



**Background Paper
of the
Task Force on Major Diseases and Access to Medicine,
Subgroup on Tuberculosis**

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Note to the reader

The Background Paper provides a preliminary overview of existing knowledge and scopes out the questions addressed by this Task Force. The analysis, conclusions and recommendations contained herein should be considered as very preliminary as they are likely to evolve as the Task Force works toward its final report at the end of 2004. Comments and suggestions are welcome. Please cite this paper as "Background Paper of the Millennium Project Task Force on Major Diseases and Access to Medicine, Subgroup on Tuberculosis".

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Table of Contents

1. Combating Tuberculosis: Introduction	4
1.1 The Target.....	6
1.2 The Current Epidemic.....	7
1.3 Historical Context.....	8
2. Obstacles and Challenges	12
2.1 Under-utilization or Absence of DOTS Programs.....	12
2.2 HIV/AIDS and Tuberculosis.....	14
2.3 Multi-Drug Resistant Tuberculosis.....	17
2.4 Deficiencies of Diagnostic Tools, Drugs, and Vaccines.....	22
2.5 Institutional/Systemic Borders and Boundaries.....	23
2.6 Other Significant Obstacles to the Implementation of DOTS.....	24
3. Recent Advances and Recommendations For Moving Forward	25
3.1 Expansion of DOTS Through Coalitions of Action.....	25
3.2 TB and HIV/AIDS: Overlapping Epidemics, Complementary Responses.....	27
3.3 Responses to Multi-drug Resistant Tuberculosis (MDR-TB).....	30
3.4 Improving the Tools.....	32
a. New Diagnostics.....	32
b. New Drugs.....	33
c. New Vaccines.....	34
3.5 Linking Parallel Systems.....	35
3.6 Mobilizing Communities.....	37
3.7 Operational Research.....	38
4. The Millennium Development Goals: Added Value for the GPSTB	40
5. Conclusion	41

Appendices

I. Cost Projections (from projections developed 1997-1998)

Appendix A: Estimated costs of DOTS implementation, National TB-Control.....	42
Programmes, and DOTS expansion in low and middle-income countries, 2001–2005 (\$ millions).	
Appendix B: Estimated Costs for MDR-TB-control in Low- and Middle-Income.....	43
Countries, 2001-2005 (\$millions)	

Appendix C: Estimated Costs of Research and Development for TB Control.....44
2001-2005 (\$millions)

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, 1952

1. Combating Tuberculosis: Introduction

Although this preliminary document is largely a summary of the recently published report entitled *The Global Plan to Stop Tuberculosis* authored by the Stop TB Partnership and Partners in Health¹, it also incorporates information obtained since the development of that report². Additionally, it will reflect ideas that emerged during the November 2002 inaugural meeting of the United Nations Millennium Development Goals Task Force on Infectious Diseases and Access to Essential Medicines³(Task Force 5). Within this paper, any discussion of the projected goals and strategies of the Task Force is to be understood as a discussion in its early stages of development.

While the focus of this paper is tuberculosis, the deadly synergy between HIV and tuberculosis combined with the global problem of access to essential medicines to treat individuals in impoverished settings infected with these treatable diseases, clearly illustrates the artificial nature of the organizational divisions within (and between) the Task Forces. One discussion during the recent meeting centered on suggested approaches to link TB and HIV/AIDS resources for prevention and treatment strategies, particularly

¹ The Global Plan to Stop Tuberculosis. 2002. Published by the World Health Organization:Geneva

² The authors wish to gratefully acknowledge the comments and suggestions provided by Dr. Mario Raviglione.

³ Task Force 5 has been divided into 4 sub-groups: Malaria, HIV/AIDS, Tuberculosis and Access to Essential Medicines.

in high-prevalence countries where, for example, both human and fiscal resources are scarce. These critical intersections will continue to be a focus of the larger Task Force as the project develops.

The Task Forces have been charged to take their work beyond the analytical and into the arena of strategic action; to proceed as if the fiscal, organizational and processual constraints experienced within international health and institutional settings did not exist. In short, we have been challenged to move beyond the accepted and economically-bounded constraints of scaling-up treatment and prevention throughout the world.

The Global Plan to Stop Tuberculosis (GPSTB) and the coalition of individuals who represented the broad spectrum of public/private organizations that contributed to its development, provide an important “template” of cooperative, multi-lateral effort towards a common goal. Through the pooling of experience, knowledge and resources, realistic goals have been set and steps towards implementation defined. The MDG sub-group on tuberculosis explicitly joins this work already in progress and seeks to participate in the realization of the goals established by the GPSTB. At the same time, it has defined themes that will be the focus of effort within the specific context of the MDG Project including: building systems of accountability; addressing human resource and infra-structural deficiencies; scaling-up case detection, and defining specific elements of program successes (and failures) in a way that permits the information to be operationalized.

1.1 The Target

Due to poverty, complacency, and neglect, tuberculosis 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 are proven, cost-effective treatments, and hundreds of thousands are becoming infected with resistant strains that are more expensive to treat. The most current estimates confirm that 50 years after the introduction of effective chemotherapy, TB remains—second only to AIDS—one of the leading infectious cause of adult mortality in the world, causing up to 2 million deaths each year.⁴

Responding to the explosion of TB, HIV/AIDS, and other infections has been explicitly adopted as a Millennium Development Goal. The challenge of halting the spread of these diseases demands solidarity, one of the fundamental values expressed in The Millennium Declaration: “Global challenges must be managed in a way that distributes the costs and burdens fairly in accordance with basic principles of equity and social justice.”⁵ It also asserts a recognition of the foundational importance of good health in the attainment of the United Nation’s Millennium Development Goals.

⁴ Bloom BR, Murray CJ. Tuberculosis: commentary on a re-emergent killer. *Science*. 1992;257:1055–64; Dolin PJ, Raviglione MC, Kochi A. Global tuberculosis incidence and mortality during 1990–2000. *Bull World Health Organ*. 1994;72:213–20; Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. *JAMA*. 1999;282:677–86; Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet*. 1997;349:1498–504; Raviglione MC, Snider DE Jr, Kochi A. Global epidemiology of tuberculosis. Morbidity and mortality of a worldwide epidemic. *JAMA*. 1995;273:220–6; World Health Organization. *Tuberculosis control: the DOTS strategy: an annotated bibliography compiled by the Global Tuberculosis Programme and the Regional Office for South-East Asia*. Geneva: World Health Organization, 1997.

⁵ The United Nations Millennium Declaration

1.2 The Current Epidemic

The World Health Organization estimates that annually, approximately two million people die from tuberculosis. And, in many parts of the developing world, the situation continues to worsen. The number of new TB cases climbed 6 percent each year between 1997 and 1999, from 8 million to 8.4 million worldwide.⁶ 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.⁷ In Zimbabwe, the noxious synergy between tuberculosis and HIV/AIDS takes as many as 3,000 lives a week.⁸ 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.⁹ 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.¹⁰

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.¹¹ Without

⁶ World Health Organization. *Global Tuberculosis Control: WHO Report 2001*. Geneva: World Health Organization, 2001

⁷ World Health Organization. *Global Tuberculosis Control: WHO Report 2001*. Geneva: World Health Organization, 2001

⁸ UNAIDS. Epidemiological Fact Sheet on HIV/AIDS and Sexually Transmitted Infections, 2000 Update: Zimbabwe. 2000

⁹ UNAIDS. Epidemiological Fact Sheet on HIV/AIDS and Sexually Transmitted Infections, 2000 Update—Zimbabwe. 2000; World Health Organization. *Anti-tuberculosis drug resistance in the world: the WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance 1994–1997*. Geneva: World Health Organization, 1997.

