 18 months and often as long as 24 months—as opposed to "only" six to eight months for patients with non-resistant TB. As mentioned earlier, MDR-TB therapy requires the use of "second-line" anti-TB drugs, which often produce adverse side effects. These can be managed successfully through measures such as social support, but infrastructure requirements to provide such support are greater for MDR-TB therapies than for short-course chemotherapy.[28]

The Green Light Committee Based on a model developed for the distribution of a meningitis vaccine, WHO and other partner institutions decided to establish the Green Light Committee (GLC), which enables a pooled procurement mechanism to buy second-line MDR-TB drugs. In discussions with drug manufacturers, those manufacturers agreed to sell second-line MDR-TB drugs only with approval from the GLC. When countries submit applications, a scientific panel evaluates their projects and determines if they have the technical capacity to take the treatment of MDR-TB forward. If the applicant countries do not have adequate capacity, the GLC will provide it and will monitor the country's progress over time. Additionally, WHO has provided public recognition to participating drug manufacturers.

From the research-based pharmaceutical companies the GLC obtained a concessional discount price of up to 95 percent off the standard price of the drugs. One of the companies even proposed providing the drugs for free; but GLC members decided the more strategic approach was to obtain the drugs at a concessional price, and allow generic manufacturers to match or better the price. Generic and research-based drug manufacturers agreed to sell their drugs only to GLC-approved projects.

Finally, the goals to which the GLC aspired have been achieved: the cost of MDR-TB drugs has decreased, and access to these drugs is restricted to good-quality programmes.

1.2.3 WITHOUT EFFECTIVE THERAPY, MDR-TB IS SPREADING UNCHECKED

In the absence of effective therapy, infectious patients with MDR-TB continue to spread their disease, producing new infections with MDR-TB strains. A growing body of epidemiological evidence indicates that drug-resistant TB and MDR-TB are passed on through institutions, communities, and even among people whose immune systems have not been compromised by HIV, malnutrition, or other factors.[29] Hospital-based outbreaks of MDR-TB have been widely reported, as have prison epidemics.[30]

The ongoing WHO/IUATLD global surveillance project confirms that primary infection with drug-resistant strains continues in over 54 geographical settings.[31] In New York, 80 percent of all MDR-TB index cases could ultimately be traced to jails and prisons.[32] Molecular biologists subsequently determined that the New York MDR-TB strains had spread not only into New York's public hospitals and homeless shelters, but all across the United States as well.[33]

The spectre of MDR-TB has caused substantial concern in industrialized countries over the last decade, particularly when MDR-TB and HIV have occurred simultaneously. Transmission patterns of MDR-TB in the Lombardy region of **Italy** typify the trend. The first harbinger of MDR-TB in Lombardy was a large hospital-based outbreak—the largest in Western Europe to date, with 116 cases of MDR-TB. The most common infecting strain was resistant to seven drugs and was isolated from 116 HIV-infected inpatients in two large hospitals in Milan.[34]

In South Africa, an estimated 42.7 percent of TB patients in 1998 were also infected with HIV.

Many factors contributed to the spread of MDR-TB in the two hospitals. As in New York during the 1980s, infection control measures were inadequate. Infectious-disease wards were overcrowded, a problem compounded by Italy's long average duration of hospital stay (31.2 days). Furthermore, continuity of care was inadequate, with patients—many of whom were TB-HIV co-infected drug users—moving frequently between health-care services, and therefore receiving only erratic therapy.

For developing countries, the spectre of HIV and MDR-TB co-epidemics looms even larger. In **South Africa**, the wealthiest country in sub-Saharan Africa, TB case notifications have risen rapidly, from 175 cases per 100,000 population in 1986 to 326 cases per 100,000 population in 1998. The proportion of new TB patients with MDR-TB in 1998 was between one and two percent, and among previously treated patients, between four and eight percent.[35] This suggests that more than 2,500 new cases of MDR-TB each year can be expected. According to nationwide estimates, 42.7 percent of TB patients in 1998 were also infected with HIV; in some provinces, the percentage was more than 50 percent.[36] HIV is now a major factor in sub-Saharan Africa's rising rates of clinical TB.[37] Epidemiologists have documented hospital-based and community-based transmission of MDR-TB.[38]

Because effective therapy programmes are still unavailable to millions of patients ill with TB and MDR-TB, those patients remain untreated—or ineffectively treated—and their disease runs its course. Patients living for years with infectious drug-resistant TB not only endure additional suffering themselves; they also hasten the spread of MDR-TB throughout the population.

1.2.4 MDR-TB THREATENS THE POTENTIAL IMPACT OF DOTS PROGRAMMES

Because short-course chemotherapy regimens cannot cure MDR-TB patients, anti-TB drug resistance threatens to undermine DOTS programmes. Identification of the telltale signs of "programmes under threat" is urgently needed. For the moment, though, poor outcomes under well-implemented DOTS programmes may be one sign that a programme is being undermined by MDR-TB.[39]

In certain regions, DOTS-type programmes have achieved poor outcomes wherever a large proportion of patients already have drug-resistant TB. The result of applying supervised short-course chemotherapy in such settings is that only 60 percent or less of patients are cured—significantly less than the 85 percent target.[40]

An effective global TB-control strategy must include efficacious therapy for patients already sick with drug-resistant TB.

What is the effect of simultaneously decreasing death rates due to improved treatment compliance, counteracted by decreasing cure rates due to growing drug resistance? Infections will increase, as the sick survive and continue to spread resistant strains. In all three settings previously mentioned—Italy, South Africa, and Russia— cure rates for drug-susceptible TB remain high, but drop as low as five percent for MDR-TB—even though death rates decrease. With such scenarios, the future looks bleak, because strains of drug-resistant TB will account for an ever-growing proportion of new infections.

Thus, there is growing consensus that an effective global TB-control strategy must include efficacious therapy for patients already sick with MDR-TB.

1.3 MDR-TB THERAPY

The example of MDR-TB in New York City described at the outset of this chapter demonstrates that MDR-TB can be contained in developed countries, given adequate political will and resources. But what of less-developed countries? The experience of the Republic of Korea may provide an example.

In 1997, the Korean NTP introduced a re-treatment programme for patients with drug-resistant tuberculosis. Many of the patients had failed initial therapy with conventional regimens that should have cured drug-susceptible TB. The NTP used four re-treatment regimens, basing their selection on drug-susceptibility test (DST) results and the previous treatment history of each individual patient.

The introduction of short-course chemotherapy for initial treatment in the early 1980s and rigorous re-treatment regimens containing rifampicin and pyrazinamide with reinforced case-management increased the overall cure rate in Korea to 80 percent by the 1990s. The rate of new TB cases dropped from 254.7 cases per 100,000 population in 1981 to almost half that by 1991, and then further to 57.3 cases per 100,000 population in 1997.[41]

The Korean NTP, then, has had success in fighting the emergence of drug resistance through the use of short-course chemotherapy and effective MDR-TB therapy. Patients treated by the national programme have showed progressively decreasing proportions of drug resistance: 25 percent in 1990 and 12 percent in a 1998 survey.[42] In the short term, the introduction of rifampicin coincided with an increase in the proportion of TB patients with resistant strains: the rate of MDR-TB increased from 1.7 to 8.5 cases per 100,000 population from 1980 to 1985.[43] However, in two nationwide surveys, MDR-TB prevalence fell from 5.3 percent of all patients in 1995[44] to 2.7 percent by 1998. But while the national cure rate has currently reached 82 percent, cure rates for private-sector patients has been as low as 62 percent.[45] Clearly, the private sector is still creating a reservoir of drug-resistant strains.

Scrupulous treatment of patients can reduce drug resistance in both relative and absolute terms. But without strict control, the use of second-line drugs to treat MDR-TB could be disastrous—producing MDR-TB-Plus "super-bug" strains resistant to all existing drugs.

The Korean example, like that of New York City, indicates that scrupulous treatment of MDR-TB patients can reduce drug resistance in both relative and absolute terms. But second-line regimens for drug-resistant TB must be used correctly. If the efficacy of these drugs is lost to the development of further drug resistance, no effective alternatives may be left available. Even in settings with effective TB-control programmes, the introduction of second-line drugs without strict control could be disastrous.[46] In places that currently lack sound TB-control systems, the introduction of second-line drugs will likely yield "MDR-TB-Plus"—strains of TB that are resistant to all available first- and second-line drugs.[47] The GLC for second-line drugs could play an important role in ensuring rational use, thus preventing the emergence of these "super-bugs".

However, the emergence of MDR-TB-Plus strains can also be avoided by strictly supervising therapy regimens for MDR-TB. Such oversight is thus a cornerstone of the MDR-TB therapy strategy called "DOTS-Plus."

2. Introducing DOTS-Plus

Peru. In August 1996, an MDR-TB treatment project was initiated in three districts of northern Lima, Peru. Patients identified as treatment failures on an NTP regimen at Ministry of Health centres were referred to the project and evaluated. Their sputum samples were sent to the United States for susceptibility testing to ten drugs at the

Dr. Arachu Castro, Partners in Health

Siblings in Lima, Peru, who recently lost a mother to untreated MDR-TB.

Massachusetts State Laboratory Institute (MSLI) in Boston. Based on DST results, patients found to have MDR-TB were treated with individualized regimens tailored to their specific resistance pattern.[48]

Today, local health-care providers and community members—trained by programme personnel in a variety of specialized clinical and programme support tasks—continue to implement the treatment strategy set up in 1996, and to manage side effects. While the initial clinical input involves transnational collaboration, training and other forms of community-building capacity continue to be central to sustaining the programme.

Under this programme, patients are initially placed on a provisional treatment regimen until DST results are available. This provisional regimen is based upon the patient's individual TB-treatment history and any available DST results. It includes at least four—and as many as eight—drugs to which the patient is likely to be susceptible. Once up-to-date DST results are obtained, an individualized treatment regimen is constructed and administered daily. Patients are monitored monthly by smear microscopy and culture. Patients receive an injectable drug for the initial phase of treatment, until six to eight months of negative cultures have been obtained. The remaining drugs are continued for a total of 18 to 24 months.

Results from a group of 50 patients show that 100 percent became smear- and culture-negative, and more than 85 percent remained that way near the end of 18–24 months of chemotherapy.[49] Thus, a community-based programme for the treatment of MDR-TB is not only feasible, but also achieves WHO-based target cure rates for TB programmes.

In 1997, the Peruvian NTP introduced a nationwide treatment programme using standardized second-line drug regimens for patients who remained or reverted to smear-positive status during a fully supervised re-treatment regimen with first-line drugs. Preliminary results suggest that standardization of second-line drugs within a strong national TB programme can be feasible and cost-effective.

Extending MDR-TB treatment to resource-poor settings In the past, the treatment of MDR-TB was considered too costly for resource-poor settings such as Lima. But more recently, in response to growing consensus regarding the urgent need to confront this problem, DOTS-based strategies have been advanced for the treatment and control of MDR-TB.[50]

In some settings, the need for therapy-based strategies is especially urgent. Until effective therapy for patients with drug-resistant TB is introduced into crowded institutions such as prisons, these settings will provide breeding ground for transmission of new drug-resistant infections. Given the undisputed efficacy of DOTS in settings in which resistance to first-line drugs is rare, "DOTS-Plus" projects—complementary DOTS-based strategies to contain MDR-TB—are currently under development.[51] Through its Working Group on DOTS-Plus for MDR-TB, WHO has issued preliminary protocols that will be tested in settings where MDR-TB already accounts for a significant proportion of sickness and death.[52]

"DOTS-Plus" projects—complementary DOTS-based strategies to contain MDR-TB—are currently under development.

Two DOTS-Plus models have been introduced: one based on individualized treatment regimens, the other on standardized MDR-TB treatment regimens. Because the former are patient-specific, they tend to be more effective and less likely to promote drug resistance.[53] However, the drawbacks of individualized treatment regimens include costly and labour-intensive laboratory testing, non-standardized dosing, and the need for close clinical management of patients whose regimens may need to be adjusted during the course of therapy.[54]

Standardized "DOTS-Plus" treatment regimens could, in principle, be used to treat MDR-TB. If patients unresponsive to the DOTS regiment are presumed to have MDR-TB, in the absence of drug-susceptibility testing they could be placed on re-treatment drug regimens tailored to the epidemiological profile of the surrounding region. These could be designed to take into account population surveillance data and resistance patterns commonly encountered in an outbreak. The advantages of standardized MDR-TB regimens under current prices include lower cost and greater ease of administration. But the disadvantages are clear: without drug-susceptibility testing, such regimens would almost certainly result in higher failure rates, given that some patients would inadvertently be deprived of drugs to which they are susceptible, while others would receive drugs to which their MDR-strain is resistant.

3. Investment Opportunities

An infusion of new resources to confront drug-resistant TB will be critical to effective MDR-TB control. There are at least three important areas where new resources are needed:

1. Creating laboratory support;
2. Defining and putting into operation programmes that can effectively deliver MDR-TB therapy;
3. Providing effective MDR-TB therapy to patients.

3.1 LABORATORY SUPPORT NETWORK

One of the most fundamental and critical components of an effective global TB-elimination strategy is laboratory infrastructure that improves both timely diagnosis and drug-resistance surveillance.

Fortunately, the groundwork for such infrastructure has already been laid. A supranational reference laboratory (SRL) network—a joint project of WHO and the IUATLD—was created in 1994. This network assesses the accuracy of drug-susceptibility test methods used in different laboratories across the world and compares surveillance data from countries participating in the Global Project on Anti-Tuberculosis Drug Resistance Surveillance.[55] The network now comprises 23 SRLs and four regional sub-networks in Africa, Asia, Europe, and Oceania; the sub-networks include several national reference laboratories (NRLs). One or more SRLs located in specific geographic regions coordinate the distribution of culture panels from the global coordinating centre. This umbrella system has brought more than 100 laboratories into the worldwide network.

Surveillance of drug-resistant TB is essential to the timely detection of areas of emerging resistance in a timely fashion. To be truly effective, the Global Project should be expanded to cover the 22 TB high-burden countries that account for 80 percent of TB incidence worldwide. In order to do this, SRLs need to be redistributed, or have their area of activities re-allocated. In contrast to the European region, which has approximately half of all the SRLs, Asia has only three; the South and Central American region and Africa have only two each; and the Eastern Mediterranean region, only one. The highest priority should be the creation and inclusion of new SRLs into the SRL network. The expanding network will need increased support, so that it can undertake further activities needed to treat MDR-TB within the DOTS-Plus framework.

3.2 OPERATIONAL RESEARCH: DOTS-PLUS FOR MDR-TB

Scaling up Combating MDR-TB globally means taking pilot projects to scale. Strategies successfully employed in the model DOTS-Plus programme in northern Lima need to be refined, adapted to other "hot spots", and integrated with other key aspects of DOTS expansion.

This process of adaptation poses a number of important operational research questions. First, the basic DOTS-Plus programme package and key outcome measures must be defined. The

package must be flexible enough to adapt effectively to settings as diverse as India and the Dominican Republic, Indonesia, Russia, and South Africa. Operational research will give central focus to questions of drug supply and programme oversight.

Exploring genomics Recent advances in genomics provide another crucial arena for operational research into MDR-TB control. New molecular and laboratory tools offer the hope of systematic, real-time responses to outbreaks of drug-resistant TB. Some provocative questions arise:

- What is the feasibility of applying new tools—such as luciferase reporter assays and "molecular beacon" technology—to probe the dynamics of emerging drug-resistance in resource-poor settings?
- In what ways might novel technologies improve control efforts during outbreaks of drug-resistant TB?

Answers to these questions will help guide investment in DOTS-Plus interventions; such targeting will serve to strengthen DOTS-programme infrastructure.

Enhancing surveillance Another vital area for operational research is information and communications systems. The Internet and satellite telemetry have profound implications for public health projects, particularly those targeted at settings with underdeveloped infrastructures. Two central concerns in managing MDR-TB therapy are proper programme oversight and large-scale surveillance. Advanced communications media could play a crucial role in this oversight. Information systems need to be developed and tailored for DOTS-Plus

Photo taken by Dr. Arachu Castro, Partners in Health

Room for female TB patients in a Siberian hospital.

programme support, building on the DOTS strategy's successful data-collection practices. Oversight could be integrated into a surveillance system that serves the broader network of DOTS and DOTS-Plus projects worldwide. Successful navigation of these issues will not only facilitate a broadly coordinated assault on TB, but may also provide the foundation for other public health initiatives.

Assessing costs and benefits Finally, DOTS-Plus operational research should yield realistic estimates of programme costs. The DOTS-Plus strategy based on individualized regimens being pursued in Lima is being expanded throughout Peru, and the costs and benefits of this strategy are being analysed. Research is also needed to estimate the impact falling drug prices and enhanced efficacy have on programme costs. Can new methodologies be developed to compare costs of alternative approaches to treating MDR-TB patients? Preliminary analysis addressing these questions is currently under way. As DOTS-Plus programme activities expand over the coming months and years, answers will be forthcoming.

4. Conclusions

The rise of drug-resistant TB demands a rapid but reasoned response. National governments, regional health authorities, civic organizations, public health specialists, and clinicians must act immediately, in well-coordinated ways. International policymakers and business and philanthropic communities must be included in the discussion.

A shortsighted failure to invest in both TB research and control has led to increased TB drug resistance at a time when few prospects exist for new drugs or vaccines. Given the explosion of the HIV/AIDS epidemic in many parts of the poor world and the continued increase in the number of drug-resistant strains of TB, there is a clear and present danger. It is clearly in the interest of every nation and international funding agency to invest substantially and expeditiously in the control of MDR-TB.

5. Economic and Financial Overview

Table 4.1: Estimated Costs for MDR-TB-control in Low- and Middle-Income Countries, 2001–2005 ($ millions) (1)

Component	5-Year Cost	Current Resources Committed			Financing Gap
		Government	External	Subtotal	
Supplying second-line drugs – In "hot spots"* – In other countries	650	200	50	250	820
Other intervention costs – In "hot spots"* – In other countries	420	0	0	0	0
DOTS-Plus for MDR-TB Working Group	16	0	2	2	14
Total	**1,086**	**200**	**52**	**252**	**834**

** MDR-TB "hot spots" are defined as locations where more than 5% of all TB cases are reported to be multidrug-resistant. (Becerra, 2000)*

Notes

1. The figures in Table 4.1 assume that only a portion of all TB cases detected throughout the 2001–2005 period will actually be diagnosed as MDR and appropriately treated. Since DOTS-Plus programmes are now being geared up, notably in Peru, and will not be phased-in immediately, even in hot spots, the economic model assumes that only approximately 40 percent of MDR cases will be managed by DOTS-Plus programmes. It further assumes that the proportion of all TB cases that are MDR currently ranges from 3.2 to 4.6 percent across all low- and middle-income countries, according to simulations included in the economic model and detailed in the *Economic Annex to the GPSTB*, (published separately). The funding gap at the country level is estimated to be on the order of 80 percent of costs, as funding costs are not currently budgeted in most low- and middle-income countries, and will concentrate in some of the poorest of these countries: India, Pakistan, China, and Nigeria.

Investing in the Future

1. The Promise of TB Research

Until quite recently, improvements in human health have been slow to evolve. In fact, the very notion of "public health" did not even emerge until the nineteenth century. However, as growing populations and urbanization catalysed a growing burden of communicable diseases, a pressing need arose to find new solutions to old health problems.

For example, in the countries that comprise Western Europe today the ancient scourges of typhoid and diarrhoeal diseases were dissipated by draining marshes, and later through the development of modern plumbing, sewage, and sanitation systems in urbanized areas. At the same time, a growing abundance of food and the gradual emergence of a middle class based on trade and disposable incomes allowed people to distance themselves from circumstances—such as poverty, malnutrition, overcrowded housing, and lack of sanitation—that had long placed them at high risk of contracting infectious diseases. One of the many results of this distancing was a dramatic decline in childhood pneumonia.

The past century, however—with innovations in medicine, epidemiology, and technology—truly witnessed a quantum leap in health care. Increasingly, nowadays, advances in health are made through the application of biomedical science. Take smallpox, for example. This dreaded disease was eradicated in the 1970s through a combination of vaccine development, operational research regarding how to use the vaccine, and the political will to see the eradication process through to the end. The imminent eradication of polio was also spurred by the determination to find a vaccine to prevent the terrible epidemics that periodically swept the world. More recently, AIDS-related deaths in industrialized countries have plummeted, thanks to the development of effective anti-AIDS drugs.

As for TB, increasing wealth in the developed countries in the early twentieth century brought better housing, ventilation, and nutrition, and enabled the quarantine of infectious cases in sanatoria. Significantly reduced death rates resulted. In some countries, these death rates were accelerated by the arrival of effective drug regimens. In other nations, the current TB vaccine (BCG) played an additional role. And the antimicrobial drugs currently used against TB were

developed through deliberate, careful research in some unexpected places.[1] The most effective drug combinations, in fact, emanated from one of the most brilliant, painstaking, rational programmes of clinical trials the world has even seen.[2] These programmes also included the invention of the randomised controlled trial.

In short, evidence abounds that improvements in health occur not only through improved socioeconomic development, but also through deliberate, rational attempts to reduce the burden of disease by the application of scientific knowledge and technology. Yet, science needs the weight of political commitment behind it for major improvements in health to be achieved.

Although the poor bear 90 percent of the world's disease burden, only 10 percent of the world's health research and development spending addresses their plight.

Unfortunately, political commitment is conspicuous in its absence when the issue of dealing with the diseases of the world's poor arises. Although the poor bear 90 percent of the world's disease burden, only 10 percent of the world's health research and development spending addresses their plight.

Tuberculosis is no exception. Annual public sector and major private foundation investment in TB research increased from approximately $19 million to $33 million between 1991 and 1993,[3] and jumped to approximately $100 million in 1995.[4] By the year 2000, investment in TB research was estimated to be $125 million. But even after a fivefold increase in eight years, TB research and development (R&D) still accounts for only 0.2 percent of global annual health-research spending. This meagre amount is for a disease that ranks eighth in the world in terms of the numbers of deaths it causes and is responsible for nearly 3 percent of the entire global burden of disease.

Yet today the prospects are better than ever that a significant return on investment in TB control and research will be realized. The technological advances of the past 50 years have, for the first time, provided humanity with the tools to systematically develop the diagnostics, drugs, and vaccines needed to combat the diseases of the poor. There is no reason why TB high-burden communities should not also benefit, provided the investment is made. The tenfold increase over the past ten years in the number of countries using DOTS provides an unprecedented opportunity for inexpensive operational research to further improve the delivery of TB care. Previous chapters have put forward the arguments for investing in TB control using currently available tools and systems. This chapter presents the rationale for investment in research.

2. Developing New TB Tools

Control of communicable diseases requires diagnosis and treatment of infectious cases and/or an effective vaccine to prevent those cases from arising in the first place. The possibility of progress at all levels—diagnostics, drugs, and vaccines—has taken a quantum leap, enabled by the complete sequencing of the genome of *Mycobacterium tuberculosis*,[5] finished in late 1998. Scientists now have a complete picture of each of the nearly 4,000 genes that make up two strains of the tubercle bacillus. The scientists can identify genes unique to *M. tuberculosis* and determine the proteins produced by those genes. This greatly increases the chances of identifying a protein—immune response to a protein—that could form the basis of a diagnostic test with far greater specificity than those currently in use.

The genome sequence is effectively a list of potential drug targets, most of which were previously unknown. The sequence also includes those proteins that give rise to virulent effects, as well as those that could create protective immunity. The genome map is already creating a paradigm shift in our understanding of the physiology of the organism, as well as of the pathology caused by *M. tuberculosis*. Now—for the first time ever—the mechanisms that underlie TB immunity and the path to a truly effective vaccine are within reach.

Now—for the first time ever—the mechanisms that underlie TB immunity and the path to a truly effective vaccine are within reach.

Hard on the heels of genome work has come the capacity to analyse the huge amounts of data generated by the genome sequencing. This capacity is known as the science of bio-informatics, which links enormous computing power to the study of the genetic sequencing of pathogens.

Other advances that stand to make enormous contributions to drug development are combinatorial chemistry, which enables medicinal chemists to rapidly produce hundreds of compounds similar to any compounds that look as though they have the potential to help address a given medical issue, and robotic screening, which enables those compounds to be rapidly evaluated. Micro-arrays of DNA allow scientists to see which genes of an organism's complete set are switched "on" or "off" under variable sets of conditions. Never before has humankind had so many opportunities to diminish the threat of tuberculosis.

2.1 NEW DIAGNOSTIC TESTS

Diagnosis: No easy task in Kenya

Shortly after the birth of her third child, Beatrice—a 23-year-old Kenyan woman—developed a cough she ignored. The delivery of the baby had not been straightforward, and Beatrice had continued to bleed profusely after the birth. Her neighbours remarked on how pale she was. Even

when the bleeding stopped, she didn't feel any stronger.

When, two months after the birth, Beatrice started sweating at night, she went back to the local health centre. The health assistant suspected TB, but the microscope was not working, so the assistant told Beatrice to go to the nearest town—a 30-minute walk to the main road and a one-hour bus ride, followed by another ten minutes on foot.

After several hours waiting in an outpatient clinic, Beatrice was asked to provide sputum and told to return the following day with another sample from her first cough of the morning. What happened next is uncertain, but Beatrice was found quite by chance by one of the hospital staff the following morning. She was squatting at the side of the road, her head in her hands and barely conscious. She had fainted on the way back to the bus station and remembered little else. Her first sputum, it turned out, was strongly positive for TB, and her haemoglobin was approximately one-fifth of normal for an African woman.

Beatrice was admitted to hospital, treatment for TB was begun, and iron supplementation started in order to cure the anaemia.

Diagnosis of TB currently relies on microscopic examination of a sputum smear (the Ziehl-Neelsen test), a technique more than 100 years old. No other laboratory diagnostic test in use today has lasted so long—a tribute to its robustness perhaps, but also a sad reflection of long neglect in TB research. The recommended approach requires three specimens of sputum produced over 24 hours, as well as a functioning binocular microscope with stains and glassware—often an impossible feat of coordination in low-income country settings. All too often in the poorest countries, patients who are deterred by transportation expenses, a husband's opposition, or sheer exhaustion from the impact of disease fail to turn up to receive their results. Yet, a speedy diagnosis is crucial if patients are to be treated effectively.

A top priority for TB diagnostics is to replace the existing test with one that can produce results in minutes; can be performed with minimal training; and has a long shelf life without refrigeration.[6] If the new test could also be used to monitor treatment progress, it would obviate routine sputum microscopy and could transform TB-control programmes.

Identifying TB in children is currently a diagnostic nightmare.

In the short-term, a test that could simply supplement the sputum smear and make diagnosis more sensitive and/or specific would be a useful advance. Areas with a high prevalence of HIV also have a desperate need for a test that will distinguish HIV-infected patients with TB (often smear-negative) from those without TB. Developing such a test represents an even greater challenge, because tests relying on antibody detection are usually insensitive in HIV-infected people. However, such tests would likely also be able to identify TB in children—currently a diagnostic nightmare.

In high multidrug-resistant settings, a second priority is the rapid detection of rifampicin-resistant cases without having to resort to costly, time-consuming, and dangerous culture and

isolation of the organism. In fact, shortage of resources currently limits the settings in which culture is even possible today; but more effective approaches to the problem of MDR-TB will demand the rapid identification of patients with this form of TB.

The scientific community and the pharmaceutical industry are starting to respond to these needs. Significant activity in new TB diagnostics development has begun. In contrast to the situation just three years ago, research is now increasingly targeting the needs of people in developing countries. Small biotechnology companies are beginning to focus on diagnostics, and a few large pharmaceutical companies have obtained diagnostics capability in TB. The necessary technology is available, but applied discovery and field development work is still required. Such work does not require upfront financial investment on the scale needed for drug or vaccine discovery and development.

The Tuberculosis Diagnostics Initiative at WHO has a database of more than 50 companies and academic research groups and is helping these groups define the necessary performance characteristics of new TB diagnostics and to overcome bottlenecks, such as the dearth of well-characterized clinical specimens. (A specimen bank has been set up to answer this need. Several thousand specimens are now stored in the bank and are being distributed to groups that request them.)

Nevertheless, the development of new diagnostic tests must be accelerated. Many of the enterprises engaged in the effort are small. Additional capital is often needed, especially to take advantage of the opportunities provided by the genome sequencing of *M. tuberculosis*. Sources of such support have thus far been limited, although a number of interesting developments have recently occurred. For example, the U.S. National Institutes of Health (NIH) offers Small Business Innovative Research (SBIR) grants. A private company, Sequella Inc., was established to take advantage of scientific developments and accelerate their conversion into useful products against TB. But much more could be done in this area.

Beyond financial support, probably the most important unmet global need for TB diagnostics is an independent system to enable companies or academic groups to rapidly evaluate the cost-effectiveness of their test under field conditions. The World Health Organization and its partners are in the best position to coordinate the development of the necessary methodologies and protocols, and to certify a test's utility to national control programmes. A rough estimate of the investment required to develop significantly improved diagnostic tests comes to $150 million for the period between 2001 and 2005. When the cost of developing new drugs for TB is considered, this price is seen to be relatively small, and the time frame relatively short.

2.2 NEW DRUGS

Luisa was in her twenties when first diagnosed with TB in one of Lima's shantytowns. Two older siblings had already died of TB; three more had developed active pulmonary disease with multidrug-resistance. Luisa was the only person in the family to have a paying job—and thus couldn't afford to quit. Her long hours away from home compromised her treatment. Over time, Luisa's TB became resistant to most drugs.

The bane of TB treatment is its length. Currently, treatment with DOTS demands a combination of at least four drugs administered over a minimum of six months. The development of new agents that will reduce treatment duration and decrease the frequency of administration and supervision by health-care workers is sorely needed. Other important goals are the development of new agents effective against MDR-TB, and drugs that can eradicate latent TB infection.

Private sector reluctance In contrast to diagnostics, TB drug discovery and development requires substantial upfront investment and greater attention to regulatory requirements. Within the pharmaceutical industry, after the discovery of the rifamycins, further attempts to discover new classes of anti-TB drugs stopped for several reasons, including perceptions that:

- tuberculosis would be defeated through the widespread implementation of the DOTS strategy alone;
- the TB drug market was too small to be of interest to a large pharmaceutical company; and
- most TB cases occurred in countries that had a questionable record in respecting intellectual property rights.

The prevailing wisdom at the time was that drug development costs far outweighed the potential global market for anti-TB drugs; thus, a sufficient return on investment could not be guaranteed. Recently, however, leaders in science and public health have been stressing the need for new anti-TB drugs and reaffirming that development of such drugs would address an unmet medical need. Furthermore, the real size of the anti-TB drug market and the likely costs for drug development have been insufficiently appreciated by industry, as will be discussed later.

Despite scientific advancements such as the disclosure of the *M. tuberculosis* genome, only five out of 19 major drug companies recently surveyed are conducting any TB research and development.[7] Of these, two are still at the basic research stage; one has until recently refused to test a promising family of anti-TB drugs; one has run out of cash to develop two unrelated compounds; and the merger of the fifth is threatening the development programme of a promising compound. Virtually no work specifically aimed at eradicating latent infection is currently being done. This omission translates to a minimal ongoing response by the pharmaceutical industry to a desperate public health need. The problem is not so much a technical one. No major barriers to identifying new agents against TB exist; rather, the problem lies in the nature of market-driven drug development.

Currently, the pharmaceutical industry is scarcely responding to this urgent public health need. The problem has less to do with technology than with market-driven drug development.

Public sector initiatives Meanwhile, the public sector has been investing in TB discovery and research. The U.S. National Institute of Allergy and Infectious Disease (NIAID, one of the institutes of the NIH) has set up what is by far the world's largest public sector anti-TB drug

discovery operation. This is part of the NIH's expanded investment in more basic TB research, which in terms of financial assistance has now reached an all-time high of approximately $60 million per year. In addition, the Centers for Disease Control have recently invested heavily in re-establishing the capability for large-scale clinical trials in the United States.

The International Union Against Tuberculosis and Lung Disease has also moved to establish a clinical trials unit to conduct studies in TB high-burden countries. The WHO/World Bank/UNDP Special Programme for Research and Training in Tropical Diseases (TDR) has added TB to its Research Capacity Strengthening Network for disease-endemic countries and is building up sites for clinical trials of drugs and diagnostics. Complementing these initiatives is the work of the Sequella Foundation, whose programme aims to assist pharmaceutical companies in identifying compounds that are effective against TB, as well as to strengthen clinical trials capacity.

Neither the public sector nor private industry alone can resolve the failure of the market. But working together, solutions may be possible. Industry is an essential partner in drug development; therefore, ways have to be found to explore common ground, evaluate more precisely the size of the TB market, design innovative means of decreasing the development costs for industry, and achieve sales that will exceed industry's investment and provide reasonable profits.

A major new initiative seeking to bridge these gaps in research and development through partnerships is the Global Alliance for TB Drug Development (GATB), an international non-profit organization formed in February 2000 to accelerate the discovery and/or development of new, cost-effective, and affordable TB drugs. The alliance is one of a new breed of public–private partnerships (PPPs) that pursue a social mission by drawing upon best practices, expertise, and resources from both public and private sectors. The Global Alliance develops a portfolio of promising drugs, outsources their development, and strategically manages intellectual property rights to balance business objectives and social benefits.

A recent publication of the GATB[8] reviews present data required for informed investment decisions by industry, foundations, governments, and world health and financial organizations. According to this analysis, the current (2000) global market for anti-TB drugs is estimated to be approximately $450 million in annual sales, increasing significantly to approximately $650 million by 2010. The report reviews development costs in depth. It estimates the total costs of developing a new anti-TB chemical entity (NCE)—including the costs of failure—to be approximately $76–115 million, depending on total development time and discount rate for pre-clinical development through Phase III clinical trials and regulatory approval. Additional costs for the earlier stage of discovery are more difficult to estimate precisely and may range between $40 million and $125 million (including failure costs). To summarize, developing a completely new drug by 2010 would require an investment of up to $240 million.[9]

The global market for anti-TB drugs in 2000 is estimated to be approximately $450 million in annual sales, and is predicted to increase significantly to approximately $650 million by 2010.

While the anti-TB drug market size may still be at the lower end of what research-based pharmaceutical firms consider attractive, it still suggests a reasonably sized market. If the industry can be persuaded that the real market for anti-TB drugs is larger than previously thought, companies may decide to take up the challenge.

More likely, some incentives from the public sector will be needed to stimulate action, such as the "push" mechanisms encapsulated in the recently created Medicines for Malaria Venture and in the GATB, and/or the "pull" of a guaranteed market, now being discussed in regard to vaccines. Others have proposed that rich countries' public sectors should create incentives for companies to work on TB vaccines by committing to buy any new, effective TB vaccine on behalf of poor countries.[10]

Whatever method is employed, the most progress will likely be made through innovative public–private partnerships. The benefits could be tremendous: a new anti-TB drug that would reduce the duration of treatment to two months, or otherwise simplify it; one that would be effective against MDR-TB and improve the treatment of latent TB infection; one that would address the needs of millions; one that would decisively accelerate the global control of the disease.

2.3 NEW VACCINES

Vaccines are usually considered the ideal public health tool because they prevent disease from occurring in the first place, and may even lead to eradication, as with smallpox and polio. The payoff from a highly effective TB vaccine would be an immense number of lives saved. This is in fact what drives research into new TB vaccines. However, the technical obstacles to development of a new, highly effective vaccine set this kind of TB research apart from research on diagnostics and drugs, where the constraints on success are primarily financial.

The current anti-TB vaccine—BCG—is a major component of global TB-control efforts. The most widely used vaccine in the world, BCG is administered to approximately 100 million infants per year—about two-thirds of all newborns.

The current anti-TB vaccine is the Bacille Calmette Guérin (BCG). It is a major component of global TB-control efforts. The most widely used vaccine in the world, BCG is administered to approximately 100 million infants per year—about two-thirds of all newborns. Unfortunately, while BCG's protection appears to be reasonably good against primary childhood disease, it is much less efficacious against adult-type disease, especially for people in developing countries. And the pulmonary adult form of TB is the form responsible for transmission and the form that generates the bulk of the TB disease burden. The epidemiological impact of BCG is thus severely limited.

Various approaches are being taken to prevent infection and also, more speculatively, to prevent re-activation of patients already infected. These approaches include DNA vaccines, recombinant BCG and other live vectors, attenuated *M. tuberculosis*, lipid antigens, and relatively simple secreted antigens.

Especially active in this area are the public sector research institutes of industrialized countries, such as the NIH of the United States, the Medical Research Council (MRC) of the United Kingdom, and Germany's Max Planck Institute. The British private foundation, the Wellcome Trust, is also quite active. And notably, the Sequella Foundation (U.S.) was granted $25 million by the Bill and Melinda Gates Foundation in 2000 for work on TB vaccines.

International coordination of these nascent vaccine research efforts has been conducted by WHO's Steering Committee on Immunology of Mycobacteria (IMMYC), which facilitates flows of information among the various players. In 1995, this forum prepared a global vaccine development strategy aimed at enhancing animal model capacity, determining correlates of protection, and developing the requirements for appropriate clinical trials. The result has been an explosion of vaccine candidates and the development of standardized methods of comparison in animals (albeit with insufficient expansion of animal model facilities, and little progress in correlates of protection).

Nevertheless, at least three major vaccine-producing companies are actively pursuing TB vaccine development: GlaxoSmithKline (in partnership with Corixa); Pasteur Mérieux Connaught; and Chiron. Each is pursuing its own distinctive strategy. Some smaller companies—Sequella Inc., EpiVax, and Intercell GmbH—are also working on novel approaches to vaccine development.

Upfront financial investments required for research and development in vaccines are of the same magnitude as for many pharmaceuticals. Like the market for TB treatments, the one for TB vaccines is perceived as high-volume but low-margin. Thus, TB vaccine development faces some of the same hurdles as drug development. Innovative attempts are being made to address this problem. One of these is the Global Alliance for Vaccines and Immunization (GAVI), which has won initial support from the Bill and Melinda Gates Foundation, and which attempts to provide existing vaccines to the poorest countries. The alliance is now turning to the issue of research and development to address high-burden diseases for which there are, as of yet, no effective vaccines.

Successful vaccine development will likely require clear descriptions of the necessary ways and means to supplement and finance them. On the technical level, a few pressing needs must first be met:

- Animal models to better imitate human TB and provide clearer indications for the probability of success of a candidate vaccine in human beings must be improved.
- The mechanisms by which TB bacilli cause disease and the ways in which human beings protect themselves must be more clearly elucidated. (This will lead to better understanding of the correlates of protection and improved clinical trials.)
- Early trials in humans to establish safety and immunogenicity must be begun. (This will require identification and, especially in the developing world, strengthening of trial site capabilities to international standards; the same is true for manufacturing facilities for candidate vaccines.)

How much will it cost to develop a new TB vaccine? Because of the considerable challenges enumerated here, a TB vaccine is unlikely to be achieved with less than $1 billion. Crude cost

estimates suggest that $700 million may be required to develop better animal models, expand testing facilities, increase knowledge of pathogenesis, and develop correlates of protection. In addition, $10 million per year may be required for clinical trials from 2001 through 2005; then, $20 million per year between 2006 and 2010. Thus, the total cost is likely to be approximately $1 billion.

How much will it cost to develop a new TB vaccine? $1 billion is a reasonable estimate.

On the political level, recognition that TB vaccine development is technically challenging and will require substantially increased investment over the long term in both the public and the private sector is critical. Basic research of this kind usually is best done through public sector funding of investigator-initiated proposals. The National Institutes of Health is particularly successful at this. But industry will also be essential to the process of successful vaccine development.

As with pharmaceuticals, progress seems most likely if a public–private partnership assumes the role of coordinator for the global TB vaccine research, development, and testing agenda. Such a coordinating group could also assume advocacy roles necessary to catalyse the work. Such a coalition should include all relevant disciplines, bringing together scientists from around the world—with strong representation from TB high-burden areas. Representatives from vaccine manufacturers, control programmes, and NGOs such as IUATLD should also be included. The Global Alliance for Vaccines and Immunization or WHO are obvious candidates to take the lead in establishing such a partnership.

Recent scientific advances, combined with increasing political will within the U.S. government as exemplified in the Presidential Challenge for Vaccines for HIV/AIDS, Malaria and Tuberculosis, are causes for optimism in TB vaccine research and development. So are the efforts of private foundations. A partnership that could make a tangible difference appears possible.

3. Research into Health Policy, Systems, and Services for TB Control

In Malawi, health systems research in TB control began in 1994 with the recognition that the NTP was in trouble. Notifications were soaring because of HIV. Cases were being diagnosed without adequate investigation. "Hot spots" of transmission were suspected. Cure rates were poor.

With modest funding—initially from WHO and later from the United Kingdom's Department for International Development (DFID)—the newly established College of Medicine and the NTP set up research studies to address these problems.[11] The ways patients came to be diagnosed were described. Different screening methods for diagnosis were explored, as were how closely health-care workers adhered to NTP guidelines. The association

between HIV and TB treatment outcome was defined. The prevalence of TB in "hot spot" areas, such as prisons and health-care institutions, was measured.

Research showed that over 40 percent of active TB patients in Malawi had spent at least one month with a traditional healer before entering orthodox medical care. The NTP has since trained more than 3,000 traditional healers in 15 districts. Also, the incidence of TB in health-care staff was found to be 3.6 percent per year. The NTP produced guidelines to reduce hospital-based TB transmission, for use in every hospital. These and other results enabled the NTP to obtain funding for an office, computers, vehicles, and a three-year programme of operational research and in-country technical assistance that included supervision and training of both health-centre staff and traditional healers. A programme management group was formed, and it developed and implemented control and research strategies. Operational research thus became an integral component of the NTP.

Research such as this into health-care delivery systems and practices can yield significant improvements in TB diagnosis and treatment in a relatively short time—and at significantly less cost than new drug development. Moreover, since programmes like Malawi's are focused on local needs and practices, they are more likely to work than are the "one-size-fits-all" approaches to TB care.

3.1 THE CASE FOR OPERATIONAL RESEARCH

It will take at least two to three years before new diagnostic tools become available. New drugs will take between 8 and 20 years to be developed. Vaccines will take 15 years or more. Successful efforts in all three areas will likely require investments in the equivalent of billions of American dollars. Meanwhile, people will continue to die at horrifying rates. However, research into the health policies, systems, and service delivery for TB-control promises significant gains in far less time and at far lower costs.

Ample evidence exists that this approach will succeed. First, existing tools are highly effective when service delivery is adapted to the circumstances. For example, as long ago as 1953, a citywide treatment programme in Edinburgh, Scotland, achieved 95 percent cure rates using less effective drugs than those available today.[12] Karel Styblo's seminal work in developing what came to be known as the DOTS strategy in Tanzania increased cure rates from around 30 percent to over 80 percent prior to the advent of HIV.[13] Facilitating expansion of the DOTS strategy and its adaptation to different conditions should significantly improve the effectiveness of TB control (as in the Malawi programme). Moreover, there are examples of the successful development of strategies for control of other diseases, such as onchocerciasis, a disease responsible for river blindness in large tracts of West Africa.

In spite of its successes, operational research has been neglected. The reasons for this are varied. Success in this type of work requires significant skills in both research and TB control, but people possessing both sets of skills are rare. The field is also very wide—it encompasses health policy research, research in health systems, sociology, ethnography, economics, behavioural sciences, epidemiology, and statistics. While courses exist in each of these fields, few if any specific training programmes exist for applying these skills to the operational issues

involved in controlling infectious diseases in the field.

While the development of new diagnostics, drugs, and vaccines will take decades, research into the health policies, systems, and service delivery for TB control promises significant gains in far less time and at far lower costs.

Also, success in disease control is perceived, somewhat incorrectly, as the product of technological and biomedical successes, such as the discovery of penicillin or the development of the measles vaccine. More fundamentally, the general perception of research in developing countries is that it is an activity carried out by the select few, removed from the everyday problems that concern disease controllers—who are, in fact, better positioned to do research than many of their counterparts in the lab. This elitist view of research can no longer be afforded. A rational attack on the major infectious causes of disease requires concerted efforts from all corners of the research community. Operational researchers must be given the opportunity to show what they can do.

3.2 HEALTH POLICY, SYSTEMS, AND SERVICES RESEARCH IN TB HIGH-BURDEN COUNTRIES

Another example of successful operational research is the International Network for the Rational Use of Drugs (INRUD), formed in 1989 with the aim of improving drug use in developing countries through high-quality research. Ghana, Nigeria, Uganda, Bangladesh, Indonesia, and Nepal each established a group that involved university and government and social scientists, and which was supported by external groups at Harvard, Karolinska, WHO headquarters in Geneva, and the University of Newcastle in Australia. A non-profit consultant, Management Sciences for Health, coordinated the network.

Field tests led to the development of standard indicators of rational drug use, to be employed in the treatment of TB patients; these guidelines were accepted by WHO.[14] The network answered many questions about improving drug use in primary-care facilities. A biannual newsletter and a bibliography of more than 3,000 references were published. Training courses now are held annually, as well as meetings to develop joint proposals, exchange visits, and intervention studies. Zimbabwe, the Philippines, and Thailand have since joined the network. The success of the network can be ascribed to collective decision-making on plans and activities; to the sharing of resources; and to frequent networking activities.

One notable lesson from the Malawi and INRUD success stories is the need to clearly identify what issues must be addressed. Over the past few years, a movement to define TB research priorities in high-burden countries has taken place. Several meetings have been convened, mostly by WHO, with controllers and researchers from high-burden countries, to better define these priorities and develop plans to address them.[15] As a result, a number of multi-centre studies have been implemented. These include programmes to:

- define the community's role in enhancing TB control in sub-Saharan Africa;
- determine the best methods of direct observation of patients within the DOTS strategy;
- develop coordinated care packages for both TB and HIV/AIDS in HIV high-burden settings;

- determine gender-based barriers to health care and the degree to which women are disadvantaged;
- design the DOTS-plus approach to MDR-TB; and, most recently,
- develop mechanisms to enable private practitioners to deliver the DOTS strategy.

However, much still remains to be done. While globally coordinated projects aimed at addressing common problems are underway, the projects are often poorly funded. In particular, they do not receive the support that enables truly rapid results to both be achieved and introduced into policy. Just as important, high-burden, low-income countries have minimal capacity to carry out country-specific operational research to identify local problems and develop local solutions. Malawi is a shining exception. Generally, existing projects are aimed at the service delivery aspects of TB control. Health-policy and health-systems research lag behind.

A clear need for research into how to conduct TB programmes in low-income countries is apparent. Such research requires structured programmes to carry out the research; competent personnel to perform the research; interaction of researchers to stimulate a productive intellectual climate; and sufficient financial support.

The structured programmes for such research clearly need to integrate the skills of academics with local knowledge of the aims and nature of control programmes. A "research culture" needs to be implanted in the NTPs, while research institutions need to be more willing to confront genuine problems. In high-burden countries, such institutions must engage in partnerships with control programmes, as was done in Malawi. Care must be taken to ensure that the efforts of country-based research programmes are not diverted toward the agenda of research-funding institutes, away from the real needs of the people.