¹⁰ World Health Organization. *World Health Report. Health Systems: Improving Performance*. Geneva: World Health Organization, 2000; World Health Organization. Online Statistical Index. Accessed on: February 7, 2001. Internet communication at:

http://www.nt.who.int/whosis/statistics/menu.cfm?path=statistics_basics&language=english

¹¹ Raviglione MC, Dye C, Schmidt S, Kochi A. Assessment of worldwide tuberculosis control. WHO Global Surveillance and Monitoring Project. *Lancet*. 1997;350:624–9; World Health Organization. *Tuberculosis and Sustainable Development: Report from the Ministerial Conference in Amsterdam*. Geneva: World Health Organization, 2000. WHO/CDS/STB/2000.6.

unprecedented efforts to improve TB control in regions hardest hit by the disease, incidence is expected to climb steadily.¹² 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.¹³

1.3 Historical Context

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.¹⁴; DNA analysis of pre-Columbian mummies in the northern Andean regions of Chile has demonstrated the pre-contact presence of TB in the Americas.¹⁵ 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.¹⁶ The epidemics of “galloping consumption” that ravaged Europe and North America in the nineteenth and early twentieth centuries 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.

In 1993, WHO declared TB to be a global emergency. Yet that same year, the World Bank's World Development Report revealed that TB control using the WHO-

¹² Dye C, Garnett GP, Sleeman K, Williams BG. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Directly observed short-course therapy. *Lancet*. 1998;352:1886-91; Murray CJL; Styblo K, and Rouillon A. Tuberculosis. In: Jamison DT, World Bank; *Disease Control Priorities in Developing Countries*. New York, N.Y.: Oxford University Press (published for the World Bank), 1993.

¹³ Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990–2020: Global Burden of Disease Study. *Lancet*. 1997;349:1498–504.

¹⁴ Cave AJE. The evidence for the incidence of tuberculosis in ancient Egypt. *British Journal of Tuberculosis*. 1939;33:142.

¹⁵ Arriaza B, Salo W. Pre-Columbian tuberculosis in northern Chile: molecular and skeletal evidence. *American Journal of Physical Anthropology*. 1995; 98(1):37-45.

¹⁶ Dye C, Scheele S, Dolin P, Pathania V, and Ravigliione MC. Global Burden of tuberculosis: estimated incidence, prevalence, and mortality by country. *JAMA*. 1999; 282(7):677-86; World Health Organization. *Global Tuberculosis Control: Who Report 1999*. Geneva: World Health Organization, 1999.

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 as much as twice those of alternative treatment programmes.

In developing countries, the toll from tuberculosis is most often experienced among individuals in prime wage-earning and child-bearing years. Therefore, the destructive impact of the disease is experienced, not only on an individual level, but within the social and economic spheres of families and entire communities. Indeed, DOTS may be one of the soundest interventions of any kind for countries struggling to pull themselves out of poverty.¹⁸

The principles of DOTS were first developed in the national TB programme in Tanzania, and subsequently expanded to six other 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 during the 70s and 80s, in the development of these innovative programmes cannot be understated. He combined a comprehensive knowledge of the epidemiology of TB with a remarkable understanding of the management principles of TB control and was tenaciously committed to excellence in his work. His contribution to TB was immense, and he will be remembered as one of the heroes of public health of the 20th century. The principles he developed in Africa were

¹⁷ 17 de Jonghe E, Murray CJ, Chum HJ, et al. Cost-effectiveness of chemotherapy for sputum smear-positive pulmonary tuberculosis in Malawi, Mozambique and Tanzania. *Int J Health Plann Manage.* 1994;9:151–81; Jha P, Bangoura O, Ranson K. The cost-effectiveness of forty health interventions in Guinea. *Health Policy Plan.* 1998;13:249–62; World Bank. *World Development Report: Investing in Health.* Washington: World Bank, 1993.

¹⁸ Kochi A. Tuberculosis control—is DOTS the health breakthrough of the 1990s? *World Health Forum.* 1997;18:225–32; discussion 233–47.

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 became 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.

DOTS cures the vast majority of active TB cases. It is remarkably effective. 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

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

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. However, the synergism that increasingly defines the current TB and HIV pandemics also suggests the potential value of future treatment and prevention models that will link resources, preventive strategies and therapeutic modalities.

¹⁹ World Health Organization. *Global Tuberculosis Control: Surveillance, Planning and Financing*. WHO Report 2002. Geneva, Switzerland, WHO/CDS/TB/2002.295.

²⁰ Raviglione MC, Dye C, Schmidt S, Kochi A. Assessment of worldwide tuberculosis control.

²¹ Murray CJ, Salomon JA. Modeling the impact of global tuberculosis control strategies. *Proc Natl Acad Sci U S A*. 1998;95:13881–6.

²² Raviglione MC; Snider DE, and Kochi A. Global epidemiology of tuberculosis: morbidity and mortality of a worldwide epidemic. *JAMA*. 1995;273(3):220–226.

²³ González E, Armas L, Alonso A. Tuberculosis in the Republic of Cuba: its possible elimination. *Tuber Lung Dis*. 1994;75:188–94; Henderson DA. The challenge of eradication: lessons from past eradication campaigns. *Int J Tuberc Lung Dis*. 1998;2:S4–8; Kok-Jensen A. [When can tuberculosis be eradicated in Denmark?]. *Ugeskr Laeger*. 1995; 157(3):273–9; Ohmori M. [Estimating the year of eradication of tuberculosis in Japan].

2. Obstacles and challenges

The absence or under-utilization of DOTS; The HIV/AIDS pandemic; drug-resistant forms of TB; the lack of new diagnostics, new drugs, and new vaccines; the deterioration of public health infrastructure; and economic and political crises also present significant challenges to many national TB-control programs.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.

2.1 Under-utilization or absence of DOTS programs

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.²⁵ According to the WHO annual (2002) report on the state of the world's TB epidemic²⁶, 148 countries, including all of the 22 TB high-burden countries have adopted DOTS. Ninety-five of these countries were already implementing this strategy for over 90 percent of their populations. Most of these 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 such as China and India²⁷, as well as Viet Nam and

²⁴ Bloom BR, Murray CJ. Tuberculosis: commentary on a reemergent killer. *Science*. 1992;257:1055–64; Fatkenheuer G, Taelman H, Lepage P, et al. The return of tuberculosis. *Diagn Microbiol Infect Dis*. 1999;34:139–46; Nolan CM. Multidrug-resistant tuberculosis in the USA: the end of the beginning. *Tuber Lung Dis*. 1996;77:293–4; Nolan CM. Nosocomial multidrug-resistant tuberculosis—global spread of the third epidemic. *J Infect Dis*. 1997;176:748–51; Raviglione MC, Rieder HL, Styblo K, et al. Tuberculosis trends in eastern Europe and the former USSR. *Tuber Lung Dis*. 1994;75:400–16.