This kind of structural development will happen only if funding agencies clearly and consistently support this kind of research—and then provide sustained support. The Special Programme for Research and Training in Tropical Diseases (TDR), an independent global programme of scientific collaboration, was established in 1975 and co-sponsored by the United Nations Development Programme (UNDP), the World Bank and the World Health Organization (WHO). TDR helps coordinate, support and influence global efforts to combat a portfolio of major diseases of the poor and disadvantaged, including TB. It provides institutional capacity-strengthening grants to support just this type of structural development. A further need exists for a mechanism to ensure that research into health policy, systems and services is positioned globally. The World Health Organization's Global TB Research Initiative (GTRI), established in 1998 under the auspices of TDR, provides a forum for debate on research priorities and for identifying and filling gaps in global TB research and funding. GTRI has succeeded in bringing together the very different communities of basic biomedical and social science research with those communities researching health policy, systems, and services.[16] But the GTRI must ensure a balance between investment in biomedical and operational areas of research.

A programme should also be initiated to identify, sponsor, and train likely candidates for careers in research in developing countries. At the same time, efforts should be directed

toward providing local research career structures, and developing means of retention, so that a critical mass of researchers is built up. These efforts will be essential to increase the number of developing-country researchers with worldwide reputations in TB research and managerial expertise. Making research an integral component of national tuberculosis programmes is essential.

All this will of course cost money. A need exists for rapidly assessing the feasibility of allocating a certain percentage of control programme funds to research in the 22 TB high-burden countries, as well as in other smaller countries with particularly high TB-incidence rates. Rough estimates suggest that establishing a health policy systems and services research (HPSSR) programme in each high-burden country would cost NTPs and academic partners $110 million over five years. A further $100 million would be required to establish similar programmes in the remaining countries that have high TB incidence but are not considered high-burden countries. Such strengthening of research capacity would also require support from a range of stakeholders (for example, WHO/TDR, the Fogarty Center, NIH) and involve additional cost in these organizations of approximately $120 million over the next five years.

4. Conclusions

In the struggle against disease, scientific research has been a sound investment. A large part of the burden of disease has been lifted from the backs of humankind by research-generated tools. Current TB-control tools are the fruits of research of one kind or another.

And yet, especially in the last quarter-century, investment in TB research has been minimal. In consequence, the research community has neglected ways of doing a better job with existing tools, and the development of new tools and systems. In spite of significant expansion in the last eight years, current expenditure on TB research is still below levels that might be expected, given the size of the impact of TB.

A three-pronged approach promises the best chance of success:

- First, the development of more efficient diagnostic tests, more powerful drugs, and more effective vaccines.
- Second, serious investments in operational research aimed at improving health policies, systems, and service delivery.
- Third, focused operational research to resolve obstacles in DOTS delivery.

The old systems for meting out development aid have failed to apply scientific advances to the health problems of the poor. Effective investment requires new mechanisms and approaches for directing and channelling it. Innovative, cooperative approaches that bring together the public sector, industry, and private foundations are already changing the face of research in tuberculosis. With good will; with sustained, careful investment; with the participation of all stakeholders; and with a modicum of luck, these new approaches could well deliver the tools the world so urgently needs to control the scourge of tuberculosis. Serious investment in TB means equally serious investment in TB research.

5. Economic and Financial Overview

Table 5.1: Estimated Costs of Research and Development for TB Control, 2001–2005 ($ millions)

Component	5-Year Cost	Current Resources			Financing Gap
		Government	External	Subtotal	
Diagnostics	150	0	47	47	103
Drugs	317	0	130	130	187
Vaccines	420	0	95	95	325
Health Policy Systems and Service Research (HPSSR)*	150	0	105	105	45
Sub-Total	**1,037**	**0**	**377**	**377**	**660**
TB Diagnostics Working Group	27	0	6	6	21
TB Drugs Working Group	30	0	6	6	24
TB Vaccine Working Group	4	0	1	1	3
Sub-Total Working Groups	**61**	**0**	**13**	**13**	**48**
Total R&D costs	**1,098**	**0**	**390**	**390**	**708**

**Notes – HPSSR cost estimates exclude $180 million covered by NTPs over the 2001 - 2005 period (of which $160 million is targeted for the 22 TB high-burden countries). This amount is budgeted in the cost estimates for DOTS expansion.*

Part 2:
The Response

Dr. Avachu Castro, Partners in Health

Doctor viewing X-rays in a Tomsk prison.

Chapter 6

The Global Partnership to Stop TB

1. Stop TB Vision

Launched in Bangkok in November 1998 by WHO Director-General Gro Harlem Brundtland, the Global Partnership to Stop TB has grown rapidly, now comprising more than 200 organizations working together to eventually eliminate TB as a global public health concern. The Partnership is a network of country partners, international organizations, public and private donors, governmental and non-governmental organizations (NGOs), and academic institutions, all of which are committed to the Partnership's mission.

The Partnership is hosted by WHO and is served by a small, Geneva-based secretariat, the activities of which are described later in this chapter.

World Health Organization

2. Mission

The mission of the Global Partnership to Stop TB is:

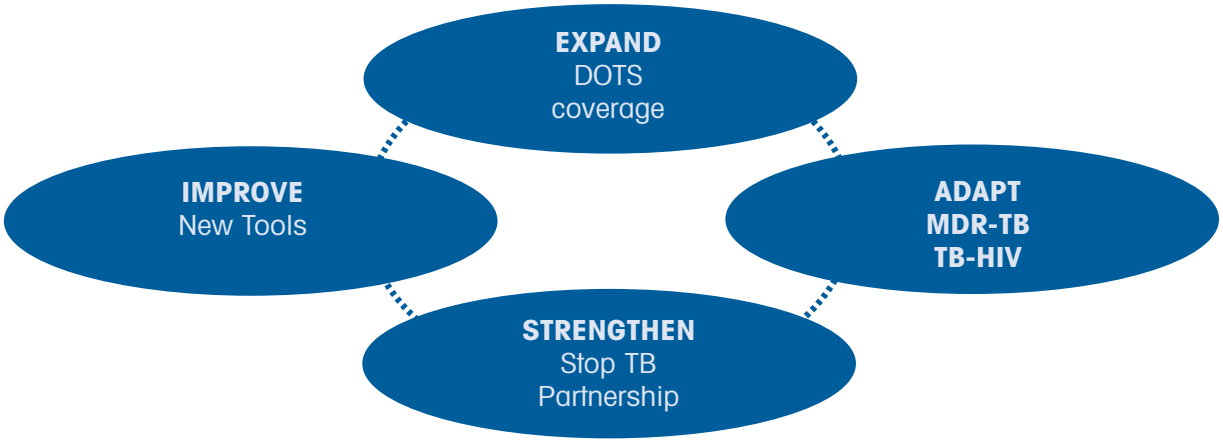
- to ensure every TB patient access to effective diagnosis, treatment, and cure;
- to stop the worldwide transmission of TB;
- to reduce the inequitable social and economic toll of TB; and
- to develop and implement new preventive, diagnostic, and therapeutic tools and strategies to eliminate TB.

3. Strategic Objectives

This *Global Plan to Stop TB* outlines four clear, specific goals in support of the Stop TB vision and mission. The goals are to:

- EXPAND the currently available anti-TB strategy—DOTS—so that all people with TB have access to effective diagnosis and treatment;
- ADAPT this current strategy to meet emerging challenges of HIV and drug resistance;
- IMPROVE existing tools by developing new diagnostics, new drugs, and new vaccines; and
- STRENGTHEN the Stop TB Partnership so that proven TB-control strategies are effectively applied.

These goals are mutually interdependent and reinforcing. The Stop TB Partnership cannot stop tuberculosis unless the Partnership achieves all of them.



Objective 1: "EXPAND" programme implementation

By expanding currently available DOTS regimens, the *Global Plan to Stop TB* seeks to:

- ensure that countries develop and implement comprehensive TB control using the DOTS strategy to achieve global targets;
- ensure that TB-control efforts are included in, and contribute to, broader health-sector and poverty-reduction strategies;
- ensure community involvement in TB programme development and implementation; and

- ensure the involvement of the private medical sector in TB programme development and implementation.

Objective 2: "ADAPT" programme development

By adapting the current DOTS programme, the Global Plan seeks to:

- develop, test, and scale-up strategies to address the dual epidemics of TB and HIV in HIV high-burden countries by ensuring collaboration between TB and HIV communities, and incorporating these strategies into TB-control programmes;
- develop, test, and scale-up strategies to control and effectively treat patients with MDR-TB, and incorporate these strategies into TB-control programmes;
- develop, test, and scale-up strategies to deal effectively with TB in special settings such as prisons, refugee camps, and so forth, and incorporate these strategies into TB-control programmes; and
- develop, test, and scale-up strategies to prevent TB and incorporate these strategies into TB-control programmes;

Objective 3: "IMPROVE" existing tools by developing affordable, new tools for low-income, high-burden settings

The *Global Plan to Stop TB* has categorized the need for new TB-control tools into three areas: diagnostics, drugs, and vaccines.

Diagnostics

Goals of improving TB diagnostics are to:

- develop new test(s) to diagnose active TB more quickly, more easily, and more accurately than sputum-smear microscopy;
- develop new test(s) to rapidly detect rifampicin resistance; and
- develop improved methods to identify infected persons at risk of developing active TB.

Drugs

Goals of improving the efficacy of anti-TB drugs are to:

- develop new drug(s) to shorten and/or simplify the treatment of TB;
- develop more effective treatment(s) for MDR-TB; and
- develop more effective treatment(s) of latent TB infection.

Vaccines

The plan's goal for improving the efficacy of TB vaccination is:

- to develop new vaccine(s) effective in protecting the uninfected and/or preventing disease among the infected.

Objective 4: "STRENGTHEN" the Stop TB Partnership

The goals of strengthening the Stop TB Partnership fall into four categories: Partnership Building, Resource Mobilization, Information and Communication, and Advocacy.

Partnership Building

The goals are:

- to build a strong TB partnership that is inclusive, transparent, responsive to all partners (particularly TB-endemic nations), and effective at controlling TB;
- to develop partnerships at the local, national, and global levels;
- to collaborate beyond the Stop TB Partnership to ensure that TB control is included in, and contributes to, poverty reduction and health-sector strategies; and
- to provide effective governance so that the Stop TB Partnership:
  - coordinates partner activities to maximize TB control;
  - maximizes value to members and donors; and
  - raises sufficient resources to eliminate TB.

Resource Mobilization

The goals are:

- to develop plans and raise the resources—human, technical, and financial—necessary to eliminate TB;
- to develop mechanisms for setting common priorities for TB control and allocating Stop TB resources; and
- to coordinate with and support the resource mobilization efforts of partners.

Information and Communication

The goals are:

- to build internal and external information and communication mechanisms to support the partnership; and
- to coordinate collection, analysis, and dissemination of information to promote effective action to stop TB.

Advocacy

The goals are:

- to develop and coordinate global advocacy campaigns to promote effective action to stop TB; and
- to assist partners and countries in local advocacy initiatives.

4. Stop TB Targets

The World Health Organization has set five- and ten-year goals:

- **By 2005:** To detect 70 percent of the estimated new active TB cases; to treat all cases detected through DOTS; and to cure at least 85 percent of all cases treated.
- **By 2010:** To reduce the global burden of TB disease (that is, death and prevalence rates caused by disease) by 50 percent from year 2000 levels.

5. Coordinating the Global Plan to Stop TB

In order to achieve the stated objectives and targets, the Global Partnership to Stop TB has established a structure to ensure the effective coordination of efforts, so as to achieve them concomitantly. The structure comprises a Partners' Forum, a Coordinating Board, working groups, and a Secretariat.

5.1 STOP TB PARTNERSHIP PRINCIPLES AND VALUES

Shared values facilitate achievement of a shared goal. Working together in partnership is both a challenge and an opportunity. The challenge is to work cooperatively towards a common goal, without foresaking the independence, mandates, and priorities of individual partners. The opportunity is to learn from one another, and evolve accordingly.

The commitment of the partners is to act now—for all,

through collective action—from here, and into the future.

To act now—for all

- **Urgency.** Nearly two million people continue to die every year from a disease that has been treatable and preventable for over half a century. Such a situation is unjust and incomprehensible. The partners commit to urgent action, which must be supported by a massive increase in resources.
- **Equity.** TB is a disease of the disadvantaged. The partners share a commitment to reducing the social and economic inequities that increase vulnerability to infection and disease, reduce access to treatment, and lead to disparities in quality of care.

To act now—through collective action

- **Shared responsibility.** TB recognizes no national borders—control and eventual elimination of TB is a global public good and the shared responsibility of all members of the global community. All partners and nations therefore have a responsibility to make efficient, effective, and equitable use of the resources available to them, and are individually accountable for their actions
- **Inclusiveness.** The Global Partnership to Stop TB welcomes all those who share the vision and values of the Partnership—individuals and organizations, public and private, rich and poor.
- **Consensus.** Recognizing the diversity of mandates and priorities of each individual partner, Stop TB functions through a process of consensus to corporately reach agreement on priorities and best practice. The Partnership acts in a coordinated manner, based on the comparative strengths of individual partners.

- **Sustainability**. TB cannot be eliminated as a global public health problem in the near future. The partners commit to effective and sustained action and to strengthening national capacities for TB control.
- **Dynamism.** The global TB epidemic continually provides new challenges. Stop TB is a dynamic, loose, and evolving partnership, seeking to develop innovative mechanisms that support effective and concerted action.

5.2 STRUCTURE OF THE GLOBAL PARTNERSHIP TO STOP TB

STOP TB PARTNERS' FORUM

The Stop TB Partners' Forum is the main assembly of the Stop TB Partnership and consists of representatives of all the partners. It meets every two years, in order to:

- identify problems and new challenges, and exchange information;
- consolidate and increase partners' commitment to the objectives of the Stop TB Partnership and maintain and reinforce high-level political commitment to the Partnership;
- create and exploit opportunities for advocacy, communications activities, and social mobilization;
- review overall progress of the Stop TB Partnership;
- review progress and monitor implementation of the GPSTB;
- guide and evaluate the management of the Global Drug Facility; and
- dialog and collaborate with the Global Fund to Fight Aids, TB and Malaria to ensure coordination and support to countries.

STOP TB COORDINATING BOARD

The Stop TB Coordinating Board represents and acts on behalf of the Global Partnership to Stop TB, and consists of 27 representatives selected from different groups of stakeholders, such as high-burden countries, geographical regions, donors, technical agencies and NGOs, and multilateral agencies. It meets two to three times a year, and has the following functions:

- to formulate priorities for action by the Partnership in line with health policy and technical advice from WHO, and in the light of the recommendations of the Stop TB Partners' Forum;
- to support Stop TB Partners according to agreed policy and strategy;
- to identify funding gaps and mobilize adequate resources for the various activities of the Stop TB Partnership;
- to coordinate and promote advocacy and social mobilization in support of the Stop TB Partnership;
- to regularly review progress of the Stop TB Partnership;
- to review progress and monitor implementation of the GPSTB;
- to guide and evaluate the management of the Global Drug Facility; and
- to dialog and collaborate with the Global Fund to Fight Aids, TB and Malaria to ensure coordination and support to countries.

STOP TB WORKING GROUPS

Stop TB Partners have established six Stop TB working groups to ensure that effective action takes place in a planned, coordinated, and efficient manner. Working groups are organized around specific areas of activity:

- DOTS Expansion
- TB-HIV
- MDR-TB
- New Diagnostics
- New Drugs
- New Vaccines

Each Stop TB working group has the following functions:

- to map out activities in the specific area, including activities by different partners, policy and research developments, opportunities for further action, and resource needs;
- to plan, implement, and monitor coordinated action, building on the mandates, interests, and comparative strengths of the different partners;
- to report to the Stop TB board and the Partners' Forum on the progress, constraints, and assistance required; and
- to coordinate with other partners, working groups, or other committees to ensure synergy of activities, including advocacy, communication, and resource mobilization.

STOP TB TASK FORCES

Several cross-cutting issues are of relevance and concern to many of the Stop TB Partners and working groups, and therefore need to be addressed through mechanisms that bring together those with interest, experience, and knowledge across the Partnership. The Stop TB Partnership is establishing task forces to address some of these issues, which include financing, and advocacy and communications.

STOP TB SECRETARIAT

The Secretariat for the Partnership is hosted by WHO within the department of Stop TB, and is headed by an executive secretary. Some of the staff is provided by WHO, and some is seconded by partners. The primary role of the Secretariat is to support partnership activities by mobilizing and coordinating partners and working groups, and disseminating information. The Global TB Drug Facility is also managed by the Stop TB Secretariat.

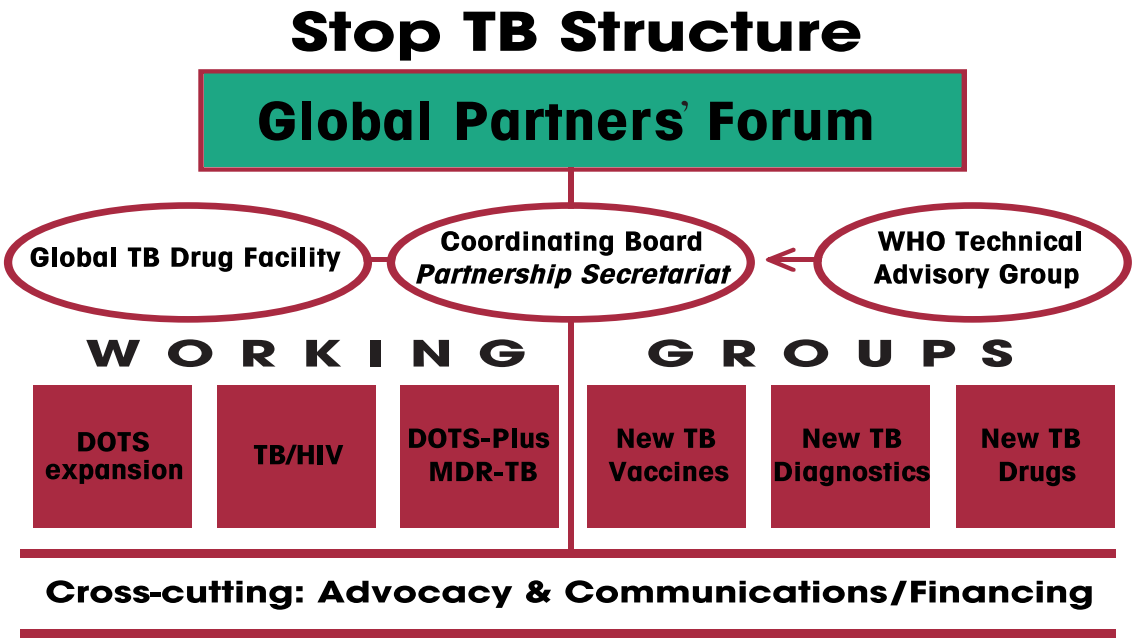
Stop TB Plans

1. Working Group on DOTS Expansion

This chapter explains in more detail the role of the Stop TB working groups. Each working group focuses on a specific area of activity, such as DOTS expansion or TB-HIV co-infection, whereas task forces address cross-cutting issues, such as financing and advocacy.

1.1 RATIONALE

In the March 2000 *Amsterdam Declaration to Stop TB*, ministers of health, finance, and development planning from 20 TB high-burden countries called for a rapid expansion of the DOTS strategy within their countries. The participants set targets for detecting at least 70



percent of infectious cases by the year 2005, and for curing 85 percent of patients. Helping countries achieve these goals is the mission of the Stop TB Working Group on DOTS Expansion.

The DOTS Expansion Working Group is composed of national tuberculosis programme managers from the 22 highest-burden countries; representatives of partner institutions; and technical experts serving in a personal capacity. Country programme managers, partner institutions, and technical experts coordinate with one another in the Working Group to support country programmes with technical advice and peer review, consultation, and support of DOTS expansion.

1.2 PURPOSE

The purpose of the Working Group on DOTS Expansion is:

- to build consensus on advice to countries, and to support technical and financial agencies in planning, expanding, and sustaining TB-control efforts in order to reach TB-control targets (70 percent detection and 85 percent cure rates) by 2005;
- to build consensus among international technical agencies as to how to assist WHO Member States with expanding and integrating DOTS smoothly within existing health systems, and with establishing country-based partnerships to build social and political support for control of TB and other infectious diseases;
- to monitor and evaluate progress made with DOTS expansion, and to monitor and evaluate the progress of controlling TB in countries; and
- to identify and mobilize resources for DOTS expansion, and to foster coordination among partners.

1.3 SPECIFIC OBJECTIVES

The DOTS Expansion Working Group has established specific targets and milestones, as shown in the following table.

Targets	2001	2003	2005
DOTS Expansion			
Detection rate of estimated smear-positive TB cases under DOTS	35 percent	50 percent	70 percent
Treatment success rate in DOTS areas	85 percent	85 percent	85 percent
Government Commitment			
Countries have a clearly detailed TB-control policy document, and management capacity to put the policy into practice	22 high-burden countries	All Regional Priority countries	All countries*
Countries have allocated sufficient human and financial resources on a sustainable basis for TB control	At least 10 high-burden countries	At least all 22 high-burden countries	All countries*

Planning			
Countries have developed – and governments have endorsed – a detailed plan to implement the DOTS strategy to control TB	22 high-burden countries have a DOTS expansion plan	All countries* have a plan to expand DOTS	All countries* have a plan to sustain DOTS
Countries have trained staff at different levels to implement the DOTS strategy and to utilize resources efficiently and effectively	All personnel of DOTS areas trained	All personnel of DOTS areas trained	All personnel of all countries are trained
Critical Elements of Implementation			
Countries have a national reference laboratory and an effective network of smear microscopy, including quality control	At least 11 high-burden countries	All high-burden countries	All countries*
Countries have in place systems of procurement and distribution of drugs that are able to deliver timely, good quality TB drugs to all health facilities treating TB cases	All DOTS areas	All DOTS areas	All DOTS areas
Monitoring and Surveillance			
Countries are monitoring and evaluating TB programmes using WHO-recommended indicators	At least all 22 high-burden countries	All countries implement monitoring	All countries sustain monitoring
Drug resistance surveillance established, or periodic survey conducted	At least 5 high-burden countries	At least 10 high-burden countries	All 22 high-burden countries
Health Sector Development			
Basic outcome measures for TB programme are incorporated as a performance indicator for overall health-sector performance	At least10 high-burden countries	At least all high-burden countries	All countries*
Health-care network, including private health-care providers and the community, are participating in the implementation of the DOTS strategy as part of the country policy for TB control	At least 10 high-burden countries	At least all high-burden countries	All countries*
Operational Research			
National capacity developed to undertake operational research in order to accelerate DOTS expansion and to improve TB control (including control of the treatment of MDR-TB)	At least 10 high-burden countries	At least all high-burden countries	Most of the high incidence countries**
Integrated care approaches within the public health community are operational, and multi-sectoral plans to control TB have been implemented	–	–	In few countries

Notes

*Countries with estimated rate of all forms of TB greater than 20 cases per 100,000 population

**High incidence is defined as an incidence of all forms of TB that occurs in greater than 100 cases per 100,000 population.

1.4 ACTIVITIES

The designated activities of the DOTS Expansion Working Group are to:

- regularly update the Global DOTS Expansion Plan (GDEP) and prepare an annual plan of action for major partners;
- facilitate the development and implementation of regional and country plans for each WHO region and (at least) for each of the 22 TB high-burden countries;
- monitor progress of DOTS expansion and adapt plans so as to achieve the global targets by 2005;
- monitor expansion of DOTS strategy in specific settings such as prisons and other special population groups;
- monitor the effects of TB control in health sector development and poverty reduction by promoting the development and the use of defined indicators;
- promote and monitor community involvement in TB control by providing guidelines and training material targeting local communities and leaders; and
- promote and disseminate examples of policies and experience in engaging private sectors and non-health sectors in TB control.

The DOTS Expansion Working Group identifies a lead technical partner for each high-burden country. This partner takes primary responsibility for responding to each country's needs. It also serves as a facilitator for the establishment of a National Interagency Coordinating Committee. Country assistance, capacity building, monitoring and evaluation, and operational research/development of new approaches are shared by government and partners. The annual plan of action defines the role and duties of each partner, as well as the resources needed to undertake activities.

1.5 RESOURCE NEEDS

The annual budget for the DOTS Expansion Working Group is $225 million per year over the next five years. The financing gap for this Working Group is currently estimated at $116 million. A summary budget and annual detail are provided in Annex 2.

2. Working Group on TB-HIV

2.1 RATIONALE

Tuberculosis, HIV, and malaria are communicable diseases of the poor that demand priority attention. The dramatic escalation of TB-incidence rates in high HIV-prevalence populations demands particularly urgent action. The Stop TB Working Group on TB among HIV-infected people provides a means of scaling up and coordinating action in response to this public health emergency. This response requires collaboration between national TB and HIV/AIDS programmes.

The internationally recommended TB-control strategy DOTS is acknowledged by the World Bank as being one of the most cost-effective interventions employed in human health programmes today; it is being rapidly implemented to control TB. But the DOTS strategy

needs to be adapted to high HIV-prevalence populations. The two diseases have a deadly synergy. Tuberculosis is a leading cause of HIV-related disease and death, and HIV is the most important factor fuelling the TB epidemic in many countries. In order to combat the scourge of TB-HIV co-infection, a new international strategy is needed, as are new approaches to combat TB in HIV-infected people, and close collaboration between HIV/AIDS and TB-control programmes.

The World Health Organization and UNAIDS are developing a new technical framework to guide national strategies for controlling TB among HIV-infected people. This framework calls for collaborative initiatives from HIV/AIDS and TB programmes in support of general health service responses to patients in high HIV-prevalence populations. The goal is to reduce TB disease and deaths as a means of reducing HIV-related disease and deaths.

The framework is relevant to all regions where high rates of HIV infection may fuel the TB epidemic, especially in sub-Saharan Africa, which bears the overwhelming brunt of HIV-related TB. It is likewise relevant to countries like the Russian Federation and Ukraine, where rates of TB and HIV infection are growing at alarming rates. The evolving international response to TB among HIV-infected people considers the perspective of people living with HIV, for whom TB is often only one illness among many. The response to TB-HIV co-infection also focuses on the public health goals of reducing both HIV and TB transmission and, thereby, reducing the burden of both diseases. The new framework represents a coherent health-service response that incorporates prioritised interventions relevant to different levels of the health-care system, while staying within a given country's resource level.

The current approach of DOTS programmes is to identify TB cases among patients presenting to general health services. In HIV-prevalent populations, this approach must be supplemented by intensified case-finding among those at high risk of TB infection, and by a series of interventions designed to decrease transmission and treat patients suffering from either or both diseases. These interventions include:

- measures to decrease HIV transmission (for example, condoms, treatment of sexually transmitted infections);
- antiretroviral therapy;
- preventive therapy aimed at the first and recurrent episodes of tuberculosis; and
- antibiotic prophylaxis against bacterial infections.

The ProTEST Initiative is an example of important operational research now underway to evaluate methods of providing these interventions and taking them to scale. Ultimately, WHO will produce policy recommendations for use by all WHO Member States, based on the lessons learned from field experiences of TB and HIV/AIDS programme collaboration, such as the ProTEST Initiative.

At the DOTS Expansion meeting in Cairo in November 2000, WHO and UNAIDS held an informal consultation with Stop TB Partners and national tuberculosis programme managers from TB high-prevalence countries. Meeting participants agreed to establish a global working group on TB among HIV-infected people, to be coordinated by WHO under the auspices of the Stop TB initiative.

At its first meeting in Geneva, 9–11 April 2001, the TB-HIV Working Group endorsed the principles set out in the draft document, *A New WHO/UNAIDS Technical Framework to Guide Country Strategies for Better Tuberculosis Control Among HIV-Infected People*. The Working Group also recommended joint activities on the part of those involved in TB and HIV control at international, national, and district levels, and proposed mechanisms for joint activities.

2.2 PURPOSE

The purpose of the TB-HIV Working Group is to ensure collaboration between TB and HIV communities in developing, testing, and scaling up strategies to reduce the burden of TB in high HIV-prevalence populations.

2.3 SPECIFIC OBJECTIVES

A principal objective of the TB-HIV Working Group is to coordinate activities of prominent partners—both individuals and institutions—who have recognized experience in controlling HIV/AIDS. Without active participation and collaboration from such individuals and organizations, the goal of the Working Group cannot be achieved. The other specific objectives are to:

- develop a new technical framework to guide country strategies to better control TB among HIV-infected people, informed by a review of the current evidence and modified in future by field experience;
- promote integration of the new technical framework into the DOTS strategy;
- form partnerships and promote collaboration between TB and HIV/AIDS programmes; and
- advocate for increased resources to tackle TB as a leading cause of illness and death among HIV-infected people.

2.4 EXPECTED OUTCOMES FOR 2001–2005

The expected outcomes and target goals of the TB-HIV Working Group for the next five years are as follows.

- **By the end of 2001**, to have developed a new technical framework to guide country strategies for better TB control among people infected by HIV, and to have the framework endorsed by WHO, UNAIDS, and the working groups.
- **By mid-2002**, to have developed and disseminated guidelines on the phased implementation of TB and HIV/AIDS programmes' collaborative activities.
- **By the end of 2002**, to have a policy resolution endorsed by the World Health Assembly on collaboration between national TB and HIV/AIDS programmes.
- **By the end of 2002**, to have initiated phased implementation of TB and HIV/AIDS programme collaborations in six sub-Saharan African sites and three elsewhere, such as in South-East Asia. This initiation is expected to establish the feasibility and effectiveness of collaborative TB and HIV programme support to general health-service providers.
- **By the end of 2003**, to have promoted national strategies in response to TB in high HIV-prevalence populations, based on experience gained from phased implementation of TB and HIV programmes' activities.
- **By 2005**, to have adapted and scaled up these national strategies in most HIV high-prevalence countries.

2.5 RESOURCE NEEDS

The total budget for the TB-HIV Working Group is $12.3 million over the 2001–2005 period. The financial shortfall for this Working Group is currently estimated to be $10 million. A summary budget and annual detail are provided in Annex 2.

3. Working Group on DOTS-Plus for MDR-TB

3.1 RATIONALE

DOTS-Plus is a new strategy being developed and tested by WHO and its international partners to treat MDR-TB, which has been shown in two separate surveys to be present in nearly all of the countries surveyed.

Multidrug-resistant tuberculosis is managed in industrialized countries using tailored treatment regimens based on the patient's drug-susceptibility pattern. DOTS-Plus is designed, likewise, to manage MDR-TB by treating patients in low- and middle-income countries with second-line anti-TB drugs. But there is as yet no conclusive evidence that this approach is feasible in resource-poor settings. In some settings, drug susceptibility testing (DST) is not widely available and second-line anti-TB drugs are not affordable. As a result, programme and management strategies need to be adapted and carefully tested before they are issued as recommendations.

3.2 PURPOSE

The Working Group on DOTS-Plus for MDR-TB exists to:

- assist in producing policy recommendations for WHO Member States regarding the management of MDR-TB, based on the results of pilot projects being conducted by working group partner organizations;
- coordinate and monitor the implementation of comparable MDR-TB pilot projects;
- establish a system that gives WHO Member States access to high-quality, second-line drugs at reduced prices and, at the same time, prevents misuse of such drugs;
- review progress achieved within the DOTS-Plus initiative; and
- identify resources to fund and implement DOTS-Plus pilot projects and assist with global coordination of the initiative.

3.3 SPECIFIC OBJECTIVES

The Working Group has established several subgroups to pursue its goals, including a scientific panel and the Green Light Committee (GLC). The objectives of these subgroups follow.

The Scientific Panel on Programmatic and Clinical Issues has three specific objectives:

- First, to prepare and review guidelines to implement DOTS-Plus pilot projects. The panel met this first objective by preparing and publishing its *Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of MDR-TB.* This document will be reviewed and revised periodically to reflect the most recent data available.

- Second, to assess the data generated by the pilot projects, in order to ultimately advise WHO in developing policy recommendations for WHO Member States.
- Last, to provide technical advice on drug procurement and resolve programmatic and clinical issues regarding the management of MDR-TB.

The GLC, which originally evolved from a Subgroup on Drug Procurement Systems, makes recommendations for increasing access to, and lowering the cost of, high-quality, second-line anti-TB drugs. As a result of the GLC's work, prices of these drugs have already fallen considerably. The subgroup also established two drug procurement arrangements that, together, will eventually supply complete treatment courses for qualifying DOTS-Plus pilot projects.

The objectives of the GLC are:

- First, to evaluate proposals from potential DOTS-Plus pilot projects to determine if those projects have adequately addressed all issues highlighted in the *Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of MDR-TB*. Qualifying projects may benefit from concessionally priced second-line anti-TB drugs obtained as a result of the work of the Subgroup on Drug Procurement Systems.
- Second, to promote technical assistance (through the partners participating in the working group) for the submission of proposals to the GLC and for implementation of the project protocols.
- Last, to periodically reassess pilot projects whose applications meet the requirements highlighted in the *Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of MDR-TB*. Where WHO deems necessary and appropriate, the reassessments may include site visits.

3.4 RESOURCE NEEDS

The total budget for the Working Group on DOTS-Plus for MDR-TB is $16 million over the next five years. The funding shortfall is $14 million. A summary budget with annual detail is provided in Annex 2.

4. Working Group on New TB Diagnostics

4.1 RATIONALE

More than a century after its original development, the microscopic examination of sputum is, in most developing countries, still the only widely available diagnostic tool for identifying TB. The lack of sensitivity of this technique for non-infectious cases, compounded by the difficulty of maintaining well-equipped laboratories to perform it, means that only a fraction of patients with TB symptoms will currently get an accurate laboratory diagnosis. The relatively poor performance of TB diagnostic tests leaves large numbers of infected patients undetected; erodes faith in public health services; impedes the expansion of DOTS; increases morbidity; and, most importantly, allows continued transmission of disease.

In addition to improving case-detection, new diagnostic tools are also urgently needed for the rapid testing of a patient's susceptibility to anti-TB drugs and for the detection of latent TB infection. 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). The result is increased morbidity, the selection of drug-resistant populations of bacteria, and the continued transmission of MDR strains. Likewise, the absence of an operationally convenient diagnostic test for latent infection that accurately predicts the risk of TB, especially TB in HIV-infected patients, restricts the use of recently validated short (two-month) regimens that effectively prevent the development of active disease.

Recently, impressive technical advances in the disparate fields of genetics, microelectronics, cell biology, polymer and combinatorial chemistry, phage biology, bioinformatics, and nanotechnologies have catalysed a revolution in infectious disease diagnostics. Harvesting this technical progress to develop new TB diagnostic tools appropriate for low-income settings is the mandate of the TB Diagnostic Initiative (TBDI). This partnership initiative of the Special Programme on Research and Training in Tropical Diseases (TDR) works with industry, academic researchers, and public health workers to facilitate the development of new TB diagnostic tools to support TB-control efforts.

However, success in TB diagnostics will require more than just improved tools. Solid information on how to use such tools will also be necessary—better data on the impact of early case detection on TB transmission; the cost-effectiveness of routine or targeted drug-susceptibility testing; and the appropriate role for treatment of latent or sub-clinical TB in disease-endemic countries (DECs).

Finally, as improved tools are generated and their proper use demonstrated, mechanisms will be needed to ensure not only that these tools are available and properly used in areas of the greatest need, but also that developing countries are protected from wasting precious health-care resources on other poorly functioning or inappropriate diagnostic kits that are rapidly becoming commercially available.

4.2 OBJECTIVES

The specific objectives of the Working Group on New TB Diagnostics are to:

- develop new, improved tools for the detection of tuberculosis disease, drug resistance, and latent infection;
- develop strategies for optimised and cost-effective use of new diagnostic tools; and
- develop methods to ensure delivery of effective tools to areas of need, as well as methods to prevent these areas from being subjected to poorly functioning or inappropriate diagnostics.

4.3 STRATEGIES AND OUTPUTS

The strategies needed to achieve the Working Group's objectives are:

- **Working with industry to facilitate development of appropriate tools.** Small business grants to directly fund the development of specific tools will be made available to appropriate industries. However, such funds will be offered only when the industries cannot be stimulated to engage in this work without external support.

- **Developing a base of evidence to identify appropriate uses of new diagnostic tests.** Solid data from well-performed clinical trials will be critical to the design of diagnostic algorithms for cost-effective TB control using new and existing tools. Steps to obtain these data include:
  - expanding the clinical trial network to ensure regional diversity (so as to include both developed and developing countries) and exploiting existing TBDI Specimen Bank sites;
  - engaging Stop TB Partners in the development of an expanded trial network capable of carrying out studies in accordance with good clinical practice (GCP) guidelines; and
  - performing trials, such as:
    - clinical evaluation of new diagnostic tests;
    - measuring impact of early detection on disease transmission;
    - regional studies to elucidate the essential factors responsible for diagnostic delay;
    - preventive therapy trials in DECs using alternative detection tools for latent infection;
    - cost-effectiveness of trials of early drug-resistance detection; and
    - efficacy of new tools to predict TB risk in migrant populations.

- **Instituting a diagnostic evaluation system.** Currently, most public health agencies in developing countries have no means of determining the quality, utility, cost-effectiveness, or local appropriateness of new diagnostic tests. Regulatory approval of diagnostic tests intended for low-income countries rarely is required. A diagnostic evaluation unit would be a sustainable resolution to this problem. Steps in the development of a diagnostics evaluation unit would involve actions to:
  - establish consensus on technical criteria for acceptable performance standards of TB diagnostic assays, by indication;
  - construct legal, technical, and administrative infrastructure for the unit and ensure its sustainability;
  - establish collaborating centres for laboratory and clinical evaluation of commercial diagnostics; and
  - with the cooperation of health ministries in disease-endemic countries, develop methods to ensure distribution of product evaluation results.

4.4 RESOURCE NEEDS

The Working Group on TB Diagnostics has a budget of $27 million over the four-year period from 2002 through 2005. The funding shortfall is $21 million. A summary budget with annual detail is provided in Annex 2.

5. Working Group on TB Drug Development

5.1 RATIONALE

The duration of the current treatment regimens recommended under DOTS protocol is six to eight months. This length poses serious operational problems for DOTS expansion. However, successfully reducing the duration of treatment is impossible with current antibiotics.

While treatment with DOTS is inexpensive, DOTS regimens can be difficult to implement. Once again, because of the length of treatment, high rates of patient non-compliance lead to more deaths, as well as to the creation of chronic, infectious, drug-resistant TB strains, against which most existing drugs are ineffective or prohibitively toxic.

In the face of the HIV/AIDS epidemic, new "sterilizing" drugs with shorter regimens are needed for those HIV/AIDS patients most at risk of latent TB infection, which could develop into active TB. New drugs are urgently needed to shorten the duration of treatment to less than three months; to treat resistant strains; and to prevent progression from latent infection to active disease.

The recent genome sequencing of *M. tuberculosis* and the development of automated discovery techniques (such as high throughput screening) underscore the potential for major new inroads to be made against TB.

Yet, virtually no new class of TB drug development has been initiated in the past 30 years. Tuberculosis is not considered a priority for investment by the private pharmaceutical industry. The message that new drugs are needed and would meet unmet medical needs has been heard only recently. Research activity remains low, at least in part because the actual size of the market, upfront research and development costs for drug development, and the attendant risks—and opportunities—are insufficiently appreciated by the pharmaceutical industry.

Coalitions and partnerships are needed to initiate investments in anti-TB drug research and development by ultimately lowering the investment burden borne by a single agency or company.

At a February 2000 meeting in Cape Town, South Africa, 120 representatives from academia, industry, major agencies, and NGOs—as well as donors from around the world—gathered to discuss the problems of TB treatment. Participants stressed the need for new TB drugs and highlighted the unprecedented scientific opportunities that allow such drugs to be developed, as well as the economic rationale for developing new TB treatments.

The resulting *Declaration of Cape Town* provided an initial road map for the Stop TB Working Group on TB Drug Development to take action. It also gave the impetus for the creation of the Global Alliance for TB Drug Development, a public–private partnership with the mission to accelerate the discovery and/or development of cost-effective, affordable, new TB drugs that will shorten treatment, be effective against multidrug-resistant TB, and improve the treatment of latent TB infection.

The Global Alliance for TB Drug Development has thus become the lead agency for the TB Drug Development Working Group, involving members and other experts in the research leading to publication of its *Scientific Blue Print for TB Drug Development* and its report on the *Pharmacoeconomics of TB Drug Development*. These publications are landmark studies to guide strategic investments in the research, acquisition and development of promising new drug candidates.

5.2 PURPOSE

The singular purpose of the Working Group on TB Drug Development is to ensure that TB-control efforts are made sustainable by developing new, effective, and affordable anti-TB drugs.

5.3 STRATEGIC OBJECTIVES

The objectives of the Working Group are twofold:

1. to develop new drug(s) to:
   - shorten and/or simplify the treatment of TB disease;
   - more effectively treat MDR-TB; and
   - treat latent TB infection more effectively.
2. to have at least one new anti-TB drug registered by 2010 and available in high-burden settings by 2012.

5.4 RESOURCE NEEDS

The total budget for the Working Group on TB Drug Development is $29.7 million over the four-year period from 2002 through 2005. The funding shortfall is $23.8 million. A summary budget with annual detail is provided in Annex 2.

6. Working Group on TB Vaccine Development

6.1 RATIONALE

The necessity to improve the effectiveness of the current tuberculosis vaccine, Bacillus Calmette Guérin (BCG), has been recognized for years. Whereas BCG is effective against severe complications of TB in children, in certain tropical areas the vaccine appears to be of little use in protecting against pulmonary TB in adults.

Now, a series of recent developments in the fields of microbiology, genetics, and biotechnology have revolutionized knowledge about *M. tuberculosis*, the microorganism responsible for TB. Consequently, for the first time in BCG's more than 70-year history, a realistic chance exists that research will lead to the availability of a new and improved TB vaccine in the foreseeable future.

The TB Vaccine Working Group is comprised of members of the Tuberculosis Vaccine Initiative Advisory Committee (TBVIAC). This committee was formed in June 2001 to advise the

Initiative for Vaccine Research (IVR), WHO, and the Global Partnership to Stop TB on activities needed to accelerate and strengthen the development, clinical testing, and introduction of improved TB vaccines for the global community.

The Global Forum on TB Vaccine Research and Development, held in July 2001, made the following recommendations to stimulate TB-vaccine development:

- Efforts should now move beyond pre-clinical testing of candidate vaccines into human clinical studies. Evaluating the safety and immunogenicity of TB-vaccine candidates in clinical trials will now be the driving force in vaccine development. Current screening of vaccine candidates using animal models requires the further development of these models to address human disease paradigms and practical issues (such as predicting vaccine dose and immunization schedules).
- Equal emphasis should be given to all important aspects of vaccine development, including pre-clinical testing, clinical testing, vaccine manufacturing and the issues of vaccine access, and introduction of new vaccine into endemic areas. Specific objectives in each of these areas should be pursued simultaneously and in parallel. Resources should be found to move forward on all unmet objectives, rather than awaiting successful completion of one major objective before proceeding to the next.
- Because communication between all parties involved in developing new TB vaccines is critical, a centralized location for the flow of information and notification of activities related to TB-vaccine development should be established.
- The pharmaceutical industry must be engaged in TB-vaccine development, if the TB Vaccine Working Group is to meet the ultimate goal of the sustained delivery of sufficient quantities of vaccines that meet the qualities and standards of Good Manufacturing Practice (GMP) to the areas of the greatest need. Currently, roughly 388 million doses of BCG vaccine are administered worldwide each year; the sheer volume of vaccine administered testifies to the need for significant high-quality manufacturing facilities to be in place to meet the demand for a new TB vaccine.
- Because the streamlined introduction of TB vaccines into developing countries requires adequate and timely supplies, a vaccine-economic analysis is needed to identify mechanisms for vaccine procurement and delivery, and to accelerate regulatory processes. Creative processes for building public–private partnerships, as well as agreements with national vaccine producers, will be vital to the success of the TB-vaccine effort.
- Additional BCG clinical studies are needed to address important questions. These questions explore topics such as the investigation of immune correlates, immunization of certain target populations, immunization of adults, and the measuring of the adjuvant properties of BCG. Results derived from the exploration of these topics will be relevant to the study of new candidate vaccines, and will provide a framework for designing clinical protocols and developing clinical site infrastructure in endemic countries. In addition, solving ongoing problems faced by the current BCG global immunization programme is imperative for the efficient introduction of novel TB vaccines. The counterproductive goals of attempting to discover a vaccine better than BCG for protection against TB while simultaneously using BCG as a vector for developing new vaccines for other indications (HIV/AIDS, malaria, and pneumococcus, for example) illustrate the need for better communication and coordination among vaccine programmes.

The objectives for a new TB vaccine vary. Controlling disease and substantially reducing TB-transmission will require a vaccine that is effective for individuals infected with *M. tuberculosis*, co-infected with HIV, and/or immunized with BCG, as well as for individuals who are not yet infected with the *M. tuberculosis* bacillus. Designing TB vaccine strategies based on the needs of these target populations may ultimately prove to be the most successful approach. Ultimately, controlling TB may also require combined prophylactic strategies including effective vaccines, treatment with potent drugs, and identification of infection and disease with specific diagnostic tools. Engagement of all parties in the complex process of accelerating TB vaccine development, especially those working directly with patients, is fundamental to the TB vaccine strategy.

6.2 GOALS

The goal of the TB Vaccine Working Group is to have a safe, effective, and reasonably priced TB vaccine licensed for global distribution by 2015, and to have the vaccine widely used in TB high-burden countries by 2020.

6.3 SPECIFIC OBJECTIVES

In order to achieve the Working Group's goal, the following objectives will need to be met by 2005:

- a minimum of five TB-vaccine candidates must be tested in clinical studies; and
- clinical site infrastructure must be strengthened to begin testing a minimum of one TB-vaccine candidate in phase III trials.

6.4 RESOURCE NEEDS

The budget for the Working Group on TB Vaccine Development amounts to $4.4 million over the next four years, excluding costs for research and development. Current financial commitments total $1 million. A summary budget and annual detail are provided in Annex 2.

Chapter 8

Supporting the Global Plan to Stop TB

1. Building the Partnership—The Stop TB Secretariat

1.1 RATIONALE

The *Global Partnership to Stop TB* has grown rapidly since its launch in November 1998. It now consists of over 200 organizations around the world, all committed to the vision, mission, and objectives of Stop TB, and working together in accordance with the values of the Partnership. Beginning in June 2001, the Secretariat invited partners to submit information on their activities to a directory of Stop TB Partners (www.stoptb.org/Partners_Directory/). Eighty-three partners, including nearly three-quarters of all major institutional partners, have thus far completed an entry. The portrait of the Partnership is presented below in Section 2, drawn from these submissions.*

To support these organizations in the fulfilment of the Partnership's vision and mission, WHO has established a Stop TB Secretariat, staffed by WHO and partner secondments. Many activities of the Secretariat are carried out in collaboration with specific partners.

1.2 OBJECTIVES

The Stop TB Secretariat has four main areas of activity, corresponding to the objectives of partnership strengthening.