²⁵ Dye C, Scheele S, Dolin P, Pathania V, and Raviglione MC. Global Burden of tuberculosis: estimated incidence, prevalence, and mortality by country. *JAMA*. 1999; 282(7):677-86

²⁶ World Health Organization. Global Tuberculosis Control. *WHO Report 2000*. Geneva: World Health Organization, 2000. Internet communication at: <http://www.who.int/gtb/publications/globrep00/index.html>.

²⁷ See Progress toward tuberculosis control—India. *Morbidity and Mortality Weekly Report*, 2002;51(11):229-32.

Peru. The latter two are the only two large countries to achieve the Stop TB targets for TB control.

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 (DOTS);
- many TB patients receive inadequate treatment in poorly organized and insufficiently monitored programs 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.

The World Health Organization identifies five crucial elements for the successful implementation of DOTS treatment programs²⁸:

1. Government commitment to sustained TB control
2. Sputum-smear microscopy to detect infectious cases
3. A standardized, short-course anti-TB treatment regimen of 6-8 months, with direct observation of treatment.
4. A regular, uninterrupted supply of quality anti-TB drugs.
5. A monitoring and reporting system to evaluate treatment outcomes for each patient diagnosed and the performance of the TB treatment programme as a whole.

Between the lines of these well-defined elements lie both the economic realities of global inequalities and the interrelated political and social exigencies of today’s world.

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,

²⁸ World Health Organization. TB, A Crossroads: Who Report on the Global Tuberculosis Epidemic. 1998. WHO: Geneva

human and financial resource constraints) or more applicable to health services in general (such as providing services to “hard to reach” population groups). In some instances, much-needed health sector reforms have been introduced without ensuring maintenance of effective TB-control efforts or other public health programs²⁹, with catastrophic results for patients.³⁰

The WHO goals of an 85% treatment-success rate and a 70% case-detection rate within existing DOTS programs, originally targeted for 2005, is now projected to be more realistically achievable by the year 2013. Only 5 (Viet Nam, Cuba, Malaysia, the Maldives, and Nicaragua) of the 139 countries providing data had met the interim goals established by WHO for the year 2000. Overall, no more than 21% of the countries increased case detection by more than 1% while still maintaining treatment success rates of 70% or above between the years 1999 and 2000.³¹

2.2 HIV/AIDS and Tuberculosis

Infection with HIV greatly increases the risk that an infected individual will develop active TB, thus inextricably linking the two epidemics. Some sub-Saharan African countries have witnessed a fourfold increase in TB cases over the last 10–15 years. Long-term (1980-2000) trending of TB case-notification rates demonstrates two

²⁹ Weil DE. Advancing tuberculosis control within reforming health systems. *International Journal of Tuberculosis & Lung Disease*. 4(7):597-605, 2000.

³⁰ Bosman MC. Health sector reform and tuberculosis control: the case of Zambia. *Int J Tuberc Lung Dis*. 2000;4:606–14.; Hanson C. Kibuga D. Effective tuberculosis control and health sector reforms in Kenya: challenges of an increasing tuberculosis burden and opportunities through reform. *International Journal of Tuberculosis & Lung Disease*. 4(7):627-32, 2000; Kumaresan JA. de Colombani P. Karim E. Tuberculosis and health sector reform in Bangladesh. *International Journal of Tuberculosis & Lung Disease*. 4(7):615-21, 2000; Kritski AL. Ruffino-Netto A. Health sector reform in Brazil: impact on tuberculosis control. *International Journal of Tuberculosis & Lung Disease*. 4(7):622-6, 2000

³¹ Dye C, Watt CJ, Bleed, D. Low access to a highly effective therapy: a challenge for international tuberculosis control. *Bulletin of the World Health Organization*. 2002; 80(6):437-44.

distinct patterns that illustrate the critical intersection between the HIV/AIDS pandemic and tuberculosis. Countries of eastern and southern Africa (with the heaviest burden of HIV/AIDS) demonstrated an increase in the number of case notifications between 1990 and 2000 that was approximately two and a half times that reported for countries of Eastern Europe.³²

In the presence of continued escalation in the incidence of untreated HIV/AIDS throughout much of the developing world, tuberculosis will be difficult if not impossible to control in HIV-infected individuals, their families and communities. The majority of co-infected persons live in sub-Saharan Africa, in some of the poorest countries in the world. The increased TB-case notifications that result from the HIV pandemic place an immense burden on TB-control efforts.

There is a need for more staff at all levels of the health sector and for increased resources such as laboratory consumables, anti-TB drugs and administrative (reporting) capabilities. The shortage of trained staff in many areas has reached critical levels. This shortage is due to several factors, paramount of which are low outputs from training institutions, inability of the public health sector to retain qualified staff because of poor conditions of service, and significant attrition rates as a result of health worker infection with HIV/AIDS and TB³³.

³² Dye C, Watt CJ, Bleed,D. Low access to a highly effective therapy: a challenge for international tuberculosis control. *Bulletin of the World Health Organization*. 2002; 80(6):437-44.

³³ Harries AD, Hargreaves NJ, Gausi F,Kwanjana JH, Salaniponi FM. High death rates in health care workers and teachers in Malawi. *Transactions of the Royal Society of Tropical Medicine & Hygiene*. 96(1):34-7, 2002 Jan-Feb.

Case fatality rates in HIV-positive TB patients are high³⁴, and many TB programmes in sub-Saharan Africa have reported escalating death rates in their TB patients over the last 10-15 years. The high case fatality rates adversely affect the cure rates which have, in the good programmes, declined from 85% to below 70%. For those patients who complete anti-TB treatment, the risk of recurrent infection is much higher in co-infected patients than in patients who are HIV-negative. Evidence is gradually accumulating that recurrence is mainly due to infection with a new organism rather than reactivation of the same organism that caused the initial infection

At present, most TB patients are unaware that they have HIV infection. If they know, they may fear a dual stigma if their TB-HIV status becomes known. This barrier of silence and fear must be broken if headway is to be made in tackling the dual epidemic. 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 themselves, their families and communities.

The opportunistic infections that characterize AIDS and the symptoms of advanced pulmonary TB frequently result in prolonged hospitalizations for infected, acutely ill individuals. The presence of infection with HIV/AIDS heightens the risk of nosocomial transmission of TB. Prolonged stays, crowded wards, atypical clinical

³⁴Dye C. Scheele S. Dolin P. Pathania V. Raviglione MC. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. *JAMA*. 1999. 282(7):677-86; Harries AD. Hargreaves NJ. Gausi F. Kwanjana JH. Salaniponi FM. High early death rate in tuberculosis patients in Malawi. [Journal Article] *International Journal of Tuberculosis & Lung Disease*. 5(11):1000-5, 2001.

presentations of TB in the presence of co-infection with HIV, and delays in diagnosis³⁵ place everyone (staff, patients and their family members) who has repeated contact with individuals with active pulmonary tuberculosis at risk of infection, but individuals infected with HIV are particularly vulnerable.