*The Partnership has grown considerably since this survey was conducted in June 2001. The eighty-three responses represented a majority of those surveyed.

1.2.1 PARTNERSHIP BUILDING

The Secretariat performs the following partnership-building activities:

- Maintenance of a web-based directory of partners (www.stoptb.org) providing contact details of organizations and identifying geographical and functional areas of interest.
- Organization of meetings of the Coordinating Board and the Partners' Forum, and assistance in organizing meetings of working groups and task forces.
- Development of regional and national partnerships, such as interagency coordinating committees on TB. Frequently, these are cross-cutting coordination mechanisms that serve several aspects of health (for example, vaccination, and HIV/AIDS, and sector-wide approaches).

1.2.2 INFORMATION AND COMMUNICATIONS

The Secretariat performs the following information and communications activities:

- Dissemination of pertinent information by e-mail, Internet, publications, and other means.
- Maintenance of the database of TB-related information for the Partnership.

1.2.3 ADVOCACY

In collaboration with other partners, the Secretariat:

- develops TB-related advocacy messages;
- organizes and coordinates World TB Day activities; and
- assists partners and countries in implementing local advocacy activities.

1.2.4 RESOURCE MOBILIZATION

In collaboration with the Stop TB Coordinating Board and other partners, the Secretariat:

- implements the resource mobilization plan for the Partnership; and
- develops financing mechanisms for the Partnership.

In addition to these activities, the Secretariat also functions as the Secretariat for the Global TB Drug Facility, managing and/or coordinating processes relating to country applications, procurement of drugs, and monitoring.

1.2.5 GLOBAL TB DRUG FACILITY

The Stop TB Secretariat also functions as Secretariat for the Global TB Drug Facility (GDF)—a new initiative of the Stop TB Partnership to increase access to high-quality TB drugs. Launched in early 2001 with funding from the Canadian government, and housed in WHO, the GDF aims to treat more than 10 million people with TB by 2005, in support of the global targets for DOTS expansion. The role of the GDF Secretariat is to manage processes relating to applications and review, procurement of drugs, and monitoring. These different functions are carried out by different partners and are coordinated by the GDF Secretariat, through contracts and agreements.

The GDF has already had a significant impact. Two rounds of applications have been reviewed, with 25 countries submitting applications by December 2001. Of these, 16 had been approved

for support, and drugs ordered for over 630,000 patients. Pooled procurement, standardisation of products, and international competitive bidding has also had a profound impact on drug prices, with a six-month course of daily treatment now costing less than $10—one-third lower than previous international prices.

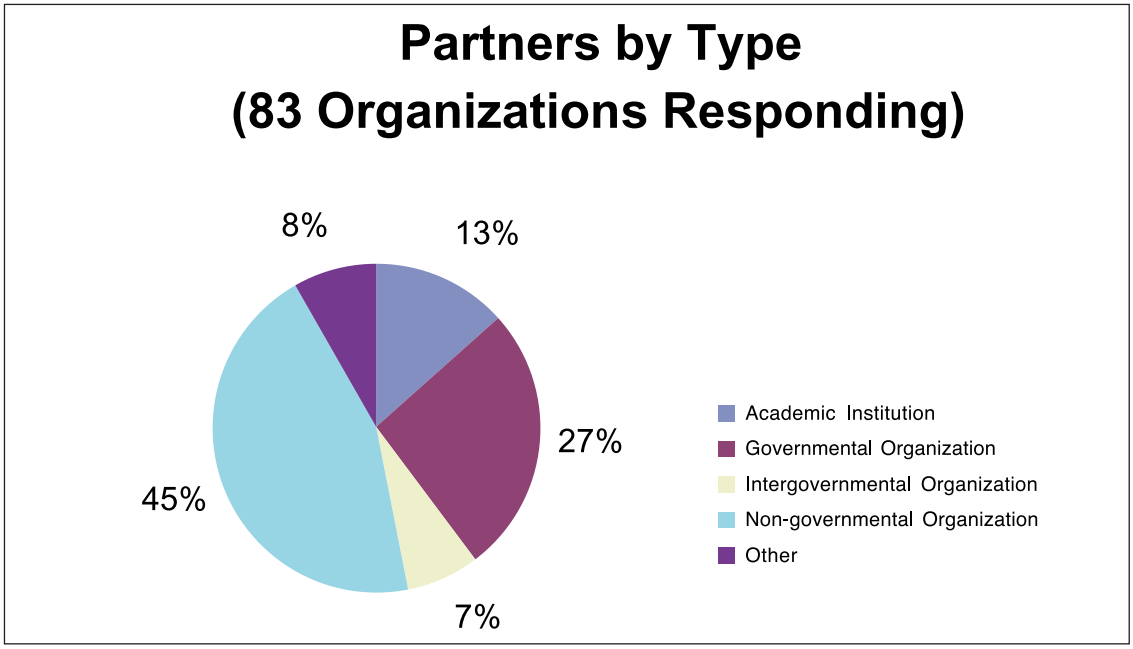
Activity area	Budget 2001 – 2005 ($ millions)*
Partnership building	6
Information and communications	4
Advocacy	10
Resource mobilization	7
Global TB Drug Facility	See DOTS Expansion budget
Total	**27**

**Projected from a two-year budget of the Stop TB Secretariat. Further detail is available from the Secretariat.*

1.3 RESOURCE NEEDS

As of December 2001, known contributions to the Secretariat amounted to some $10 million, leaving a resource gap of $17 million.

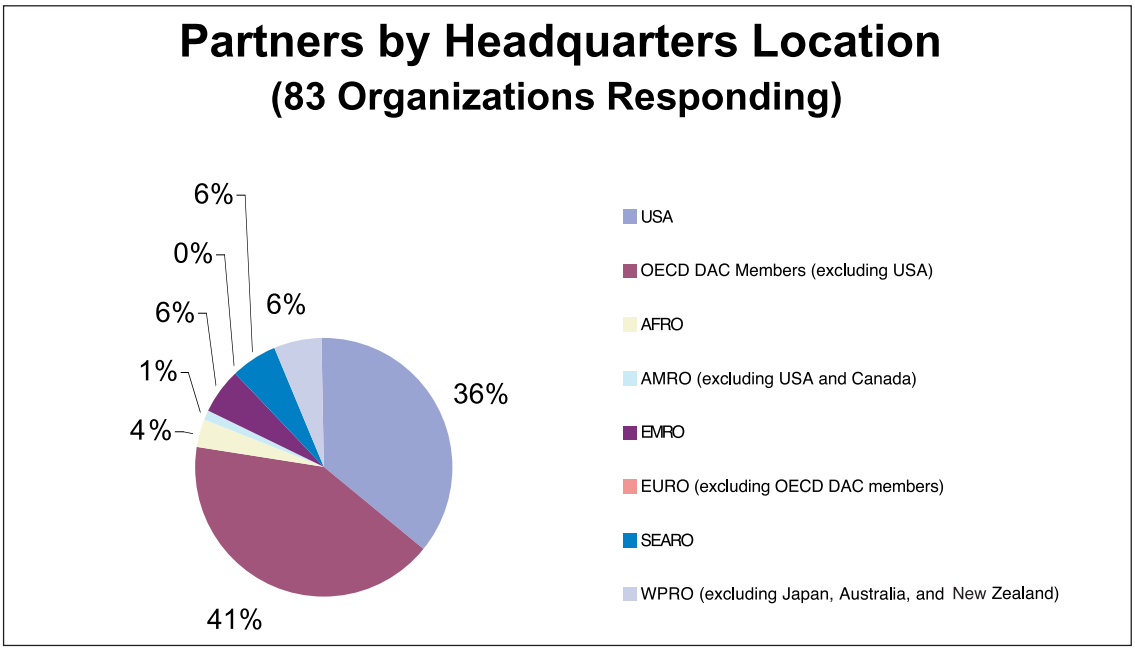
2. Building the Partnership: Who Are the Partners?



The Stop TB Partnership embraces organizations of many types: for-profit corporations; non-governmental organizations (NGOs); governmental public health agencies, both national and sub-national; bilateral aid agencies; multilateral organizations; and others. Nearly half of the respondents to the directory were NGOs. Approximately 25 percent were governmental bodies, split almost evenly between technical and donor agencies.

Partners also vary greatly in the depth and scope of their TB-related work. The number of professional staff working on activities related to TB and the amount spent on TB activities in 2000 were used to gauge the depth of partners' work. Nearly 50 percent of respondents reported five or fewer professional staff working on TB, while 25 percent reported between six and ten. Still, 11 percent of all partner organizations reported more than 20 such staff. Of the 53 partners providing information on expenditures, 25 percent spent less than $100,000; 33 percent spent between $100,000 and $1 million; another 33 percent spent between $1–10 million; and the remainder spent more than $10 million on TB control.

Partners reported on both present and projected work. They reported ongoing work in more than 90 countries. In five countries—Bangladesh, India, the Philippines, Russia, and the United States—five or more partners were reportedly working simultaneously. Twenty-eight countries in the WHO Regional Office for Africa (AFRO) and eight countries in the WHO Regional Office for South-East Asia (SEARO) reported at least one active partner. Regarding projects in the planning stages, 18 partners noted plans for 35 projects in 23 countries, including four new countries—El Salvador, Malawi, Mozambique, and Somalia—where no partners are currently active.



In summation, the Partnership is remarkably diverse as far as the types of organizations it includes and the intensity and scope of their TB efforts. This diversity is regrettably not matched by "geo-economic" diversity. Nearly 80 percent of respondent organizations were headquartered in one of the 21 Organization for Economic Cooperation and Development's (OECD's) Development Assistance Committee (DAC) countries.

Only three respondents to the Stop TB directory were based in AFRO, and only five in SEARO. Doubtless, a significant proportion of partners that did not respond were smaller organizations based in high-burden countries (HBCs), or other low- or middle-income countries. Yet, including both respondents and non-respondents, fully half of all partners are based in the OECD DAC countries.

This imbalance points to the need for the global partnership to encourage and, where necessary, to fund active participation by organizations based in HBCs or other low- and middle-income countries. It also suggests the need for Stop TB to develop strong regional and country-level partnerships, and foreshadows the challenges such an endeavour may involve.

2.1 PARTNERS' WORK IN TB HIGH-BURDEN COUNTRIES

The portrait reported here of Partners' activities is unfortunately not comprehensive, but a partial portrait follows below.

Overview: Twenty-five partners presently work in one or more countries designated as high-burden; there are sixty-nine distinct interventions. Each HBC has at least one partner presently active while nine HBCs, including five of the highest burden countries, have two or fewer. Furthermore, twelve HBCs, including nine of the highest burden countries, now find themselves with meagre prospects for welcoming new partners. For these countries, the number of partners planning future work, combined with the number of partners interested in taking on work given substantially greater resources, was either one or zero.

TB-HIV: Thirteen HBCs had no partners reporting either present or planned work on TB-HIV; a further five HBCs had just one such partner. Among these 18 countries were eight in which more than two percent of adults were estimated to be living with HIV/AIDS at the end of 1999. (These countries include D.R. Congo, Ethiopia, Nigeria, Uganda, and Zimbabwe.) Kenya (three partners) and Russia (four partners) were associated with the most partners working or planning work in this area.

MDR-TB: Thirteen HBCs had no partners reporting either present or planned work on MDR-TB, including most notably Brazil, China, Thailand, and Zimbabwe. A further three countries had just one such partner each. India, with what is likely to be the world's largest number of new MDR-TB cases each year, had two. Russia had six.

Technical Support: Seventeen HBCs had two or fewer partners reporting either present or planned provision of technical support. Afghanistan, Thailand, Viet Nam, and D.R. Congo had no partners. South Africa, Uganda, and Zimbabwe had just one. India, Indonesia, Nigeria, Pakistan, and Russia had three or more. Others had two.

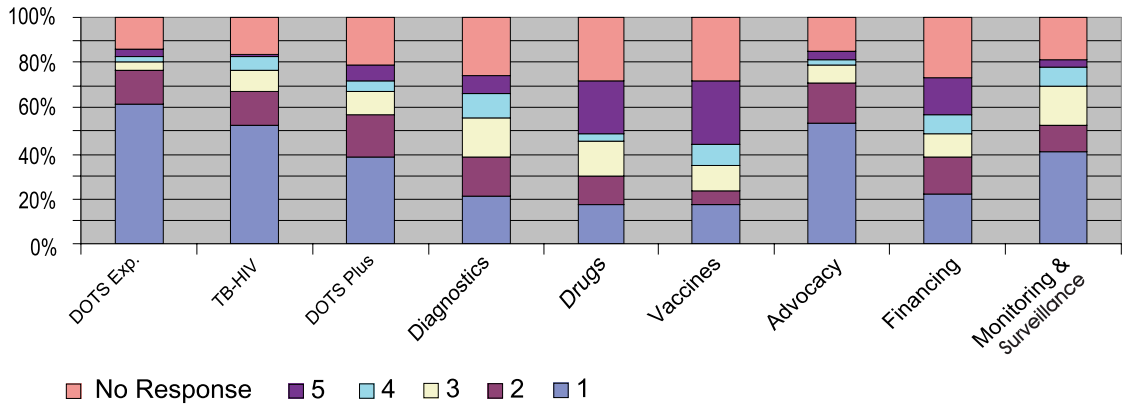
2.2 WHAT PARTNERS BRING TO THE PARTNERSHIP AND WHAT THEY EXPECT FROM IT

Partners were asked to name the most important things they could bring to the Partnership. Responses were grouped according to type of organization, and tended to cluster predictably within types. That said, some unexpected regularities appeared across types. For instance, intergovernmental and governmental organizations (whether donors or technical agencies)

often cited TB-HIV as an area in which they could bring value to the Partnership. In contrast, NGOs (whether foundations or general/technical organizations) more often stressed advocacy and resource mobilization capabilities.

Partners were also asked to rate their interest in participating in the Partnership's working groups and task forces. They expressed relatively strong interest in the working groups on DOTS Expansion, TB-HIV, and in the newly formed Advocacy and Communications Task Force—but relatively weak interest in the working groups on Drug Development, Vaccine Development, and newly formed Financing Task Force.

Partners' Interest in Participating in Stop TB Working Groups and Task Forces
(82 Organizations Responding)



Finally, partners were asked to explain what services would be most useful and appreciated from the Partnership and its Secretariat. The two most common responses were remarkably consistent across all organization types. They said that the Partnership (that is, the Secretariat) should serve as:

- a "network hub", facilitating communications among partners and between partners and others, while also serving as a central repository for information about the partners, their activities, and the countries in which they work; and as
- an "information disseminator", propagating research findings, technical guidelines, lessons learned, and best practices; it should also amplify successes of individual partners, both within the Partnership and to the world at large.

3. Supplemental Advocacy and Communications for the Global Partnership to Stop TB

3.1 RATIONALE

Successfully implementing the *Global Plan to Stop TB* will require sustained support, internationally and at national and local levels, especially in the 22 TB high-burden countries.

Advocacy and communications efforts to generate this support must go well beyond the efforts of recent years, and will require support beyond what is currently budgeted by the Stop TB Secretariat. These supplemental efforts will be aimed at three key target audiences: decision-makers, health-sector professionals, and communities.

Health-communication programmes can inform, influence, and motivate these target audiences by increasing awareness of public health problems, the issues they encompass, and the solutions available to resolve them. A good outreach programme will positively affect attitudes towards support and public investment. It can also profile the skills and dedication of those working to control an epidemic as well as increase demand for services, reinforce awareness of supportive behaviour, influence opinions, and encourage attitudes such as optimism, compassion, and commitment.

Stages in the health communication process are as follows:

- planning and selection of strategies to reach specific target audiences;
- developing consistent and compelling messages;
- selecting communication channels and materials;
- developing and pre-testing materials;
- implementing strategies;
- assessing the strategies' effectiveness; and
- incorporating feedback to refine the programme.

To ensure a coordinated approach to advocacy and communication efforts, partners in Stop TB are creating an Advocacy and Communications Task Force. The purpose of this task force is to prioritise, plan, develop, and coordinate advocacy and communications strategies for the Stop TB Partnership, and to support the advocacy and communications activities of partner organizations.

3.2 OBJECTIVES

The objectives of the Advocacy and Communications Task Force are to:

- Identify advocacy and communications priorities for the Global Partnership to Stop TB.
- Plan, organize, and coordinate advocacy and communications activities and events, and develop tools in support of the mission of the Stop TB Partnership and the *Global Plan to Stop TB*.
- Develop consistent and compelling messages and advocacy tools in support of the key objectives of the Stop TB Partnership at both the global and national levels.
- Develop mechanisms to support communication between partners, and provide communications/advocacy assistance to partners, working groups, and other organizations at the country level.
- Develop and implement partnership mechanisms to evaluate the effectiveness of the advocacy and communications efforts of the Stop TB Partnership.

At the global level, the Advocacy and Communications Taskforce will contribute to:

- A stronger TB partnership that is consistent in terms of the messages and information disseminated to promote effective action to stop TB.
- Closely coordinated global advocacy campaigns to promote effective action to stop TB.

- Raising resources necessary to support the work of partners and countries in controlling TB.
- More effective use of existing partner resources, both technical and human, to better serve members and TB-endemic countries.

At the country level, the Advocacy and Communications Task Force will contribute to:

- Heightened awareness of TB-related issues among policy-makers, opinion leaders, and influential groups.
- Increased tendencies among policy-makers to adopt and implement policies and programmes in support of achieving TB-control targets as defined by WHO for 2005, 2010, and beyond.
- Better training and awareness of internationally recommended strategy for TB control on the part of public and private health-care workers, and better compliance with this strategy.
- Increased social mobilization in support of TB control and eventual elimination.

3.3 RESOURCE NEEDS

Early estimates place the supplemental resource needs for advocacy programmes at around $20 million over the next five years. However, this estimate is not yet supported by a detailed budget.

4. Financing the Global Plan to Stop TB

4.1 RATIONALE

The Global Partnership to Stop TB has recognized the need of countries and global programmes for financial and economic capacity, information, and resources. Furthermore, the Partnership is an important part of exciting global developments in finance for disease control. In order to coordinate these activities, the Stop TB Partnership has established a task force on financing.

The purpose of this task force is to identify and resolve challenges in financing TB control and research and development across the Partnership in support of the goals of the *Global Plan to Stop TB*, including health-systems development and poverty reduction.

4.2 OBJECTIVES

The Stop TB Financing Task Force has five main objectives:

1. **To assess TB financing at global, regional, and country levels.** To identify financing needs, existing resources, and gaps for TB control. To assess the utilization of financing and its efficiency.

2. **To improve TB finance.** To identify mechanisms for sustainable financing and strategies for resource mobilization.

3. **To improve financial planning, management and accountability**. To stimulate financial capacity building and mainstreaming of health systems issues.

4. **Priority setting.** To provide guidance to the Coordinating Board on priority-setting mechanisms for the allocation of funds.

5. **To act beyond TB.** Coordinate with broader health-system financing agencies and public health priorities at all levels, including disease control initiatives, such as the Global Fund to Fight AIDS, TB and Malaria, the Global Alliance for Vaccines and Immunizations (GAVI), Roll Back Malaria (RBM), UNAIDS, Poverty Reduction Strategy Papers, Sector Wide Approaches (SWAP), WHO's Evidence and Information for Policy cluster, incentives for new products, and so forth.

4.3 RESOURCE NEEDS

The supplemental resources needed are currently estimated at $12.5 million over the coming five years. However, this estimate is not yet supported by a detailed budget.

5. Setting Priorities

Stop TB Partners will regularly monitor and assess progress in reducing the burden of TB and in meeting the principal objectives of the *Global Plan to Stop TB*. The Stop TB Coordinating Board will want to promote particular priorities and concerns based on its assessments of progress, and in response to changing circumstances and opportunities. These priorities and concerns will influence the Coordinating Board's decisions for allocating pooled partnership resources. They will also motivate the board to urge partner organizations and TB-control donors to direct energies and resources to the specified priorities and concerns.

Carefully considered and well-articulated priorities can help Stop TB partner organizations to agree upon their work plans, coordinate them, and implement them effectively. Donors need to recognize and clearly understand the Partnership's priorities if they are to increase funding for TB control. Yet as priorities become more specific, achieving consensus may become more difficult.

This suggests several principles to guide the Partnership in setting its priorities:

- The priorities should be simple and clear, and the reasons for them obvious.
- The process for analysing priorities should not be laborious or overly complex.
- The Partnership's goals in setting priorities should not be overly ambitious. Consensus priorities will be most useful if they build trust and common direction among the partners. By articulating specific priorities, the Partnership will hope to influence marginal change in the activities and resources supporting TB control, not to supersede independent decisions of partner organizations and donors.

The Coordinating Board will establish a process to identify and regularly review its priorities.

6. Monitoring the Global Plan to Stop TB

6.1 RATIONALE

A systematic approach to monitoring is essential to assess implementation of the *Global Plan to Stop TB*. The importance of accurate and systematic global monitoring has long been recognized by those working in TB control. The WHO standardized system for reporting DOTS performance, based on case detection and treatment outcome, is one of the most comprehensive and robust global disease reporting systems in the world.

Monitoring of the *Global Plan to Stop TB* is not limited to national TB-control programme performance; it will incorporate assessment of resource flows, surveillance of drug resistance, and the fulfilment of working group objectives. Many of these monitoring mechanisms are already in place and usually implemented by WHO, which has the lead role in monitoring global trends in health and disease.

The Stop TB Coordinating Board is responsible for overall monitoring of the *Global Plan to Stop TB*, and will report on progress at the Stop TB Partners' Forum.

6.2 OBJECTIVES

The primary objectives of monitoring the plan implementation are to monitor:

- progress towards fulfilling the objectives of the *Global Plan to Stop TB*;
- trends in disease burden and impact;
- TB-control programme performance; and
- activities and investments.

6.3 MECHANISMS

The following monitoring systems will be utilized by the Stop TB Partners to assess progress towards fulfilling the objectives of the *Global Plan to Stop TB*:

- annual reports on national TB-control programme performance, published by WHO, such as the Global Tuberculosis Control Report;
- surveillance of drug resistance, as part of the WHO/IUATLD global project on anti-TB drug-resistance surveillance;
- annual monitoring of TB-control investments by donors and high-burden countries, as well as of research, which will be monitored and published by WHO; and
- annual progress reports by Stop TB working groups to the Stop TB Coordinating Board.

6.4 RESOURCE NEEDS

The resources needed are currently estimated at $15 million over the coming five years. However, this estimate is not yet supported by a detailed budget.

7. Assessing Risk

Because the targets and objectives of this plan are so ambitious, there is clearly a risk that they will not be achieved. Identifying potential risks beforehand can mitigate likely effects.

7.1 DISEASE BURDEN RISKS

Failure to contain the HIV epidemic has obvious and serious consequences for containing TB. Predicting the course of the epidemic is fraught with difficulties, particularly in Eastern Europe and South Asia, where recent rapid increases in the prevalence of HIV are of great concern, and huge populations are at potential risk. If HIV-prevalence rates reach those of countries in sub-Saharan Africa, there will be an enormous increase in the TB epidemic; the capacity of public health services will be further strained; and the likelihood of reaching the global TB-control targets for 2005 and 2010 will be diminished.

Similarly, a rapid and uncontrolled increase in MDR-TB would have catastrophic consequences for TB control worldwide, substantially increasing the disease burden and resource requirements.

7.2 OPERATIONAL RISKS

Delivery of diagnostic and treatment services relies to a great extent on an effective and coordinated health service infrastructure, provided by public health services, NGOs, or the private sector. In parts of some countries, health-care services are nonexistent or poorly developed. Successful implementation of this plan will depend on the ability to scale up service provision through strengthened public health services and innovative approaches. Effective and sustainable coordination mechanisms are required to ensure continuity of standardized care for people moving between different types of service providers, and to ensure comprehensive reporting.