2.3 Multi-Drug Resistant Tuberculosis

The second threat to the effectiveness of treatment is the emergence of MDR-TB that occurs with inadequate or interrupted TB treatment and subsequent transmission of resistant strains to others: “It is alarming to note the presence everywhere of strains resistant to at least one anti-TB drug. The rise on every continent of strains resistant to all major anti-TB drugs is a disastrous and explosive trend”³⁶.

High levels of drug resistance mean that the standard DOTS treatment regimens fail at unacceptably high rates, when compared to regular TB strains.³⁷ Multi-drug-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.³⁸ If TB-control efforts had been well organized

³⁵ Greenaway C., Menzies D., Fanning A., Grewal R., Yuan L., Fitzgerald JM., Canadian Collaborative Group in Nosocomial Transmission of Tuberculosis. Delay in diagnosis among hospitalized patients with active tuberculosis: predictors and outcomes (comment) *American Journal of Respiratory and Critical Care Medicine*; 2002; 165(7):927-33.

³⁶ Freire M, Roscigno G. Joining forces to develop weapons against TB. (Editorial). *Bulletin of the World Health Organization* 2002 80 (6).

³⁷ Espinal MA, Kim SJ, Suárez PG, et al. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. *JAMA*. 2000;283:2537–45.

³⁸ Iseman MD. Tailoring a timebomb. Inadvertent genetic engineering. *Am Rev Respir Dis* 1985;132:735–6.

decades ago, the dimensions of this problem—which by 1999 had been reported in over 100 countries or territories—would likely be significantly smaller today.³⁹

The well-documented obstacles to the expansion of DOTS must also be understood as, at times, insurmountable barriers to both the detection and treatment of drug-resistant cases of the disease. Drug resistant strains of the disease result in unacceptably high rates of treatment failures⁴⁰, undermining not only the health of the individuals but public confidence in the treatment. Many of the countries with the highest disease burden do not have systems in place to accurately report disease incidence, even less to monitor for and to document microbial resistance. In high-income countries (e.g. Israel, the United Kingdom, and Sweden)⁴¹ where treatment protocols (and the resources necessary to implement them) exist, regular testing for therapeutic efficacy of drug regimens demonstrates that patients with drug resistance show a consistent social profile that frequently includes their status as immigrants from high-burden countries. While it is not possible to extrapolate overall rates of drug-resistance in the countries from which immigrants have come, these studies may indicate heretofore undetected “hotspots” of resistant strains.

Today, drug-resistant strains of tuberculosis, and even more ominously, of multidrug-resistant tuberculosis (MDR-TB), are spreading quietly, insidiously—within

³⁹ Program in Infectious Disease and Social Change. *The global impact of drug-resistant tuberculosis*. Boston: Harvard University and Open Society Institute, 1999.

⁴⁰ Espinal MA, Kim SJ, Suarez PG, Kam KM, Khomenko AG, Migliori GB, Baez J, Kochi A, Dye C, Raviglione MC. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries.[comment]. [Journal Article] *JAMA*. 283(19):2537-45, 2000.

⁴¹ See: Drobniewski F, Eltringham I, Graham C, Magee JG, Smith EG, Watt B. A national study of clinical and laboratory factors affecting the survival of patients with multiple drug resistant tuberculosis in the UK. *Thorax*, 2002 57(9):810-16.; Ghebremichael S, Koivula T, Hoffner S, Romanus V, Petrini B, Noren B, Sylvan S, Kallenius G. Resistant tuberculosis is spreading in Sweden: Molecular epidemiological strain identification by “fingerprinting” can make the infection tracing easier. *Lakartidningen*, 2002. 99(23):2618-2623.; Chemtob D, Leventhal A, Weiler-Ravell D. Tuberculosis in Israel: Main epidemiological aspects. *Harefuah*, 2002. 141(3):226-32.

families, institutions, and communities, and across national borders⁴². 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.

Both the complexity and urgency of the emergence of MDRTB can be succinctly illustrated by the following history:

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.⁴³ As of February 1996, all six passengers remained free of signs and symptoms of active tuberculosis.⁴⁴ 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.

The prospect of MDR-TB is so alarming that the mainstream press has given MDR-TB the singular epithet, "Ebola with wings".⁴⁵ 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

⁴² See for example: Quitugua TN, Seaworth BJ, Weis SE, Taylor, JP, Gillette JS, Rosas II, Jost KC Jr, Magee DM, Cox RA. Transmission of drug-resistant tuberculosis in Texas and Mexico. *Journal of Clinical Microbiology*, 2002, 40(8):2716-24.

⁴³ Kenyon TA, Valway SE, Ihle WW, et al. Transmission of multidrug-resistant *Mycobacterium tuberculosis* during a long airplane flight. *N Engl J Med*. 1996;334:933-8.

⁴⁴ Kenyon TA, Valway SE, Ihle WW, et al. Transmission of multidrug-resistant *Mycobacterium tuberculosis* during a long airplane flight. *N Engl J Med*. 1996;334:933-8.

⁴⁵ World Health Organization. Anti-tuberculosis drug resistance in the world: the WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance 1994-1997. Geneva: World Health Organization, 1997; Zimmermann, T. Fighting TB: a second chance to do it right. US News and World Report. March 31, 1997.

stop it”, warned the World Health Organization (WHO) in 1997.⁴⁶ But MDR-TB has already been unleashed.

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.⁴⁷ For some high-prevalence areas, 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.⁴⁸ Another review found reports of patients with drug-resistant TB in over 100 countries.⁴⁹

Recent literature details the continuing upward trending of drug-resistant TB. For example: A nine-month study⁵⁰ in Mozambique studied 709 individuals diagnosed with tuberculosis at randomly selected health centers. MDR-TB was diagnosed in 3.4% of patients with no prior history of treatment, and 5.2% of patients without prior treatment demonstrated resistance to isoniazid and streptomycin. A study situated in Bombay,

⁴⁶ Pablos-Méndez A, Raviglione MC, Laszlo A, et al. Global surveillance for antituberculosis-drug resistance, 1994–1997. World Health Organization–International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. *N Engl J Med.* 1998;338:1641–9.

⁴⁷ World Health Organization, International Union Against Tuberculosis and Lung Disease. Anti-tuberculosis drug resistance in the world: The WHO/IUATLD Global Project on Anti-tuberculosis Drug Resistance Surveillance 1994–1997. Geneva: World Health Organization, 1997; WHO Global Tuberculosis control: WHO report 2000. Geneva: World Health Organization, 2000; World Health Organization. Anti-TB drug resistance in the world. Report n° 2. Geneva: WHO/IUATLD Global Project on antituberculosis drug resistance surveillance, 2000. WHO/CDS/TB/2000.278.