7.3 FUNDING RISKS

Sustainable financing of TB control is essential and will be required for many decades to come. Donor priorities have been notoriously fickle in the past, with frequent changes limiting the capacity of countries to predict resource flows over time. Equally, the capacity of some countries to disburse funds efficiently has been compromised by inadequate governance.

Potential threats to sustainable financing include changes in donor priorities and increasing economic difficulties in low-income countries. Paradoxically, success may also pose a threat, as the history of TB in several high-income countries has demonstrated that a decline in TB is frequently followed by a profound reduction in resources, leading to a recrudescence of disease—the so-called U-shaped curve of concern.

ANNEX 1
Explanation of the GPSTB Cost Projections and TB Control Analysis

The *Global Plan to Stop TB* (GPSTB) estimates that TB-control activities over the next five years will cost $9.1 billion, covering all major TB-control activities:

- Expanding DOTS ($6.2 billion) in all TB high-burden countries and in all other low- and lower middle-income countries[1] (that is, countries with a GNP per capita of $3,000 per year or less[2]).
- Adapting and improving DOTS ($1.7 billion) to cope with TB-HIV co-infection and with multidrug-resistant TB.
- Research for new TB diagnostic tools, drugs, vaccines, and operational improvements ($1.1 billion).
- Partnership initiatives ($75 million)—including advocacy, communications, coordination, and resource development.

Expanding, adapting, and improving DOTS accounts for 87 percent of the GPSTB costs. This annex explains in brief how cost estimates for these components of the plan were analysed and evaluated. Complete detail of the methodology for cost estimates and the epidemiological projections is being published separately as *The Economic Annex to the Global Plan to Stop TB*.

The financial gap between five-year TB-control costs and the available resources is estimated at $3.8 billion, roughly 41 percent of total plan costs. The largest component of this gap is associated with DOTS expansion ($1.6 billion), and is estimated from national TB programme plans that are the basis for WHO's Global DOTS Expansion Plan (GDEP). The GDEP was first published in May 2001, and has been recently revised based on revisions to national TB-control plans (for example, in Indonesia, Pakistan, China, and India). Among these revisions are improved estimates of the general health-system capacity of high-burden countries to support DOTS expansion. The estimated financial gap in this GPSTB is consistent with these new GDEP estimates. The estimated financial gap between needed and available resources for DOTS expansion in other low- and lower-middle income countries is based on an extrapolation from what is known about the capacity in high-burden countries.

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[1] The total estimated plan costs shown in this table exceed the estimate of resources required for global TB control in a recent analysis conducted by WHO (see K. Floyd, L. Blanc, M. Raviglione and J.W. Lee, "Resources Required for Global Tuberculosis Control" Science 2002, in press). This is because the latter focuses on the costs for DOTS implementation, and does not include an assessment of resources needed for MDR-TB, TB/HIV, new diagnostics, drugs and vaccines, and partnership activities. Estimates for DOTS implementation in both publications are similar. In the analysis undertaken by WHO, it is estimated that $6 billion is required for DOTS implementation in the 22 HBC and in the low- and lower-middle income countries outside the 22 HBC during the period 2001-5 ($225 million less than is projected in this plan), and that the resource gap is about $1.5 billion (compared to $1.6 billion in this plan). The differences arise because the two studies were conducted independently and used slightly different methods to project cases to be treated, costs, and available resources. However, the fact that the two studies are broadly consistent strengthens the validity of both estimates. The main difference lies in the cost estimates for low- and lower-middle income countries outside the 22 HBC. This is to be expected given the limited data and the need for more assumptions in estimating costs for these countries. Both sets of estimates will be updated as more data become available.

[2] Appaix, Olivier. Tuberculosis Control: Financial Evaluation for the 2001-2005 Period (in Low- and Lower Middle-Income Countries). Economic Annex to the Global Plan to Stop TB Boston: Partners In Health, to be published in 2002.

The estimated financial gap for TB-HIV prophylactic strategies ($604 million) is projected based on current investment in TB-HIV pilot projects by donors and host governments, but not on any detailed national plans or budgets. Likewise, the gap projected for MDR-TB treatment ($834 million) is based on assumptions of likely national support for successful and cost-effective DOTS-Plus programmes. The projected gap for research and development efforts ($708 million) is based on known research and development commitments in 2001, and assuming that those commitments remain in place over five years. The estimated financial shortfall for the Stop TB Partnership ($65 million) is projected for five years, net of current partnership support, which is assumed to remain constant for the five-year period.

DOTS EXPANSION

Modelling DOTS Expansion in 114 Countries: To accurately capture the costs of TB control in high-burden and low- and lower-middle income countries, the authors of this study constructed a model that projects TB-control costs on a country-by-country basis over the 2001–2005 period. The model builds unit costs for specific TB-control elements in each country, deriving cost from national TB-control programmes plans for 13 high-burden countries, and from health-care cost studies and data from 17 additional low- and middle-income countries. This information was supplemented with questionnaires and personal communications with national programme coordinators from most of the 22 high-burden countries, and with WHO officials around the world. Where specific cost information was lacking, cost estimates for TB-control inputs in specific countries were derived by extrapolating from known costs in neighbouring countries, and/or from countries with analogous socio-economic and epidemiological profiles. Cost projections do not include any inflation adjustments. Costs are calculated in 2000 U.S. dollar equivalents.

Table 1: Cost Projections for DOTS Expansion[3] (in $ millions)

5-Year Costs	
In the 22 high-burden countries	
• TB Programmes	1,560
• General Health Services	3,000
Other low- and middle-income countries	
• TB Programmes	590
• General Health Services	850
DOTS Expansion Working Group	225
Total	**6,225**

[3] See footnote on the preceding page regarding the separate analysis of DOTS expansion costs, which estimated substantially similar costs using somewhat different methodologies.

The GPSTB estimates costs for all TB-control activities in the 114 countries it covers, including the following:

- All activities of national TB programmes—Training, operational research, diagnostic capacity (such as laboratories and equipment), public education awareness initiatives, and a reliable supply of quality drugs, including drugs supplied through the Global TB Drug Facility.
- Expenses for expanding existing DOTS programmes and establishing new programmes—providing capacity adequate to detect and treat the numbers of patients anticipated by the TB-control goals for 2005 and by WHO epidemiological projections.
- Costs for clinical management of routine TB as it is practiced in each country, including costs for the use of hospitals, clinics, dispensaries, and sanatoriums, regardless of whether they are under the control of the national TB-control programme.
- Administrative expense for the management and supervision of increasingly large and complex programmes.

DOTS expansion costs were estimated on a cash basis: how much will the country spend throughout the 2001–2005 period if it expands DOTS as required to meet the targets? The projections include, therefore, the full capital costs of new laboratories, for example, instead of amortizing depreciation costs over the useful life of these facilities.

Estimating the costs to general health-care systems of treating the expanded caseload is fraught with difficulty, not the least of which is uncertainty about the capacity constraints of existing systems. Being unable to predict whether or by how much general health services will have to expand facilities to treat increased numbers of TB patients, the model generated a range of possible costs. The low end of this cost range ($3.2 billion) assumed that, with the efficiencies introduced by expanding DOTS, there will be adequate capacity in health service facilities to handle increased patient populations. The high end of this range ($4.5 billion) assumed that facilities are now at capacity, and that increasing caseloads will require increased capacity. The cost of new capacity was then estimated by assuming that the incremental cost of expansion would be equal to the current average cost (per patient or unit of service) of existing facilities, times the increased number of patients in expanded programmes. In this case therefore, the cost projections include depreciation, and thereby approximate the capital costs of new facilities and equipment.

Within this range—$3.2 to $4.5 billion—we chose a midpoint of $3.85 billion as the estimated cost to general health-care systems of expanded TB control ($3.0 billion in high-burden countries and $850 million in other low- and lower middle-income countries). This represents over half the estimated cost of DOTS expansion. It is necessarily a tentative estimate, and will have to be carefully reconsidered as we learn more about health services capacity in individual countries and as DOTS expansion progresses.

The GPSTB cost projections substantially confirm parallel cost estimates made in the World Health Organization's *Global DOTS Expansion Plan* (GDEP), published last year (May, 2001), despite having used a slightly different methodology, and are consistent with updated GDEP cost estimates that will be published in 2002.

There are important limitations in our ability to project TB-control costs:

- Epidemiological uncertainty due to rapid change in factors affecting incidence of TB, MDR-TB, or TB-HIV co-infection. Estimates will change as we improve our ability to predict disease trends, when incidence falls as a result of TB-control investment, or with unexpectedly rapid progression of TB.
- Uncertainty of cost data. The quality of health-care cost information provided by countries varies considerably, and these costs are moving targets as countries reorganize health-care delivery and reallocate resources. Likewise, estimating the share of a nation's general health-care system devoted to TB control requires gross assumptions that provide indicative, but not fully accurate, cost estimates. This is due in part to evolving protocols and practices.

There are reasons to be cautious in estimating TB incidence, as the *WHO Global TB Control Report 2001* points out: "For high-burden countries, the difference between the lower and upper estimates of (TB) incidence is typically twofold."[4] The GPSTB used the WHO's epidemiological data for 1999 (the most recent available in September 2001). Assuming stable incidence rates, it projected the number of TB cases needed to be detected and treated in each country over the five-year period to achieve the WHO goals for detection of new cases (70 percent) and for successful treatment (85 percent). In 1999, there were an estimated 8.4 million new cases of TB, of which roughly 44 percent were infectious or sputum-smear positive (SS+). Assuming level progress towards the targets, the GPSTB estimates that there will be nearly 43 million new TB cases in the 114 countries covered over the 2000–2005 period, and that 44 percent of cases will be infectious, as shown in Table 2.

Table 2: TB-Control Projections for 2001–2005 in Low- and Lower-Middle Income Countries (cases in millions)

	Current Level of TB Control		Stop TB Goals	
	All Cases	SS+ Cases	All Cases	SS+ Cases
Number of New Cases (Incidence)	42.9	18.9	42.9	18.9
Cases Detected and Treated	19.1	7.7	26.0	11.3
• Covered by DOTS	8.7	4.7	21.5	10.0
• Covered by other protocols	10.4	3.0	4.5	1.3

As this table shows, the plan projects that TB cases detected and treated under DOTS will more than double, if proposed GPSTB investments are made. DOTS programmes will recruit 850,000 additional TB cases each year, of which at least 350,000 will be infectious

[4] World Health Organization. *Global TB Control: WHO Report 2001.* Geneva: World Health Organization, 2001, p.32.

(SS+ cases)[5]— that is, 5.3 million additional smear positive cases over five years. The projected growth in DOTS programme patients will be a function of two factors, reflecting the WHO goals—an increase in TB case detection (+ 6.9 million cases) and in increased DOTS treatment of TB patients whose cases are now being treated under non-DOTS protocols (+ 5.9 million cases).

DOTS is the recommended and generally accepted strategy for TB control throughout the world, but in many countries it is not the exclusive mechanism. Currently, only 46 percent of patients treated for TB worldwide are cared for under DOTS programmes. The remaining patients are treated by other means—often less efficiently and effectively—in national TB programmes, in private practices, or through general health services. In India, for example, only 6 percent of estimated smear-positive TB cases were notified and treated under DOTS (1999), but the DOTS treatment success rate in India is high (84 percent) and the country is expanding its DOTS coverage rapidly. In Russia, to take a second example, TB case notification rates are quite high, but less than 2 percent of smear-positive cases were notified and treated under DOTS in 1999.

The goal of the GPSTB is for all countries to achieve DOTS coverage of 100 percent of their population by 2005, and that 70 percent at least of all new TB cases will be detected and managed by DOTS programmes. The plan projects that DOTS case detection and treatment in each country will increase on a straight-line basis from current DOTS detection and treatment rates to the 2005 target rates, except in countries where credible projections show that targets will be met earlier. But, as noted, this study does not attempt to predict how quickly or to what extent the existing cost structure for TB control in specific countries will change with the increasing use of DOTS.

If DOTS programmes expand as projected and successfully treat 85 percent of patients, they could save some 3.4 million patients who will otherwise die of TB. As noted above, of the additional patients treated in expanded DOTS programmes, 6.9 million will be the result of increased case detection capability. Roughly 3.6 million of these patients will be SS+, and absent treatment, 65 percent of these patients will likely die, as will roughly 40 percent of the remaining, non-infectious TB patients. These figures alone, adjusted for mortality rates of SS+ patients within DOTS programmes (4 percent), yield a conservative estimate of 3.4 million lives that could be saved through DOTS expansion.

DOTS expansion in the 22 high-burden countries is projected to cost $6.2 billion over five years, an increase of $1.66 billion over what is now being spent for TB control. If these cost projections prove accurate, the incremental cost of detecting an additional 6.9 million cases and of treating these patients would thus be $240/patient, and the incremental cost per life saved would be $485. Assuming 24 years of life per death averted produces a cost for DOTS expansion of over $20 per year of life gained, on average.

[5]For comparison, in the Global Tuberculosis Control Report 2002, WHO estimates that an extra 330,000 SS+ cases will need to be treated each year if control targets are to be met. The fact that the 2 figures are very similar strengthens the validity of both estimates."

ADAPTING AND IMPROVING DOTS

Cost estimates for adapting and improving DOTS to cope with multidrug-resistant TB (MDR-TB) and with TB-HIV co-infection are preliminary. Strategies to deal with these health threats are still evolving. Furthermore, epidemiological data on these enormous challenges is more uncertain than that available for routine tuberculosis.

Table 3: Cost Projections for Adapting and Improving DOTS (in $ millions)

	5-Year Cost
TB-HIV Country Needs	**630**
• Voluntary Counselling ans HIV Testing	290
• TB Testing, Screening, and Programme Costs	330
• Drug Cost—INH Preventive Therapy	10
MDR-TB Country Needs	**1,070**
• Drugs	650
• Other Costs	420
Total	**1,700**

TB-HIV Co-infection TB-HIV co-infection is a terrible and complex problem confronting patients and health workers around the world. There still are too few programmes confronting the deadly synergy of these two diseases, and reliable data on those that are being implemented is still scarce. As a result, predicting the cost of widespread intervention is extremely difficult. Yet a Global Plan to Stop TB could not possibly pass over this central problem of TB control.

The GPSTB begins to estimate the costs of responding—shown above in Table 3— by drawing on preliminary cost information and promising results from ProTEST projects in sub-Saharan Africa and from other preliminary studies. Costs have been projected for voluntary counselling and testing (VCT) of roughly 28 million people in twelve sub-Saharan countries. The twelve countries are four that have established ProTEST projects (Malawi, Uganda, South Africa, and Zambia), four in which ProTEST projects are being established (Mozambique, Ethiopia, Kenya, and Tanzania) and four others (Rwanda, Congo DR, Cote D'Ivoire, and Senegal). An estimated 3.3 million of these patients (12%) are projected to be HIV-positive, and then half of these are projected to be co-infected with TB. These co-infected patients are assumed to receive INH preventive therapy to prevent the onset of active TB.

There are considerable limitations in these estimates. ProTEST provides an excellent model for how TB-HIV co-infection will have to be addressed, but reliable cost data from the projects is not yet available. There are also uncertainties regarding the extent of co-infection, the willingness of patients to volunteer for testing and the extent of the synergy between these two diseases. In addition, treating TB-HIV co-infection will likely require a larger set of

interventions. Cotrimoxazole, for example, is now being used by a number of African countries to prevent bacterial and parasitological complications of HIV. It will likely be used more extensively in the future, as further evidence on its effectiveness is assembled. As a result, the summary table at the end of Chapter 3 notes other likely components of TB-HIV control, even though they have no cost associated with them, in order to highlight their importance and the need for more complete cost information.

MDR-TB: Two scenarios were used in estimating the proportion of all TB cases that are multidrug resistant—one providing an MDR-TB rate of 3.2 percent and the second a rate of 4.6 percent. This study assumed the worse incidence, which would result in 1.9 million cases of MDR-TB. The GPSTB urges the rapid expansion of capacity to treat MDR-TB, yet it is very difficult to predict how rapid this DOTS-Plus expansion will be. Hence, we have made a necessarily tentative assumption that 40 percent of all MDR-TB cases detected will be appropriately treated over the next five years (494,000 of the 1.2 million estimated cases detected). This assumption will need to be reviewed in light of the progress of countries in initiating DOTS-Plus programmes.

Table 4: MDR-TB-Control Projections for 2001–2005 in Low- and Lower-Middle Income Countries (cases in millions).

	Current Level of TB Control	Stop TB Goals
Number of New Cases (Incidence)	**1.9**	**1.9**
Cases Detected and Treated	**0.9**	**1.2**
• Covered by DOTS-Plus	0.06	0.5
• Not Appropriately Treated	0.9	0.7

Cost estimates for MDR-TB treatment must be derived from very limited data. We have relied mostly on data from programmes in Peru, and have extrapolated those known costs to all other countries with likely MDR-TB problems. As further data is available from Peru and elsewhere, these estimates of treatment costs will need to be revised.

Expensive second-line drugs account for roughly 60 percent of the projected five-year cost estimate of $1.1 billion. The projected per patient cost for drugs is $1,317, on average, at current levels for standardized regimens. Other DOTS-Plus costs consist of programme costs of $170 million ($344/patient) and general health service system costs of $250 million ($507/patient), reflecting likely difficulties of initiating and scaling up DOTS-Plus programmes. These projections will be revised as further data becomes available.

[6] There are now roughly 7,000 patients worldwide being treated for MDR-TB under approved DOTS-Plus programmes.

Annex 2 Stop TB Working Group Plans and Budgets

Stop TB Working Groups	Lead Agency	Working Group Chair
DOTS Expansion	WHO	Dr. Mario Raviglione (WHO) raviglionem@who.ch
TB-HIV	WHO	Dr. Gijs Elzinga (RIVM) gijs.elzinga@rivm.nl
DOTS-Plus for MDR-TB	WHO	Dr. Jim Yong Kim (Partners in Health) jimkimpih@pih.org
TB Diagnostics	TDR	Dr. Carlos Morel (TDR) morelc@who.int
TB Drug Development	Global Alliance for TB Drug Development	Dr. María Freire (Global Alliance) maria.freire@tballiance.org
TB Vaccine Development	WHO/TDR	Dr. Ann Ginsberg (NIAID/DMID) AGINSBERG@niaid.nih.gov

Working Group on DOTS Expansion

Lead Agency: ***World Health Organization***
Chair: ***Dr. Mario Raviglione, Coordinator, WHO STB/TBS***

Summary 5-Year Work Plan

Objectives	Targets	Activities	Budget ($)
Objective 1: Ensure that countries are provided with technical and strategic assistance for comprehensive DOTS expansion	• Medium-term: To achieve year 2005 global TB-control targets (70% case detection rate and 85% cure rate) • Short-term: By end 2001, at least all high-TB-burden countries will have developed medium term DOTS expansion plans	• Further develop and refine interim targets, one year and five year plans • Address key challenges to TB-control effectiveness in specific countries through technical assistance, coordination, capacity building, and human resource development • Promote and monitor community involvement in TB control by providing guidelines and training material for such programmes • Promote and disseminate examples of policies and experiences of engagement of private sectors and other sectors in TB control	207,000,000
Objective 2: Support and coordinate national, regional, and global TB control	• Establish regional advisory groups and inter-agency coordinating committees • Impact of TB control on health sector and poverty	• Monitor DOTS expansion progress at global, regional, and country level and define next steps to achieve the global targets by 2005. • Monitor the effects of TB control in health sector development and poverty reduction by promoting development and use of outcome indicators.	16,080,000
Objective 3: Monitor and report annually on DOTS expansion and on the progression of the disease	• Annual updates on country places of action, country needs, and gaps	• Organized annually - DOTS Expansion Working Group meeting.	1,150,000
Objective 4: Advocate to increase commitment and financial resources	• Significant increase in resources to support DOTS expansion	• Advocacy campaign and social mobilization	1,000,000
TOTAL			**225,230,000**

Working Group on DOTS Expansion

2001 Annual Plan

Activities	Indicators	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Technical Assistance		**39,000,000**	**16,000,000**	**23,000,000**
• Capacity building and human resources development for DOTS implementation	• International training courses including training of consultants • Training material, coordination of training • In-service training	23,000,000	10,000,000	13,000,000
• Direct NTP assistance, advisors, missions and tools	• Medium-term plans including budget • DOTS coverage	16,000,000	6,000,000	10,000,000
Objective 2: Support and Coordination		**1,000,000**	**500,000**	**500,000**
• Regional strategic plans to cover endemic countries	• Meeting held	100,000	100,000	0
• Regional Advisory Groups and Inter-agency Committee		600,000	300,000	300,000
• Updating plans, country needs and gaps for 22 HBC	• Plans updated	200,000	50,000	150,000
• Updating of plans and budget for agencies (WHO/partners) supporting countries in DOTS expansion	• Budget available for agencies	100,000	50,000	50,000
Objective 3: Monitoring and reporting		**230,000**	**200,000**	**30,000**
• DOTS Expansion WG meeting	• Meeting held	180,000	150,000	30,000
• DOTS Expansion report No. 1	• Global DOTS Expansion Plan published	30,000	30,000	0
• DOTS Expansion report	• Global DOTS Expansion Plan published	20,000	20,000	0
Objective 4: Advocacy		**200,000**	**100,000**	**100,000**
TOTAL YEAR 2001		**40,430,000**	**16,800,000**	**23,630,000**

Working Group on DOTS Expansion

2002 Annual Plan

Activities	Indicators	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Technical Assistance		**42,000,000**	**21,500,000**	**20,500,000**
• Capacity building and human resources development for DOTS implementation	• International training courses including training of consultants • Training material, coordination of training • In-service training	24,000,000	12,000,000	12,000,000
• Direct NTP assistance, advisors, missions and tools	• Medium-term plans including budget • DOTS coverage	18,000,000	9,500,000	8,500,000
Objective 2: Support and Coordination		**3,770,000**	**1,370,000**	**2,400,000**
• Regional action plans for 50% of endemic countries	• Complete December 2002	1,000,000	500,000	500,000
• Regional Advisory Groups and Inter-Agency Committees	• TAG & ICC meetings	600,000	300,000	300,000
• Update action plans, country needs/gaps, and budgets for agencies supporting countries in DOTS expansion	• GDEP report published	170,000	70,000	100,000
• National inter-agency committees	• Established in regional priority endemic countries	2,000,000	500,000	1,500,000
Objective 3: Monitoring and Reporting		**230,000**	**130,000**	**100,000**
• DOTS Expansion WG meeting in Canada	• Meeting held	200,000	100,000	100,000
• DOTS Expansion report No. 3	• Report published	30,000	30,000	0
Objective 4: Advocacy		**200,000**	**0**	**200,000**
TOTAL YEAR 2002		**46,200,000**	**23,000,000**	**23,200,000**

Working Group on DOTS Expansion

2003 Annual Plan

Activities	Indicators	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Technical Assistance		**42,000,000**	**21,500,000**	**20,500,000**
• Capacity building and human resources development for DOTS implementation	• International training courses including training of consultants • Training material, coordination of training • In-service training	24,000,000	12,000,000	12,000,000
• Direct NTP assistance, advisors, missions, and tools	• Medium-term plans including budget • DOTS coverage	18,000,000	9,500,000	8,500,000
Objective 2: Support and Coordination		**3,770,000**	**1,370,000**	**2,400,000**
• Action plans all of endemic countries	• Complete by December 2003	1,000,000	500,000	500,000
• Regional Advisory Groups and Inter-Agency Committees	• TAG & ICC meetings	600,000	300,000	300,000
• Update action plans, country needs/gaps and budgets for agencies supporting countries in DOTS expansion	• GDEP report # 3	170,000	70,000	100,000
• National inter-agency committees	• Established all countries	2,000,000	500,000	1,500,000
Objective 3: Monitoring and Reporting		**230,000**	**130,000**	**100,000**
• DOTS Expansion WG meeting in late 2003	• Meeting held	200,000	100,000	100,000
• DOTS Expansion report No. 4	• Report published	30,000	30,000	0
Objective 4: Advocacy		**200,000**	**0**	**200,000**
TOTAL YEAR 2003		**46,200,000**	**23,000,000**	**23,200,000**