⁴⁸ Dye C, Espinal M, Watt C, Mbiaga C, Williams B, *Worldwide incidence of multidrug-resistant tuberculosis*, unpublished; Espinal MA, Laszlo A, Simonsen L, et al. Global trends in resistance to antituberculosis drugs. World Health Organization—International Union against Tuberculosis and Lung Disease Working Group on Anti-Tuberculosis Drug Resistance Surveillance. *N Engl J Med.* 2001;344:1294–303; Mercedes Becerra (personal communication); World Health Organization, International Union Against Tuberculosis and Lung Diseases, *Anti-tuberculosis Drug Resistance in the World, Report n°2 Prevalence and trends, WHO–IUATLD Global project on anti-tuberculosis drug resistance surveillance.* Geneva: World Health Organization, 2000. WHO/CDS/TB/2000; Program in Infectious Disease and Social Change. *The global impact of drug-resistant tuberculosis.* Boston: Harvard University and Open Society Institute, 1999.

⁴⁹ Program in Infectious Disease and Social Change. *The global impact of drug-resistant tuberculosis.* Boston: Harvard University and Open Society Institute, 1999.

⁵⁰ MacArthur a., Gloyd S., Perdigo P., Noya A., Sacarlal J., Kreiss J. Characteristics of drug resistance and HIV among tuberculosis patients in Mozambique. *International Journal of Tuberculosis and Lung Disease,* 2001; 5(10):894-902.

demonstrated that 10% of patients newly diagnosed with first-time TB infections and 50% of those newly diagnosed who related histories of previous treatment were found to have resistance to at least one primary drug.⁵¹

Japan does country-wide surveys at five-year intervals. The 1997 survey demonstrated that, in patients with no previous history of treatment, the rate of MDR-TB was found to be 0.8%. In patients with a previous history of treatment, the rate was 19.7% (both figures indicate increases over the previous survey conducted in 1992)⁵². One study noted that in Iran, among individuals who had a history of previous treatment, 48% were found to have drug-resistant strains⁵³. In the same article, it was noted that in Cuba and Uruguay (two countries with long histories of national DOTS programs). “...almost all previously-treated patients had drug-resistant strains”⁵⁴.

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.

The empirical knowledge necessary to treat tuberculosis (and to prevent its occurrence) has existed for decades. In developed countries, this is consistently demonstrated by the near-eradication of the disease in segments of the population characterized by their access to essential resources. The continued rise of both primary

⁵¹ Davies PD. Drug-resistant tuberculosis. *JRSM*, 2001. 94(6):261-263

⁵² Abe C. Anti-tuberculosis drug resistance in Japan and in the world. *Kekkaku*, 2001. 76(11):699-706.

⁵³ Espinal M.A., Laszlo A., Simonsen L., Boulabal F., Kim S.J., Reniero A., Sven R., Hans L., Binkin N., Dye C., Williams R., Raviglione M.C. Global trends in resistance to antituberculosis drugs. *New England Journal of Medicine*, 2001; 344(17):1294-1303

⁵⁴ Ibid

TB and MDR-TB in many parts of the world is not about the “science” of these diseases. Like many diseases (often classified as “tropical diseases”), their continued proliferation serve as ever-present reminders of dangerous intra- and international inequalities.

2.4 Deficiencies of Diagnostic Tools, Drugs, and Vaccines

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.

The bane of TB treatment is its length. Currently, treatment with DOTS demands a combination of at least four drugs administered in combination 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. As are new agents effective against MDR-TB, and drugs that can eradicate latent TB infection. 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. 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.

But even in the face of the explosive increase in tuberculosis and 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.⁵⁵ 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.

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 the most severe childhood forms of the disease, it is much less efficacious in adults. The epidemiological impact of BCG is thus severely limited.

2.5 Institutional/Systemic Borders and Boundaries

Parallel but unlinked health care providers (e.g. prison systems, community public health providers, private practitioners, etc.) can serve as points of entry for patients with symptoms of tuberculosis. Without formalized links to a national or regional TB treatment program, these individuals may never be diagnosed or, if correctly diagnosed, may not receive adequate treatment. The accompanying lack of centralized reporting renders these cases virtually invisible to surveillance systems whose purpose is to determine the overall burden of disease. Further, unlinked providers/systems cannot be

⁵⁵ Chang-Blanc D, and Nunn P. Incentives and disincentives for new anti-tuberculosis drug development: situational analysis. Geneva: World Health Organization, 2000. WHO/TDR/PRD/TB/00.1.

held accountable for failures in diagnosis and treatment and they remain outside of standardized educational and informational networks that provide operational guidance.

2.6 Other Significant Obstacles to the Implementation of DOTS

Although prospects for TB treatment in the world are rapidly changing, the legacy of obstacles to rapid DOTS expansion includes: 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.⁵⁶ 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.⁵⁷

Geographically remote regions such as some rural areas in both developed and developing countries, 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 remote 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

⁵⁶ World Health Organization. Global tuberculosis programme. Report of the ad hoc committee on the tuberculosis epidemic. Geneva: World Health Organization, 1998.

⁵⁷ Hurtig AK, Porter JD, Ogden JA. Tuberculosis control and directly observed therapy from the public health/human rights perspective. *Int J Tuberc Lung Dis.* 1999;3:553–60.

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 societies⁵⁸, and health systems do not always respond to patients' needs in a supportive manner. The WHO's World Health Report 2000 analyzed 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.⁵⁹

3. Recent Advances and Recommendations For Moving Forward

3.1 Expansion of DOTS Through Coalitions of Action

In 2000 a broad partnership, hosted by the World Health Organization and comprised of a wide-spectrum of public and private agencies, formed The Stop-TB Partnership. With the 2002 publication of *The Global Plan to Stop Tuberculosis* (GPSTB), the partnership elaborated a plan to reverse the incidence of TB throughout the developing world while working towards the ultimate goal of eliminating TB as a public health threat. The partnership has identified four basic goals:

- **To expand** the current strategy—DOTS—so that all people with TB have access to effective diagnosis and treatment:
 - Increase** the supply of funds for DOTS
 - Increase** the demand for DOTS programmes
 - Increase** the capacity for implementing DOT
 - Increase** sustainable supplies of quality TB drugs for National

⁵⁸ See, for example: Long N.H., Johansson E., Diwan V.K., Winkvist A. Different tuberculosis in men and women: Beliefs from focus groups in Vietnam. *Social Science and Medicine*, 1999, 49(6):815-22; Liefoghe R., Baliddwa J.B., Kipruto E.M., Vermeire C., Demuynck A.O. From their own perspective: a Kenyan community's perception of tuberculosis. *Tropical Medicine and International Health*, 1997; 2(8):809-21

⁵⁹ World Health Organization. *World Health Report 2000. Health systems: Improving performance*. Geneva: World Health Organization, 2000.

Tuberculosis Control Programmes (NTPs)

- **To adapt** this strategy to meet the emerging challenges of HIV and TB drug resistance.
- **To improve** existing tools by developing new diagnostics, new drugs, and a new vaccine.
- **To strengthen** the Global Partnership to Stop TB so that proven TB-control strategies are effectively applied.

The accelerated expansion of DOTS will require wide-scale and rapid implementation of all of the crucial elements identified by WHO as well as the resources needed to create new programs and expand existing ones.