Working Group on DOTS Expansion

2004 Annual Plan

Activities	Indicators	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Technical Assistance		**42,000,000**	**21,500,000**	**20,500,000**
• Capacity building and human resources development for DOTS implementation	• International training courses including training of consultants • Training material, coordination of training • In service training	24,000,000	12,000,000	12,000,000
• Direct NTP assistance, advisors, missions, and tools	• Medium-term plans including budget • DOTS coverage	18,000,000	9,500,000	8,500,000
Objective 2: Support and Coordination		**3,770,000**	**1,370,000**	**2,400,000**
• WG missions for evaluation of progress (2000-2003) in all endemic countries	• Evaluation report (see below) Reports of visits	1,000,000	500,000	500,000
• Regional evaluations, Advisory Groups and Inter-Agency Committees	• AG & ICC meetings	600,000	300,000	300,000
• Update country needs/gaps and budgets for agencies supporting countries in DOTS expansion	• GDEP report updated	170,000	70,000	100,000
• National inter-agency committees	• National ICC meetings report TB control evaluation	2,000,000	500,000	1,500,000
Objective 3: Monitoring and Reporting		**230,000**	**130,000**	**100,000**
• DOTS Expansion WG meeting in late 2004	• Meeting held	200,000	100,000	100,000
• DOTS Expansion report No. 5	• Report published	30,000	30,000	0
Objective 4: Advocacy		**200,000**	**0**	**200,000**
TOTAL YEAR 2004		**46,200,000**	**23,000,000**	**23,200,000**

Working Group on DOTS Expansion

2005 Annual Plan

Activities	Indicators	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Technical Assistance		**42,000,000**	**21,500,000**	**20,500,000**
• Capacity building and human resources development for DOTS implementation	• International training courses including training of consultants • Training material, coordination of training • In-service training	24,000,000	12,000,000	12,000,000
• Direct NTP assistance, advisors, missions, and tools	• Medium-term plans including budget • DOTS coverage	18,000,000	9,500,000	8,500,000
Objective 2: Support and Coordination		**3,770,000**	**1,370,000**	**2,400,000**
• Review of action plans for sustainability in all endemic countries	• Plans by December 2005	1,000,000	500,000	500,000
• Regional Advisory Groups and Inter-Agency Committees	• AG & ICC meetings	600,000	300,000	300,000
• Update country needs/gaps and budgets for supporting agencies	• GDEP report updated	170,000	70,000	100,000
• National inter-agency committees	• National ICC established in all countries	2,000,000	500,000	1,500,000
Objective 3: Monitoring and Reporting		**230,000**	**130,000**	**100,000**
• DOTS Expansion WG meeting in late 2005	• Meeting held	200,000	100,000	100,000
• DOTS Expansion report No. 6	• Report published	30,000	30,000	0
Objective 4: Advocacy		**200,000**	**0**	**200,000**
TOTAL YEAR 2005		**46,200,000**	**23,000,000**	**23,200,000**

Working Group on TB-HIV

Lead Agency: ***World Health Organization***
Chair: ***Dr. Gijs Elzinga, The Netherlands***

Summary 5-Year Work Plan

Objectives	Targets	Activities	Budget ($)
Objective 1: Develop effective new strategies to combat TB in HIV-infected people	• New technical framework to guide country strategies, endorsed by WHO & UNAIDS by end 2001 • Disseminate guidelines on phased implementation of TB & HIV programme collaborations (mid-2002)	• Develop framework • Model impact of interventions • Develop prioritised essential package • Develop and disseminate guidelines	**965,000**
Objective 2: Promote implementation and scale-up of control programmes responding to the deadly synergy of these diseases	• Initiate implementation of collaborative activities in 8 sub-Saharan sites (PIA-TB/HIV*), and expand to other high-burden countries by end 2004	• Establish pilot projects and coordinate project network	**10,520,000**
Objective 3: Promote global partnership for collaboration between TB- and HIV-control programmes	• Promote national and regional strategies for control of TB in high HIV-prevalence settings linked with DOTS expansion (end 2003) • National strategies adapted and scaled up in most high HIV-prevalence countries (end 2005)	• Promote international and national partnerships to maximize synergies in health service treatment of co-infected people	**645,000**
Objective 4: Advocate for increased resources	• Raise $10.25 million by end 2005	• Target advocacy and fundraising	**220,000**
TOTAL			**12,350,000**

** The phased implementation of TB/HIV activities (PIA-TB/HIV) is the name for the planned collaborative activities to control TB (and HIV) in high-burden countries. It is the successor to the WHO-coordinated ProTEST projects, which are ongoing and which have provided much of the experience on which PIA-TB/HIV is based.*

Working Group on TB-HIV

2001 Annual Plan

Activities	Indicators	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Develop and Adapt TB/HIV Strategy • Development of strategic framework for TB/HIV • Commence modelling impact of interventions to inform development of prioritised essential package • Produce revised TB/HIV estimates	• Draft finalised, 2001 • First draft, 2001 • Complete paper, 2001	**125,000**	**125,000**	**0**
Objective 2: Promote Implementation • Develop ProTEST project evaluation framework • Plan implementation of post-ProTEST activities (PIA-TB/HIV) • First draft of technical guidelines for establishment of PIA-TB/HIV projects (including a generic protocol) • Coordinate network of ProTEST pilot projects • Monitor existing projects in Africa • Plan development of training tools and education materials	• Completed 2001 • First workshop, Feb. 2002 • Concluded 2001 • Regional plan ready • Regional plan ready End 2001	**730,000**	**730,000**	**0**
Objective 3: Form Global Partnership • Hold 1st annual meeting of Global TB/HIV Working Group • Appoint Working Group Coordinator	• Met April 2001 • WG Coordinator appointed Oct 2001	**25,000**	**25,000**	**0**
Objective 4: Advocacy for Increased Resources • Advocacy for ProTEST projects	• Plan complete mid-2002	**20,000**	**20,000**	**0**
TOTAL YEAR 2001		**900,000**	**900,000**	**0**

Working Group on TB-HIV

2002 Annual Plan

Activities	Indicators	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Develop and Adapt TB/HIV Strategy		**290,000**	**260,000**	**30,000**
• Complete, develop consensus on, publish, and disseminate strategy, technical, and clinical guidelines	• By end 2002	80,000	80,000	0
• Adapt framework for different regions	• By end 2002	50,000	50,000	0
• Two meetings of scientific panel (guidelines on recurrence of TB among HIV+ patients and operational research)	• Draft by end 2002	60,000	30,000	30,000
• Complete modelling of, focus for, and impact of interventions to inform development of prioritised essential package	• By end 2002	100,000	100,000	0
• Publish new TB/HIV estimates (no cost)	• By mid 2002			
Objective 2: Promote Implementation		**1,390,000**	**1,005,000**	**385,000**
• Establish PIA-TB/HIV projects in four additional countries	• Implement mid-2003	1,000,000	665,000	335,000
• Coordinate network of PIA-TB/HIV projects	• Consultant visits 'Q4	200,000	200,000	0
• Monitor existing ProTEST projects	• Ongoing	40,000	40,000	0
• Completion of ProTEST project evaluation	• Report, end-2002	80,000	80,000	0
• WHO regional office support	• AFRO TB/HIV plan, end-2002	20,000	20,000	0
• Develop human resource plan	• End, 2002	50,000	0	50,000
Objective 3: Form Global Partnership		**155,000**	**55,000**	**100,000**
• Five virtual and one actual meeting for core group of Working Group	• As scheduled	30,000	30,000	0
• Hold 2nd annual meeting of Global TB/HIV Working Group	• As scheduled	75,000	25,000	50,000
• First meeting of inter-agency collaboration group	• As scheduled	50,000	0	50,000
Objective 4: Advocacy for Increased Resources	• $1.25 million raised	**50,000**	**0**	**50,000**
TOTAL YEAR 2002		**1,885,000**	**1,320,000**	**565,000**

Working Group on TB-HIV

2003 Annual Plan*

Activities	Indicators	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Develop and Adapt TB/HIV Strategy		**230,000**	**0**	**230,000**
• Adaptation of framework and guidelines for different regions	• Adapted for 3 regions, early 2003	50,000	0	50,000
• Dissemination of guidelines		20,000	0	20,000
• Two meetings of scientific panel	• As scheduled	60,000	0	60,000
• Economic modelling to compare interventions	• Report by mid-2003	100,000	0	100,000
Objective 2: Promote Implementation		**2,800,000**	**0**	**2,800,000**
• Establish new PIA-TB/HIV projects	• 9 new projects by end 2003	1,000,000	0	1,000,000
• Technical support to existing PIA-TB/HIV projects	• Consult reports, end 2003	1,000,000	0	1,000,000
• Maintain and coordinate network of PIA-TB/HIV projects	• Report to WG 2003	250,000	0	250,000
• Monitor and evaluate country-level PIA-TB/HIV projects	• Mentors reports to WG 2003	250,000	0	250,000
• Support implementation of human resource development plan	• Training plan implemented, end 2003	200,000	0	200,000
• Report and publish results on country projects	• As scheduled	100,000	0	100,000
Objective 3: Form Global Partnership		**155,000**	**0**	**155,000**
• Five virtual and one actual meeting for core group of WG	• As scheduled	30,000	0	30,000
• Hold 3rd annual meeting of Global TB/HIV WG	• As scheduled	75,000	0	75,000
• 2nd meeting of TB/HIV interagency collaboration group	• As scheduled	50,000	0	50,000
• Coordinate with regional and national inter-agency coordination groups (no cost)	• TB/HIV integrated with DOTS expansion plans			
Objective 4: Advocacy for Increased Resources		**50,000**	**0**	**50,000**
• Advocacy for ProTEST projects	• Various ($2 million raised)			
TOTAL YEAR 2003		**3,235,000**	**0**	**3,235,000**

** Estimates as of January 2002. At least $1.3 million will likely be obtained from existing sources, but as yet there are no firm pledges.*

Working Group on TB-HIV

2004 Annual Plan*

Activities	Indicators	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Develop and Adapt TB/HIV Strategy		**160,000**	**0**	**160,000**
• Two meetings of scientific panel	• As scheduled	60,000	0	60,000
• Further mathematical modelling for strategic decision-making	• Reports published	100,000	0	100,000
Objective 2: Promote Implementation		**2,800,000**	**0**	**2,800,000**
• Technical support to existing PIA-TB/HIV projects	• Project and consultant reports for each country, end 2004	2,000,000	0	2,000,000
• Maintain and coordinate network of PIA-TB/HIV projects		250,000	0	250,000
• Monitor and evaluate country-level PIA-TB/HIV projects		250,000	0	250,000
• Support implementation of human resource development plan	• Consultant and trainer reports end 2004	200,000	0	200,000
• Report preparation and publication of results	• 3 peer-reviewed publications	100,000	0	100,000
Objective 3: Form Global Partnership		**155,000**	**0**	**155,000**
• Five virtual and one actual meeting for core group of WG	• As scheduled	30,000	0	30,000
• Hold 4th annual meeting of Global TB/HIV WG	• As scheduled	75,000	0	75,000
• 3rd meeting of TB/HIV inter-agency collaboration group	• As scheduled	50,000	0	50,000
• Coordinate with regional and national inter-agency coordination groups	• Reports of these bodies			
Objective 4: Advocacy for Increased Resources	• $3 million raised	**50,000**	**0**	**50,000**
TOTAL YEAR 2004		**3,165,000**	**0**	**3,165,000**

** Estimates as of January 2002. At least $1.3 million will likely be obtained from existing sources, but as yet there are no firm pledges.*

Working Group on TB-HIV

2005 Annual Plan*

Activities	Indicators	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Develop and Adapt TB/HIV Strategy		**160,000**	**0**	**160,000**
• Two meetings of scientific panel	• As activities	60,000		60,000
• Further mathematical modelling for strategic decision-making	• Reports for publication	100,000		100,000
Objective 2: Promote Implementation		**2,800,000**	**0**	**2,800,000**
• Technical support to existing PIA-TB/HIV projects	• Project & consultant	2,000,000	0	2,000,000
• Maintain & coordinate network of PIA-TB/HIV projects	reports for each country	250,000	0	250,000
• Monitor & evaluate country-level PIA-TB/HIV projects	end 2004	250,000	0	250,000
• Support implementation of human resource development plan		200,000	0	200,000
	• Consultant & trainer	100,000	0	100,000
• Report preparation and publication of results from countries	reports end 2004			
	• 3 peer-reviewed publications			
Objective 3: Form Global Partnership		**155,000**	**0**	**155,000**
• Five virtual and one actual meeting for core group of WG	• As scheduled	30,000	0	30,000
• Hold 4th annual meeting of Global TB/HIV Working Group	• As scheduled	75,000	0	75,000
• 3rd meeting of TB/HIV inter-agency collaboration group	• As scheduled	50,000	0	50,000
• Coordinate with regional and national inter-agency coordination groups	• Reports of these bodies			
Objective 4: Advocacy for Increased Resources	• $4 million raised	**50,000**	**0**	**50,000**
TOTAL YEAR 2005		**3,165,000**	**0**	**3,165,000**

** Estimates as of January 2002. At least $1.3 million will likely be obtained from existing sources, but as yet there are no firm pledges.*

Working Group on DOTS-Plus for MDR-TB

Lead Agency: ***World Health Organization***
Chair: ***Dr. Jim Yong Kim, Partners in Health***

Summary 5-Year Work Plan

Objectives	Targets	Activities	Budget $
• **Objective 1:** Initiate and support pilot projects, through partner organizations, for the diagnosis and treatment of MDR-TB	• Pilot project guidelines issued: 2000 • Continue to expand number of pilot projects at a rate of approximately 3-6 per year	• Six MDR-TB pilot projects underway • Nine new MDR-TB projects scheduled • Continue to revise and improve DOTS-Plus project guidelines • Provide ongoing technical advice on clinical issues of MDR-TB management	**7,800,000**
• **Objective 2:** Establish drug access system to provide and prevent misuse of high-quality, second-line drugs	• Prices reduced on many drugs • Two procurement mechanisms operating • GLC to meet 12 times p.a. on country applications, and to discuss operational activities	• Make recommendations for increasing access/lowering price of second-line drugs • Establish and monitor procurement mechanisms	**1,190,000**
• **Objective 3:** Coordinate and monitor implementation of DOTS-Plus pilots; assess data; and help produce policy recommendations	• Regular data collection and review of pilot projects at least once a year	• Pre-approval site visits to projects applying for GLC drugs • Monitoring visits for GLC-approved projects • Develop DOTS-Plus data clearinghouse • Coord. operational research studies from projects	**6,890,000**
• **Objective 4:** Advocacy and resource development for new DOTS-Plus projects	• Increase visibility of the GLC and the working group • Increased funding for projects	• Increase visibility of DOTS-Plus efforts • Work with funders to provide an evidence-based approach to drug-resistant TB	**600,000**
TOTAL			**16,480,000**

Working Group on DOTS-Plus for MDR-TB

2001 Annual Plan

Activities	Indicators	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Pilot Projects		**2,100,000**	**100,000**	**2,000,000**
• Establish three pilot projects ($200,000 per project)	Projects established (Philippines, Peru, Orel)	600,000	100,000	500,000
• Training sessions in clinical management	• 4 sessions held in HBCês	500,000	0	500,000
• Piloting of new diagnostic tools	• In-pilot projects	1,000,000	0	1,000,000
Objective 2: Drug Access System		**330,000**	**130,000**	**200,000**
• Technical assistance for GLC applications, and monitoring of projects	• Application training for 3 countries, and monitoring visits to 4 projects	200,000	100,000	100,000
• Evaluate drug-procurement process	• Procurement strategies developed	50,000	30,000	20,000
• Staff IDA for registration and procurement activities	• Drug prices down by over 90% • As placed	80,000	0	80,000
Objective 3: Monitoring and Policy Development		**1,650,000**	**200,000**	**1,450,000**
• Collect and analyse data	• Papers submitted on Peru programme	50,000	20,000	30,000
• Operational research	• Protocols implemented	1,500,000	150,000	1,350,000
• Annual meetings of working group	• Annual meeting held	100,000	30,000	70,000
• Preparation and publication of policy document				
Objective 4: Advocacy and Resource Development		**200,000**	**70,000**	**130,000**
• Advocacy for pilot projects	• Press releases and newsletters	100,000	20,000	80,000
• Advocacy for GLC	• Press releases and newsletters	100,000	50,000	50,000
TOTAL YEAR 2001		**4,280,000**	**500,000**	**3,780,000**

Working Group on DOTS-Plus for MDR-TB

2002 Annual Plan

Activities	Indicators	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Pilot Projects		**2,400,000**	**150,000**	**2,250,000**
• Establish three pilot projects ($200,000 each)	As established	600,000	100,000	500,000
• Training sessions in clinical management	• Hold sessions in 2 countries	500,000	0	500,000
• Piloting of new diagnostic tools	• In-pilot projects	1,000,000	0	1,000,000
• Support to ongoing pilot projects		300,000	50,000	250,000
Objective 2: Drug Access System		**330,000**	**130,000**	**200,000**
• Technical assistance for GLC applications, and monitoring of projects	• Training session at working group meeting and in-country training in 2 countries monitoring visits to 3 projects	200,000	100,000	100,000
• Evaluate drug-procurement process	• Report on drug-procurement progress	50,000	30,000	20,000
• Staff IDA registration and procurement	• As placed	80,000	0	80,000
Objective 3: Monitoring and Policy Development		**1,650,000**	**200,000**	**1,450,000**
• Collect and analyse data	• Establish data clearinghouse at WHO	50,000	20,000	30,000
• Operational research				
• Annual meetings of working group	• Protocols accepted and established	1,500,000	150,000	1,350,000
• Preparation and publication of policy document	• Annual meeting in Estonia	100,000	30,000	70,000
Objective 4: Advocacy and Resource Development		**200,000**	**70,000**	**130,000**
• Advocacy for pilot projects	• Press releases and newsletters	100,000	20,000	80,000
• Advocacy for GLC	• Press releases and newsletters	100,000	50,000	50,000
TOTAL YEAR 2002		**4,580,00**	**550,000**	**4,030,000**

Working Group on DOTS-Plus for MDR-TB

2003 Annual Plan

Activities	Indicators	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Pilot Projects		**1,800,000**	**50,000**	**1,750,000**
• Training sessions in clinical management	• Hold sessions in 2 countries	500,000	0	500,000
• Piloting of new diagnostic tools	• In-pilot projects	1,000,000	0	1,000,000
• Support to ongoing pilot projects		300,000	50,000	250,000
Objective 2: Drug Access System		**330,000**	**130,000**	**200,000**
• Technical assistance for GLC applications, and monitoring of projects	• Training session (at working group meeting); training in 2 countries. • Visits to 3 projects	200,000	100,000	100,000
• Evaluate drug procurement process	• Report on procurement progress	50,000	30,000	20,000
• Staff IDA registration and procurement	• As placed	80,000	0	80,000
Objective 3: Monitoring and Policy Development		**1,750,000**	**250,000**	**1,500,000**
• Collect and analyse data	• Establish clearinghouse at WHO	50,000	20,000	30,000
• Operational research	• Protocols accepted and established	1,500,000	150,000	1,350,000
• Annual meetings of working group	• As scheduled	100,000	30,000	70,000
• Preparation and publication of policy document		100,000	50,000	50,000
Objective 4: Advocacy and Resource Development		**100,000**	**50,000**	**50,000**
• Advocacy for GLC	• Press releases and newsletters	100,000	50,000	50,000
TOTAL YEAR 2003		**3,980,000**	**480,000**	**3,500,000**

Working Group on DOTS-Plus for MDR-TB

2004 Annual Plan

Activities	Indicators	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Pilot Projects		**1,500,000**	**0**	**1,500,000**
• Training sessions in clinical management	• Hold sessions in 2 countries and at working group meeting	500,000	0	500,000
• Piloting of new diagnostic tools	• In-pilot projects	1,000,000	0	1,000,000
Objective 2: Drug Access System		**200,000**	**100,000**	**100,000**
• Technical assistance for GLC applications, and monitoring of projects	• Training session (at working group meeting); training in 2 countries. • Visits to 3 projects	200,000	100,000	100,000
Objective 3: Monitoring and Policy Development		**1,750,000**	**240,000**	**1,510,000**
• Collect and analyse data		50,000	20,000	30,000
• Operational research	• Protocols accepted and established	1,500,000	150,000	1,350,000
• Annual meetings of working group		100,000	30,000	70,000
• Preparation and publication of policy document	• As scheduled	100,000	40,000	60,000
Objective 4: Advocacy and Resource Development		**100,000**	**50,000**	**50,000**
• Advocacy for GLC	• Press releases and newsletters	100,000	50,000	50,000
TOTAL YEAR 2004		**3,550,000**	**390,000**	**3,160,000**

Working Group on DOTS-Plus for MDR-TB

2005 Annual Plan

Activities	Indicators	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Pilot Projects		**0**	**0**	**0**
Objective 2: Drug Access System		**0**	**0**	**0**
Objective 3: Monitoring and Policy Development • Annual meetings of working group • Preparation and publication of policy document	 • As scheduled • As published	**90,000** 90,000	**30,000** 30,000	**60,000** 60,000
Objective 4: Advocacy and Resource Development		**0**	**0**	**0**
TOTAL YEAR 2005		**90,000**	**30,000**	**60,000**

Working Group on TB Diagnostics

Lead Agency: ***UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases***
Chair: ***Dr. Carlos Morel, TDR***

Summary 4-Year Work Plan

Objectives	Targets	Activities	4-Year Budget ($)
Objective 1: Facilitation To promote and facilitate the development, evaluation, and appropriate use of improved TB diagnostics to assist disease control in endemic settings, including: • Simpler, faster, or more sensitive case detection tools • Faster and less laborious drug susceptibility testing methods • More practical and more predictive latent infection detection tests	• At least 5 diagnostic candidates identified and evaluated in phase I/II trials by 2005 • Evidence base for best use of TB diagnostics (timing and target populations) for improved disease control developed by 2004 • Phase III trials of at least 1 case detection tool and at least 3 new drug susceptibility testing methods completed by 2005 • International system for evaluation of TB diagnostics in place by 2005 • Guidelines for use of new TB tests published by 2007	• Coordinating outputs of discovery research and facilitating commercial uptake • Multi-step facilitation of commercial R&D for TB diagnostics relevant for DECs • Providing reagents and technical support to enhance the quality of diagnostics being developed • Developing diagnostics trial capacity and coordinating evaluation of new tools • Streamlining and strengthening the diagnostics regulatory process • Advocacy and establishment of an information resource centre • Planning and coordination by working group and ad hoc task forces	**25,855,000**
Objective 2: Advocacy and Information			**600,000**
Objective 3: Coordinate Activities			**600,000**
TOTAL			**27,055,000**