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.⁶⁰

China has demonstrated the feasibility and effectiveness of rapid DOTS expansion: Between 1991 and 1995, access to DOTS was expanded to cover more than 90% of the targeted populations (roughly half of China’s population). Case detection goals remain to be reached but, by the year 2000, 1.8 million TB cases were diagnosed and 1.3 received free treatment with more than 90% of these individuals concluding their treatment successfully⁶¹.

⁶⁰ World Health Organization. *Involving Private Practitioners in Tuberculosis Control*. Geneva: World Health Organization, 2001.

⁶¹ Xianyi C. Fengzeng Z. Hongjin D. Liya W. Lixia W. Xin D. Chin DP. The DOTS strategy in China: results and lessons after 10 years. *Bulletin of the World Health Organization*. 80(6):430-6, 2002.

The prevalence of active pulmonary tuberculosis [in Sichuan province], the bacteriological positive prevalence and smear positive prevalence of pulmonary tuberculosis in 2000 were 544/100,000, 250/100,000 and 144/100,000, respectively, decreased by 41.8%, 30.0% and 35.0% respectively in comparison with 1990, and the annual reduction rates were 5.3%, 3.5% and 4.2% respectively during the past 10 years⁶².

The scale-up in China also illustrates the value and importance of multilateral collaborations that involve multiple invested partners from local, national, international and public/private agencies and institutions. The same can be said of Peru where, through the widespread and focused implementation of DOTS between 1991 and 1999, the decline in the rate of incidence doubled. Current projections predict that new cases of tuberculosis in Peru will continue to be halved every ten years⁶³. Public-private agency collaboration in Peru has also contributed to new standards of treatment for drug-resistant tuberculosis in limited resource settings. Focused community activism and mobilization continue to be a dominant feature of the success of the program in Peru. Organized, local demands for essential services fuel political will: an essential element in expansion of DOTS.

3.2 TB and HIV/AIDS : Overlapping Epidemics, Complementary Responses

HIV/AIDS has become the greatest public health threat of the last 500 years. HIV is the most potent risk factor known in the progression from latent infection with *Mycobacterium tuberculosis* to active disease. The increased cases seen in individuals co-infected with HIV pose a proportional increase in risk to the larger community. The parallel but separate responses by TB and HIV/AIDS programmes in the past are

⁶² Wu J. Xiong G. Feng S. Cao H. Rao Z. Jiang T. Liu Y. Duan W. Tang X. Study on epidemic trend and control policy of tuberculosis in Sichuan province. *Chung-Hua Chieh Ho Ho Hu Hsi Tsa Chih Chinese Journal of Tuberculosis & Respiratory Diseases*. 25(1):12-4, 2002.

⁶³ <http://www.who.int/inf-new/dnldpdf/tuberculosis.pdf>

increasingly giving way to unified health sector strategies as the realization that the control of TB/HIV is an integral part of the response to HIV/AIDS. These general health sector strategies include⁶⁴:

- Increased funding for improved general health service provider capacity (human resources, infrastructure, commodities).
- Shift in policy away from vertical HIV/AIDS services towards a strengthened response to meet the needs of high-prevalence populations.
- Operational research on TB and HIV programme collaboration in supporting health providers
- Effective coordination of many role players⁶⁵.
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 published⁶⁶ 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 HAART⁶⁷). These latter interventions should also be considered as indirect interventions against TB;
- prioritization 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.

⁶⁴ Maher D. (Stop TB Department, WHO) *Strategic Framework for TB/HIV* Presented at IUATLD World Conference on Lung Health; Montreal, October, 2002: http://www.who.int/gtb/whats-new/montreal_oct02/iatld/maher-tbhiv.ppt

⁶⁵ *ibid.*

⁶⁶ Maher D, Floyd K, Raviglione M. A strategic framework to decrease the burden of TB/HIV. WHO/CDS/TB/2002.296 World Health Organization, Geneva.

⁶⁷ Harries A.D., Hargreaves N.J., Chimzizi R., Salaniponi F.M. Highly active antiretroviral therapy and tuberculosis control in Africa: synergies and potential. *Bulletin of the World Health Organization*, 2002; 80(6): 464-469

Additional/specific recommendations include:

- Promotion of better links between HIV testing and access to TB prevention and care
- 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 counseling and testing facilities, and those that have a well-functioning DOTS programme.
- Development of a comprehensive research agenda to decrease the burden of HIV-related TB.

Balancing the drug combinations utilized as well as the length of treatment of tuberculosis in individuals infected with HIV requires specialized attention⁶⁸. Combining efforts between existing country-and community-level agencies to cooperatively address TB and HIV/AIDS will require a focused process of outreach and negotiation between long-existing and often zealously-guarded bureaucratic boundaries. Once achieved, this collaboration will be fruitful: preventing the transmission of HIV and the use of HAART for the treatment of AIDS will have profound and lasting impact on decreasing the incidence of tuberculosis. Utilizing the same organizational structure that defines DOTS to deliver HAART has been demonstrated to be highly effective, even in the most impoverished settings⁶⁹.

One of the most critical elements in the implementation of these proven, effective strategies is the maintenance of an uninterrupted supply of high-quality drugs. Drug procurement strategies that utilize regional and trans-national resource-pooling,

⁶⁸ Atomiya A.N., Uip D.E., Leite O.H. Evaluation of disease patterns, treatment and prognosis of tuberculosis in AIDS patients. *Brazilian Journal of Infectious Diseases*, 2002; 6(1):29-39. Dean G.L., Edwards S.G., Ives N.J., Matthews G., Fox E.F., Navaratne L., Fisher M., Taylor G.P., Miller R., Taylor C.B., de Ruitter A., Pozniak A.L. Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. *AIDS*, 2002; 16(1):75-83.

⁶⁹ Farmer P., Leandre F., Mukherjee J., Gupta R., Tarter L., Kim J.Y. Community-based treatment of advanced HIV disease: introducing DOT-HAART (directly observed therapy with highly active antiretroviral therapy). *Bulletin of the World Health Organization*, 2001; 79(12):1145-51.

epitomized by the Global Drug Facility and the, as yet, largely unrealized potential of The Global Fund⁷⁰, hold great promise in the fight to both reverse disease incidence and to lessen global inequalities. This promise will only be realized with unprecedented cooperative effort between public and private sectors. Multinational corporations and the governments and international agencies that provide them with support and trade protection will continue to play a critical role in determining the success or failure of treatment strategies.

Protecting health workers and immune-compromised individuals from infection with TB in hospital settings is challenging in limited-resource settings. Isolation rooms and barrier supplies (masks, respirators, gowns, etc) are frequently not available or in limited supply. However, the risk of nosocomial transmission of tuberculosis in hospitalized individuals infected with HIV and among health workers with prolonged exposure to infected individuals can be addressed pro-actively, even in low-resource settings⁷¹.

3.3 Responses to Multi-drug Resistant Tuberculosis (MDR-TB)

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 through irrational use and the development of further drug resistance, no effective alternatives will be available .

⁷⁰ http://www.stoptb.org/coordinatingboard/GFATM_STBP_1stDraft_MOU.pdf

⁷¹ See: WHO. *Guidelines for the Prevention of TB in Health Care Facilities in Resource-Limited Settings*. World Health Organization, 1999; WHO TB/99.268. Full text available on-line at: <http://www.who.int/gtb/publications/healthcare/index.htm>

The emergence of “super MDR-TB” strains can also be avoided by strictly supervising therapy regimens for MDR-TB. Such supervision is thus a cornerstone of the MDR-TB therapy strategy called “DOTS-Plus.” 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. Thus, in the context of functioning DOTS programs, complementary DOTS-based strategies to contain MDR-TB are currently under development.⁷² Through its Working Group on DOTS-Plus for MDR-TB⁷³, WHO has issued preliminary protocols that will be tested in settings where MDR-TB already accounts for a significant proportion of sickness and death.⁷⁴ The Working Group established the Green Light Committee to oversee the review of DOTS program compliance and the systematic implementation of DOTS-Plus.

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:

- creating laboratory support;
- defining and putting into operation programmes that can effectively deliver MDR-TB therapy;
- providing effective MDR-TB therapy to patients.

⁷² Farmer P, Kim JY. Community based approaches to the control of multidrug resistant tuberculosis: introducing “DOTS-plus”. *BMJ*.1998;317:671–4; Farmer PE, Kim JY, Mitnick C, Timperi R. Responding to outbreaks of MDR-TB: Introducing “DOTS-Plus”. In: Reichman LB, Hershfield ES; *Tuberculosis a Comprehensive International Approach*. New York: Marcel Dekker, 2000; World Health Organization. *Coordination of DOTS-Plus pilot projects for the management of MDR-TB*. Geneva: World Health Organization, 1999. WHO/CDS/CBC/TB/99.262.

⁷³ <http://www.who.int/gtb/policyrd/PDF/DOTSGLC.pdf>

⁷⁴ World Health Organization. *Coordination of DOTS-Plus pilot projects for the management of MDR-TB*. Geneva: World Health Organization, 1999. WHO/CDS/CBC/TB/99.262.

Through operational research, central focus will be given to questions of drug supply, and program oversight as well as development and expansion of information and communication systems. Recent advances in genomics provide another crucial arena for operational research into MDR-TB control.

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. International policymakers and business and philanthropic communities must understand the seriousness of the threat and participate in the discussion.

3.4 Improving the tools

a. New Diagnostics

In March, 2001, the Bill and Melinda Gates Foundation awarded \$10 million to the UNDP/World Bank/WHO/TDR towards the development of new tests to diagnose symptomatic TB more rapidly and accurately. The grant, which supports the Tuberculosis Diagnostic Initiative, will also facilitate research on the rapid detection of drug-resistant strains of the bacillus. It is this type of significant public/private collaboration that will advance this critical and strategic research. Beyond financial support, probably the most important global need for TB diagnostics is an independent system to enable companies or academic groups to rapidly evaluate the effectiveness of diagnostic methods under field conditions. Top priorities for TB diagnostics are to:

- develop new test(s) to diagnosis 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.

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 and time-consuming 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.

b. New Drugs

The 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.

While there has been significant work done in the public sector, there continues to be a lack of responsiveness to the need for new tuberculosis treatments within the private sector. This lack is attributable to the market-driven nature of drug development. 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 an international nonprofit 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 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 detailed assessment of the complex issues that surround the provision and maintenance of adequate supplies of essential drugs is the focus of another of the subgroups of Task Force Five.

c. 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. The 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.

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. One proposal is 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.⁷⁵ 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 catalyze the work.

3.5 Linking Parallel Systems

Once again, we return to the importance of public-private cooperative process⁷⁶. Inherent in this is the knowledge that each country, each region will identify its own issues of structure, power and culture⁷⁷. Navigating entrenched institutional boundaries, creating networks of treatment and information between previously unconnected public health providers⁷⁸ and introducing (and monitoring) standards of care in the private sector will first require detailed local knowledge.

When we speak of linking systems, it may be more useful to recognize this as a process of network expansion and reorganization. As such, research conducted within systems theory, resource dependency theory, and neural network modeling may provide us with valuable tools:

⁷⁵ Sachs J. Helping the world's poorest. *The Economist*. August 12, 1999; Sachs J. A new map of the world. *The Economist*. June 24, 2000.

⁷⁶ See: Murthy KJR, Frieden TR, Yazdani A, Hreshikesh P. Public-Private partnerships in tuberculosis control: experience in Hyderabad, India. *International Journal of Tuberculosis and Lung Disease*. 1997; 5:354-9.; Uplekar M, Pathania V, Raviglione, M. Private practitioners and public health: weak links in tuberculosis control. *Lancet*, 2001; 358: 912-16; Raviglione, MC. The TB epidemic from 1992-2002. 2003, *Tuberculosis* (In Press).

⁷⁷ Mur-Veeman I., Eijkelberg I., Spreeuwenberg C. How to manage the implementation of shared-care: A discussion of the role of power, culture and structure in the development of shared care. *Journal of Management in Medicine*, 2001; 15(2):142-155.

⁷⁸ See: WHO and International Committee of the Red Cross. Tuberculosis control in prisons: A manual for programme managers. Geneva, Switzerland, 2000. WHO/CDS/TB/2000.281.

As networks supercede hierarchy as the predominant form of organization, fluid processes and flexible teams need to replace fixed reporting lines and familiar functions. The barriers to achieving this are more often cultural and emotional than they are commercial and technological. (It is proposed that)...effective knowledge-based businesses will be built on human network connections. This requires much greater investment in social processes of integration and in our individual ability to connect with each other. Without this human agenda, the openness and learning on which the generative knowledge-based environment depends will remain beyond our reach, together with our ability to work and transfer knowledge across complex and shifting organizational boundaries⁷⁹.

In one study of the promotion of cooperative effort between care providers, the authors argue that, "...the nature of (resource) dependencies that are conditioned, shaped and secured by institutions determines the characteristics of these relationships"⁸⁰. They maintain that since the design of government (and international funding) policy can shape these dependencies, it can be designed to deliberately enhance co-operation.

It becomes apparent that the most advantageous, sustainable outcomes for impoverished individuals throughout the world with infectious diseases such as TB and HIV/AIDS will require a sophisticated and concerted effort to re-configure structural, governmental, and operational networks and the relationships on which they are built from the global to local levels⁸¹. Anything less may address immediate needs but will not contribute to the creation of the sustainable, ultimately transformative processes that will be necessary to address the underlying issues of poverty and inequality.

⁷⁹ Palmer, J. The human organization. *Journal of Knowledge Management*, 1997; 1(4):294-307.

⁸⁰ Van Raak A., Paulus A., Mur-Veerman I. Governmental promotion of co-operation between care providers: a theoretical consideration of the Dutch experience. *International Journal of Public Sector Management*, 2002; 15(7): 552-64.

⁸¹ See Palmer, A. Linking external and internal relationship building in networks of public and private sector organizations. *International Journal of Public Sector Management*, 1996; 9(3):51-60. Berman E.M., Werther W.B. Jr. Broad-based consensus building. *International Journal of Public Sector Management*, 1996; 9(3): 61-72. Behara R.S., Fisher W.W., Lemmink, J..G.A.M. Modelling and evaluating service quality measurement using neural networks. *International Journal of Operations and Production Management*, 2002; 22(10):1162-85.