Working Group on TB Diagnostics

2002 Annual Plan

Activities	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1:Facilitation	**6,780,000**	**2,130,000**	**4,650,000**
• Develop consortium to evaluate sputum processing methods	60,000	30,000	30,000
• Develop antigen discovery and evaluation programme	400,000	150,000	250,000
• Maintain bank of clinical reference materials for case detection tool R&D	450,000	250,000	200,000
• Perform market analysis, global use portrait, and economic analysis	800,000	150,000	650,000
• Coordinate phase III trials of DST methods	750,000	250,000	500,000
• Coordinate laboratory evaluation of case detection tools	250,000	100,00	150,000
• Coordinate programme to strengthen DEC laboratory capacity to evaluate and use new diagnostics in a network of trial sites	1,600,000	350,000	1,250,000
• Develop MTB strain bank to facilitate R&D and testing of DST methods	550,000	300,000	250,000
• Model impact of new case detection tools	60,000	20,000	40,000
• Coordinate multinational measure of TB diagnostic delay and dropout	250,000	150,000	100,000
• Coordinate phase III trials of case detection tool	950,000	300,000	650,000
• Regulatory harmonization workshops	400,000	50,000	350,000
• Develop strategy for global evaluation system for TB diagnostics marketed in developing countries	60,000	10,000	50,000
• Develop a comprehensive advocacy and information strategy for new TB diagnostics	200,000	20,000	180,000
Objective 2: Advocacy and Information	**150,000**	**20,000**	**130,000**
Objective 3: Coordination • Annual working group meeting • Ad hoc meetings of regional task forces	**150,000**	**0**	**150,000**
TOTAL YEAR 2002	**7,080,000**	**2,150,000**	**4,930,000**

Working Group on TB Diagnostics

2003 Annual Plan

Activities	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Facilitation	**6,210,000**	**1,300,000**	**4,910,000**
• Support consortium to evaluate sputum processing methods	60,000	0	60,000
• Develop antigen discovery and evaluation programme	300,000	100,000	200,000
• Maintain bank of clinical reference materials	400,000	100,000	300,000
• Complete market analysis, global use portrait, and economic analysis	800,000	150,000	650,000
• Coordinate phase III trials of DST methods	750,000	250,000	500,000
• Coordinate laboratory evaluation of case detection tools	200,000	100,000	100,000
• Coordinate programme to strengthen DEC laboratory capacity to evaluate and use new diagnostics in a network of trial sites	1,600,000	0	1,600,000
• Maintain MTB strain bank to facilitate R&D and testing of DST methods	250,000	100,000	150,000
• Model impact of new case detection tools	60,000	20,000	40,000
• Coordinate multinational measure of TB diagnostic delay and dropout	150,000	50,000	100,000
• Coordinate phase III trials of case detection tools	950,000	300,000	650,000
• Regulatory harmonization workshops	400,000	50,000	350,000
• Develop strategy for global evaluation system for TB diagnostics marketed in developing countries	150,000	40,000	110,000
• Complete a comprehensive advocacy and information strategy for new TB diagnostics	100,000	20,000	80,000
• Model early detection impaction disease transmission	40,000	20,000	20,000
Objective 2: Advocacy and Information	**150,000**	**20,000**	**130,000**
Objective 3: Coordination	**150,000**	**0**	**150,000**
• Annual working group meeting			
• Ad hoc meetings of regional task forces			
TOTAL YEAR 2003	**6,510,000**	**1,320,000**	**5,190,000**

Working Group on TB Diagnostics

2004 Annual Plan

Activities	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Facilitation	**6,140,000**	**1,090,000**	**5,050,000**
• Maintain consortium to evaluate sputum processing methods	150,000	0	150,000
• Complete antigen discovery and evaluation programme	400,000	0	400,000
• Maintain bank of clinical reference materials	450,000	150,000	300,000
• Circulate market analysis, global use portrait, and economic analysis	200,000	0	200,000
• Coordinate phase III trials of DST methods	750,000	250,000	500,000
• Coordinate laboratory evaluation of case detection tools	250,000	100,000	150,000
• Coordinate programme to strengthen DEC laboratory capacity to evaluate and use new diagnostics in a network of trial sites	800,000	0	800,000
• Distribute MTB strain bank to facilitate R&D and testing of DST methods	250,000	0	250,000
• Coordinate phase III trials of case detection tools	1,000,000	300,000	700,000
• Regulatory harmonization workshops	300,000	50,000	250,000
• Implement strategy for global evaluation system for TB diagnostics marketed in developing countries	350,000	100,000	250,000
• Develop expert advisor team for diagnostics assistants to NTP	600,000	0	600,000
• Collect field data to determine kinetics of community TB transmission	600,000	120,000	480,000
• Model early detection impaction disease transmission	40,000	20,000	20,000
Objective 2: Advocacy and Information	**150,000**	**20,000**	**130,000**
Objective 3: Coordination	**150,000**	**0**	**150,000**
• Annual working group meeting			
• Ad hoc meetings of regional task forces			
TOTAL YEAR 2004	**6,440,000**	**1,110,000**	**5,330,000**

Working Group on TB Diagnostics

2005 Annual Plan

Activities	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Facilitation	**6,725,000**	**1,440,000**	**5,285,000**
• Support technology transfer of improved diagnostics	700,000	130,000	570,000
• Maintain bank of clinical reference materials	250,000	50,000	200,000
• Coordinate phase III trials of DST methods	350,000	150,000	200,000
• Coordinate evaluation of latency surrogates	400,000	100,000	300,000
• Coordinate programme to strengthen DEC laboratory capacity to evaluate and use new diagnostics in a network of trial sites	800,000	0	800,000
• Distribute MTB strain bank to facilitate R&D and testing of DST methods	150,000	0	150,000
• Model impact of new case detection tools on transmission	60,000	20,000	40,000
• Coordinate phase IV trials of case detection tools	1,350,000	200,000	1,150,000
• Implement strategy for global evaluation system for TB diagnostics marketed in developing countries	750,000	100,000	650,000
• Model early detection impaction disease transmission	40,000	20,000	20,000
• Diagnostic trial support programme	300,000	200,000	100,000
• Develop usage guidelines for new diagnostics	75,000	50,000	25,000
• Develop expert advisor team for diagnostics assistants to NTP	600,000	200,000	400,000
• Collect field data to determine kinetics of community TB transmission	900,000	220,000	680,000
Objective 2: Advocacy and Information	**150,000**	**20,000**	**130,000**
Objective 3: Coordination	**150,000**	**0**	**150,000**
• Annual working group meeting			
• Ad hoc meetings of the regional task forces			
TOTAL YEAR 2005	**7,025,000**	**1,460,000**	**5,565,000**

Working Group on TB Drug Development

Lead Agency: ***Global Alliance for TB Development***
Chair: ***Dr. María Freire, Global Alliance***

Summary 4-Year Work Plan

Objectives	Targets	Activities	Budget ($)
Objective 1: Develop new drug(s) to: • Shorten and/or simplify the treatment of TB disease • Develop more effective treatment(s) for MDR-TB • Develop more effective treatment(s) of latent TB infection.	• Have at least 5 drug candidates through preclinical trials by 2005 • Have at least 3 drugs through phase I and II by 2007 • Have 2 drugs in phase III by 2010 • Have at least one new drug registered by 2010	• Map activities in TB Drugs R&D: establish and update drug database • Establish partnership with industry • Undertake studies to define surrogate markers • Develop High Endemic Countries Network for clinical trials • Promote introduction of surrogate markers in regulatory package	**27,300,000**
Objective 2: Advocacy and Information		• Advocacy for TB Drugs R&D	**2,000,000**
Objective 3: Coordination: Annual working group meeting		• Working group activities	**400,000**
TOTAL			**29,700,000**

Working Group on TB Drug Development

2002 Annual Plan

Activities	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Facilitation /Enabling the Environment	**7,200,000**	**1,550,000**	**5,650,000**
• Map activities in TB drug R&D: establish and update drug data base	500,000	150,000	350,000
• Establish partnership with industry	200,000	100,000	100,000
• Undertake studies to define surrogate markers for clinical activity	3,000,000	350,000	2,650,000
• Develop HEC clinical trials network and strengthen laboratory capacity	3,000,000	700,000	2,300,000
• Promote introduction of surrogate markers within the regulatory harmonization process	500,000	250,000	250,000
Objective 2: Advocacy and Information	**500,000**	**250,000**	**250,000**
Objective 3: Coordination: Annual working group meeting	**100,000**	**0**	**100,000**
TOTAL YEAR 2002	**7,800,000**	**1,800,000**	**6,000,000**

Working Group on TB Drug Development

2003 Annual Plan

Activities	Budget ($)	Funding ($)	Resource Gap ($)
Objective 3: Facilitation /Enabling the Environment	**7,200,000**	**1,550,000**	**5,650,000**
• Map activities in TB drug R&D: establish and update drug data base	500,000	150,000	350,000
• Establish partnership with industry	200,000	100,000	100,000
• Undertake studies to define surrogate markers for clinical activity	3,000,000	350,000	2,650,000
• Develop HEC clinical trials network and strengthen laboratory capacity	3,000,000	700,000	2,300,000
• Promote introduction of surrogate markers within the regulatory harmonization process	500,000	250,000	250,000
Objective 2: Advocacy and Information	**500,000**	**250,000**	**250,000**
Objective 3: Coordination: Annual working group meeting	**100,000**	**0**	**100,000**
TOTAL YEAR 2003	**7,800,000**	**1,800,000**	**6,000,000**

Working Group on TB Drug Development

2004 Annual Plan

Activities	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Facilitation /Enabling the Environment	**6,700,000**	**1,300,000**	**5,400,000**
• Map activities in TB drug R&D: establish and update drug data base	500,000	150,000	350,000
• Establish partnership with industry	200,000	100,000	100,000
• Undertake studies to define surrogate markers for clinical activity	3,000,000	350,000	2,650,000
• Develop HEC clinical trials network and strengthen laboratory capacity	3,000,000	700,000	2,300,000
Objective 2: Advocacy and Information	**500,000**	**250,000**	**250,000**
Objective 3: Coordination: Annual working group meeting	**100,000**	**0**	**100,000**
TOTAL YEAR 2004	**7,300,000**	**1,550,000**	**5,750,000**

Working Group on TB Drug Development

2005 Annual Plan

Activities	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Facilitation /Enabling the Environment	**6,200,000**	**500,000**	**5,700,000**
• Establish partnership with industry	200,000	0	200,000
• Undertake studies to define surrogate markers for clinical activity	3,000,000	0	3,000,000
• Develop HEC clinical trials network and strengthen laboratory capacity	3,000,000	500,000	2,500,000
Objective 2: Advocacy and Information	**500,000**	**250,000**	**250,000**
Objective 3: Coordination: Annual working group meeting	**100,000**	**0**	**100,000**
TOTAL YEAR 2005	**6,800,000**	**750,000**	**6,050,000**

Working Group on TB Vaccine Development

Lead Agency: ***World Health Organization/TDR***
Chair: ***Dr. Ann Ginsberg, US-NIH/NIAID***

Summary 4-Year Work Plan

Objectives	Targets	Activities	Budget ($)

Objective 1: Facilitation	• An improved TB vaccine to:
	  • provide long-lasting primary protection
	  • prevent disease in individuals already infected
	• Stimulate and support the study of 5 –10 vaccine candidates in phase I/II trials by 2005.
	• Launch phase III efficacy trials of at least one TB vaccine candidate by 2007
		• Pre-clinical evaluation of vaccine candidates
		• Preparation of clinical evaluation of candidate vaccines and correlates of protection
		• Validation and distribution of standardized reagents
		• Coordination of fast-track transition of vaccine candidates from academia to industry
			3,400,000

Objective 2: Advocacy and Information		• Advocacy and establishment of an information resource centre	**700,000**
Objective 3: Coordinate Activities		• Planning and coordination by working group and ad hoc task forces	**400,000**
TOTAL			**4,500,000**

Working Group on TB Vaccine Development

2002 Annual Plan

Activities	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Facilitation	**850,000**	**250,000**	**600,000**
• Establish a primate TB vaccine testing network	400,000	100,000	300,000
• Identify potential clinical phase III testing sites	250,000	100,000	150,000
• Vaccino-economic analysis and cost-effectiveness modelling	50,000	0	50,000
• Coordinate/build international consensus on standardized reference reagents. Support development and distribution.	150,000	50,000	100,000
Objective 2: Advocacy and Information	**200,000**	**50,000**	**150,000**
• Develop a comprehensive advocacy and information strategy for new TB vaccines			
Objective 3: Coordination of Activities	**100,000**	**50,000**	**50,000**
• Annual meeting of the working group			
• Ad hoc meetings of preclinical and clinical task forces			
TOTAL YEAR 2002	**1,150,000**	**350,000**	**800,000**

Working Group on TB Vaccine Development

2003 Annual Plan

Activities	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Facilitation	**1,050,000**	**200,000**	**850,000**
• Establish a primate TB vaccine testing network	100,000	50,000	50,000
• Validate primate testing facilities	300,000	50,000	250,000
• Establish network of potential phase III clinical testing sites	100,000	50,000	50,000
• Build capacity for clinical testing of vaccine candidates	200,000	0	200,000
• Develop Points-to-Consider document for clinical trial protocols	50,000	0	50,000
• Coordinate/build international consensus on standardized reference reagents.	150,000	50,000	100,000
• Identify available GMP manufacturing capacity for pilot lots of vaccine candidates	50,000	0	50,000
• Coordinate/facilitate transition of potential candidates from academia to private sector, as appropriate and necessary	100,000	0	100,000
Objective 2: Advocacy and Information	**150,000**	**50,000**	**100,000**
• Develop a comprehensive advocacy and information strategy for new TB vaccines			
Objective 3: Coordination of Activities	**100,000**	**50,000**	**50,000**
• Annual meeting of the working group			
• Ad hoc meetings of task forces			
TOTAL YEAR 2003	**1,300,000**	**300,000**	**1,000,000**

Working Group on TB Vaccine Development

2004 Annual Plan

Activities	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Facilitation	**750,000**	**100,000**	**650,000**
• Validate primate testing facilities	100,000	50,000	50,000
• Build capacity for clinical testing of vaccine candidates	300,000	50,000	250,000
• Develop adult immunization strategy	150,000	0	150,000
• Coordinate fast-track transition of vaccine candidates from academia to industry	150,000	0	150,000
• Identify and support development of needed GMP manufacturing capacity	50,000	0	50,000
Objective 2: Advocacy and Information	**150,000**	**50,000**	**100,000**
• Develop a comprehensive advocacy and information strategy for new TB vaccines			
Objective 3: Coordination of Activities	**100,000**	**50,000**	**50,000**
• Annual meeting of the working group			
• Ad hoc meetings of task forces			
TOTAL YEAR 2004	**1,000,000**	**200,000**	**800,000**

Working Group on TB Vaccine Development

2005 Annual Plan

Activities	Budget ($)	Funding ($)	Resource Gap ($)
Objective 1: Facilitation	**750,000**	**100,000**	**650,000**
• Capacity building for clinical testing of vaccine candidates	300,000	50,000	250,000
• Coordination of fast-track transition of vaccine candidates from the academic/industrial interface	150,000	0	150,000
• Building awareness among national TB control staff	100,000	0	100,000
• Building in-country infrastructure for monitoring and ethical review of clinical trials	200,000	50,000	150,000
Objective 2: Advocacy and information	**200,000**	**50,000**	**150,000**
• Develop a comprehensive advocacy and information strategy for new TB vaccines			
Objective 3: Coordination of Activities	**100,000**	**50,000**	**50,000**
• Annual meeting of the working group			
• Ad hoc meetings of task forces			
TOTAL YEAR 2005	**1,050,000**	**200,000**	**850,000**

ANNEX 3
COUNTRIES INCLUDED IN THE GPSTB ANALYSIS

High-burden and low- and lower-middle income countries(1)

Clusters	All low- and lower-middle income countries, excluding 22 High-Burden Countries		22 High-Burden Countries
Sub-Saharan Africa	45	Angola, Benin, Botswana (2), Burkina Faso, Burundi, Cameroon, Cape Verde, Central African Republic, Chad, Comoros, Congo, CÙte d'Ivoire, Djibouti, Eritrea, Gambia, Ghana, Guinea, Guinea-Bissau, Guinea (Equatorial), Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique (b), Namibia, Niger, Rwanda, Sao Tome & Principe, Senegal, Sierra Leone, Somalia, Sudan, Swaziland, Togo, Zambia	Congo DR, Ethiopia, Kenya, Nigeria, Uganda, South Africa, Tanzania (United Rep. of), Zimbabwe
Middle East & Northern Africa	12	Algeria, Egypt, Gaza & West Bank, Iran, Iraq, Jordan, Libya, Morocco, Syria, Tunisia, Turkey, Yemen	
Eastern Europe and the Newly Independent States	19	Albania, Armenia, Azerbaijan, Belarus, Bosnia-Herzegovina, Bulgaria, Georgia, Kazakhstan, Kyrgyzstan, Latvia, Lithuania, Macedonia, Moldova, Romania, Tajikistan, Turkmenistan, Ukraine, Uzbekistan	Russian Federation
Latin America & the Caribbean	19	Belize, Bolivia, Colombia, Costa Rica, Cuba, El Salvador, Ecquador, Guatemala, Guyana, Haiti, Honduras, Jamaica, Nicaragua, Paraguay, Dominican Republic, St. Vincent & Grenadines, Suriname	Brazil, Peru (3)
Asia	19	Bhutan, Korea (DPRK), Laos, Maldives, Mongolia, Nepal, Papua New Guinea, Sri Lanka	Afghanistan, Bangladesh, Cambodia, China, India, Indonesia, Myanmar, Pakistan, Philippines, Thailand, Viet-Nam
Total	**114**	**92**	**22**

(1) Countries are grouped as shown only for the purpose of the GPSTB economic analysis.

(2) Botswana had a GNP/capita of $3,240 per year in 1999. However, it was included in the present evaluation given the very high burden of TB in the country (the highest incidence rate in the world as of 2000 with approximately 7% of its population being dually infected by MTB and HIV).

(3) Mozambique joined the 22 HBC list in 2001, replacing Peru. However, cost estimates used for the GPSTB are based on the list for the year 2000, which included Peru but not Mozambique.

Annex 4 Contributors

CHAPTER 1

Coordinator

Jim Yong Kim

Contributors

Dennis Ahlburg
Olivier Appaix
Marijke Becx-Bleumink
Daniel Bleed
Angela Bone
Arachu Castro
Gavin Churchyard
Christopher Dye
Paul Farmer
Peter Godfrey-Fausset
Rajesh Gupta
Phillip Hopewell
Jim Yong Kim
Arata Kochi
Heidi Larson
Edward Nardell
Mario Raviglione
Aaron Shakow

Reviewers

Dirgh Singh Bam
Paola Bollini
Richard Laing
Fabio Luelmo
Aryeh Neier
James Orbinski
Vulimiri Ramalingaswami
Mark Rosenberg
Richard Skolnik
Ian Smith
Paul Zintl

CHAPTER 2

Coordinator

Ian Smith

Contributors

Olivier Appaix
Ivan Bastian
Daniel Bleed
Adrienne Brown
Arachu Castro
Daniel Chin
John Crofton
Christopher Dye
Don Enarson
Anne Fanning
Thomas Frieden
Christy Hanson
Nobatsu Ishikawa
Akramul Islam
Enamul Karim
Javaid Ahmed Khan
GR Khatri
Richard Laing
Dermot Maher
Giovanni Battista Migliori
Bess Miller
Kolluri Murthy
James Newell
Saleh Ottmani
Vikram Pathania
Françoise Portaels
Mario Raviglione
Leen Rigouts
Ian Smith
Sergio Spinaci
Pedro Guillermo Suárez
Hamadou Traore
Mukund Uplekar
Ros Walley
John Walley
Diana Weil
Zhao Fen Zeng

Reviewers

Francis Adatu-Engwau
Dongil Ahn
Ruri Arnadottir
Dirgh Singh Bam
Frank Bansu
Enis Baris
Nils Billo
Jaap Broekmans
Rodolfo Rodríguez Cruz
Tom Kenyon
Daniel Kibuga
Jim Yong Kim
Tunde Madaras
Eddie Maganu
Toru Mori
Jai Narain
Richard Laing
Hans Rieder
Mark Rosenberg
Akihiro Seita
Paul Zintl

CHAPTER 3

Coordinator
Maarten Bosman

Contributors
Olivier Appaix
Maarten Bosman
Arachu Castro
Dick Chaisson
Christopher Dye
Paul Farmer
Peter Godfrey-Fausset
Peter Gondrie
Anthony Harries
Phillip Hopewell
Richard Laing
Kitty Lambregts-van Weezenbeek
Dermot Maher
Jintana Ngamvithayapong-Yanai
James Orbinski
Peter Piot
Holger Sawert
Jeroen van Gorkom
Karin Weyer

Reviewers
Sandra Anderson
John Crofton
Drevin de Cock
Guus Eskens
Jim Yong Kim
Rudolf Knippenberg
Afriano Kritski
Alwyn Mwinga
Richard Laing
Mikhail Perelman
Jos Perriens
Wiwat Rojanapithayakorn
Mark Rosenberg
Eric Sawyer
Ian Smith
Eric van Praag
Paul Zintl

CHAPTER 4

Coordinator
Jim Yong Kim

Contributors
Olivier Appaix
Jaime Bayona
Mercedes Becerra
Fadila Boulahbal
Arachu Castro
Christopher Dye
Marcos Espinal
Paul Farmer
Paula Fujiwara
Andrea Gori
Jim Yong Kim
Sang Jae Kim
Adalbert Laszlo
Maria Luisa Moro
Aaron Shakow
Pedro Guillermo Suárez

Reviewers
John Crofton
Thomas Frieden
Daniel Kibuga
Richard Laing
Bess Miller
Joia Mukherjee
Françoise Portaels
Mario Raviglione
Lee Reichman
Mark Rosenberg
Max Salfinger
Richard Skolnik
Ian Smith
Jaap Veen
Richard Zaleskis
Paul Zintl

CHAPTER 5

Coordinator
Paul Nunn

Contributors
Olivier Appaix
Mercedes Becerra
Martien Borgdorff
Arachu Castro
Louis Currat
Don Enarson
Marcos Espinal
Paul Fine
Katherine Floyd
John Foulds
Ann Ginsberg
Peter Godfrey-Fausset
Anthony Harries
Dean Jamison
Richard Laing
Carlos Morel
Paul Nunn

Richard O'Brien
Ariel Pablos-Mendez
Mark Perkins
Rajeswori Ramachandran
Hans Remme
Giorgio Roscigno
Ian Smith
Fabio Zicker

Reviewers
Leopold Blanc
Barry Bloom
Richard Bumgarner
Gijs Elzinga
Jim Yong Kim
Richard Laing
Fabio Luelmo
Mario Raviglione
Mark Rosenberg
Paul Zintl

CHAPTERS 6–8

Writing Group
Arachu Castro
Alan Hinman
Daniel Kibuga
Ian Smith
Paul Zintl

Planning Group
Francis Adatu
Dong Il Ahn
Steve Barid
Richard Berlin
Nils Billo
Amy Bloom
Jaap Broekmans
Ken Castro
Fran DuMelle
Gijs Elzinga
Zuhair Hallaj
Alan Hinman
Phil Hopewell
Daniel Kibuga
GR Khatri
Jim Yong Kim
Jacob Kumaresan
JW Lee
Marl Mantala
Bess Miller
Paul Nunn
Rick O'Brien
Mario Raviglione
Alastair Robb
Giorgio Roscigno
Mark Rosenberg
Carl Schieffelbein
Richard Skolnik
Ian Smith
Diana Weil
Charles Wells
Paul Zintl

Contributors
Joel Brenner
Michael Brennan
Leopold Blanc
Sarah England
Marcos Espinal
Katherine Floyd
Ulli Fruth
Ann Ginsburg
Dermot Maher
Rick O'Brien
Mark Perkins
Giorgio Roscigno
Jeannette Sanchez

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