3.6 Mobilizing Communities

Community awareness and involvement in care and education is critical. A mobilized community is instrumental to the development of sustainable activities to eliminate disease and promote health. In many regions, 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.

A fully mobilized community demanding services, high-level political commitment, and effective leadership creates an enabling environment for effective TB control. For example, in Churachandpur District, India during 1998, in the presence of open conflict between two ethnic groups that resulted in casualties and displacement, the TB program continued with successful completion of 86% of the smear-positive cases of pulmonary TB. Both default and mortality rates were 3%:

The main factors that were specific to the success of the programme were the commitment of the local community and the effort and commitment of the local staff. Also vital was the recognition by local leaders that TB was a major problem in their communities. Furthermore, the Society for HIV/AIDS Lifeline Operation in Manipur had been established for a number of years in the area and the directors were well known and respected locally. The involvement of the Society played a large part in ensuring community acceptance of and support for the programme, which might not have been so readily forthcoming had reliance been placed exclusively on an unknown international body⁸².

⁸² Rodger, A.J., Toole M., Lalnuntluangi B., Muana V., Deutschmann P. DOTS-based tuberculosis treatment and control during civil conflict and an HIV epidemic, Churachandpur District, India. *Bulletin of the World Health Organization*, 2002; 80(6): 451-456.

3.7 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 of billions of (US) dollars. Meanwhile, people will continue to die at horrifying rates. A rational attack on the major infectious causes of disease requires concerted efforts from all corners of the research community. 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. 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.⁸³

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. These and other obstacles to expanding operational research initiatives must be overcome.

The value and potential of operational research (defined here as “research aimed at developing interventions that result in improved policy-making, better design and

⁸³ Styblo K, Chum HJ. Treatment results of smear-positive tuberculosis in the Tanzania National Tuberculosis and Leprosy Programme: standard and short-course chemotherapy. In: *Proceedings of the XXVI IUAT World Conference on Tuberculosis and Respiratory Diseases*. Tokyo: Professional Postgraduate Services, 1987:122–6.

implementation of health systems, and more efficient methods of service delivery”⁸⁴) is evident in places such as India and Malawi⁸⁵. The integration of operational research and programme development and implementation has facilitated the production and exchange of information leading to analysis that can be rapidly applied to practice. For example, in Malawi, it was found that large numbers (40%) of smear-positive TB patients also sought treatment from traditional healers. The National Tuberculosis Control Program has since initiated a program that provided focused training for over 3000 traditional healers.

In spite of its successes and even with recent increases in operational research conducted on the national-program level, some strategically important areas of investigation (e.g. the lack of political commitment and the inadequacy of financial systems apart from cost-effectiveness assessments) remain undeveloped⁸⁶. The reasons for this are varied, for example, success in this type of work requires significant skills in both research and TB control: people possessing both sets of skills are rare.

A systematic and multilateral plan to increase the use of operational research relating to TB control will address the following⁸⁷:

- Ensuring that sufficient, qualified operational researchers are available in low-income countries.
- Assessing training needs systematically (e.g. the development of region-specific field-training manuals)
- Bridging the gulf between disease control personnel and academic researchers.
- Generating opportunities for operational researchers to interact, especially at the regional and country levels

⁸⁴ Nunn P. Harries A. Godfrey-Faussett P. Gupta R. Maher D. Raviglione M. The research agenda for improving health policy, systems performance, and service delivery for tuberculosis control: a WHO perspective. *Bulletin of the World Health Organization*. 80(6):471-6, 2002.

⁸⁵ See Salaniponi F., Harries AD., Nyirenda T., Banerjee A., Nyangulu D., et al. Putting research into policy and practice: the experience of the Malawi National Tuberculosis Programme. Geneva: World Health Organization. 1999 Unpublished document WHO/CDS/CPC/TB 99.268.

⁸⁶ Nunn P. Harries A. Godfrey-Faussett P. Gupta R. Maher D. Raviglione M. The research agenda for improving health policy, systems performance, and service delivery for tuberculosis control: a WHO perspective. *Bulletin of the World Health Organization*. 80(6):471-6, 2002.

⁸⁷ *ibid.*

- Providing adequate funding.

4.0 The Millennium Development Goals: Added Value for the GPSTB

As discussed earlier, the MDG sub-group on tuberculosis within Task Force 5 has situated itself within the existing coalition of the *Stop TB Partnership*. Many of the individuals within the sub-group contributed to the formulation of the Global Plan to Stop TB and are familiar with the intricacies of the process to build and maintain complex, multi-lateral coalitions. Discussions at the first meeting of the sub-group in November of 2002 included the identification of key issues that will provide added value to existing initiatives and to further the cause of global TB control. These included:

- Elaboration of the processes that led to the successful formation of the GPSTB (as a model for global partnerships, shared priorities, and epidemiological data) in a manner that permits duplication for other targets.
- The need for more prevalence surveys utilizing tools such as DNA analysis to improve the denominator (at the present much of the modeling continues to be based on databases that date to the 60s and 70s.)
- Identification of cross-cutting issues within the Task Force 5 sub-groups and between other Task Forces in the MDG project. Suggested issues include: human resource development, surveillance, gender and ethnicity issues, internal financial flow, disbursement mechanisms, decentralization vs. vertical programs, and inherent policy contradictions between various international financial agencies (e.g. simultaneous demands on impoverished countries to repay debt and at the same time to fund the expansion of health services for their populations).
- Detailing the role of social mobilization in program success and a summary of proposed grass-root elements that will contribute to expansion and success of programs (e.g. increasing the role of nurses and community health workers).
- Revision of the projected costs of program implementation and scaling-up of existing programs to enhance case detection. Develop dependent scenarios: for example, what would be the impact on cost-control and efficiency if we had improved diagnostic tools? Appendices A-C provide the original cost-estimates developed for The GPSTB. Since the time of these estimates, there have been significant changes in the cost of some of the drugs utilized to treat both TB and MDR-TB .
- Description of actual program successes and failures, the elements that contributed to these outcomes and the way this information can be formalized and utilized. Focused examination of the ways in which adaptations in treatment

strategies on the local level have addressed community concerns, increasing the appropriateness of and receptiveness to interventions.

- The utilization of mapping technologies (CIESIN) to visually document the variable disease incidence within and between nations, existing elements of health service infrastructure and human resources.
- Elaboration of strategies to enhance communication between existing TB and HIV/AIDS programs to develop complementary strategies.
- Develop clearly defined guidelines to determine and assign accountability for program successes and failures across the entire service spectrum (from local to international).

Conclusion

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.

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 channeling 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.

Appendix A⁸⁸

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	4,560	3,300	250	3,550	1,010
– TB programmes (2)	1,560				
– Health-care services (3)	3,000				
Other low- and middle-income countries	1,440	1,000	0	1,000	440
– TB programmes	590				
– Health-care services	850				
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).

⁸⁸ As discussed earlier the tables included in the Appendices contain projected costs that were developed on information from the years 1998-2000. Recent developments, including the development of the Global Fund, will require revision to reflect current cost estimates.

Appendix B

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

1. The figures in Table 2 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*. 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.

Appendix C

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.