Report on Tuberculosis

3 – 6 October 2005
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Report of the Scientific Working Group meeting on Tuberculosis

Geneva, 3–6 October, 2005
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Executive summary

Tuberculosis is a major global health problem, responsible for more than 4500 deaths each day. A decade of intensified efforts at tuberculosis (TB) control has reduced global incidence except in Africa, where the disease continues to rise, driven by the HIV pandemic and poverty. However, unprecedented efforts to address deficiencies in TB control – including developing new drugs, new diagnostics, new vaccines, and new strategies to implement proven interventions – bring hope of tangible progress in TB control. Led by the Stop TB Partnership, the global community of TB public health officials, clinicians and researchers is poised to achieve within ten years the Millennium Development Goal target for tuberculosis, which aims to halt and begin to reverse the incidence of TB by 2015. These efforts strive towards eliminating tuberculosis as a global health problem by mid-century.

This report reflects the consensus of the Scientific Working Group on Tuberculosis, convened in Geneva in October 2005; it provides guidance to the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) and partners involved in TB research and control. The proposed research agenda accommodates the public health concerns expressed in the Stop TB Partnership’s Second Global Plan to Stop TB (2006–2015), and aims to work towards the unified objective of addressing the growing epidemic and meeting the ambitious, though realistic, targets for 2015. The challenges are many, but the time is ripe for action and for moving forwards in TB research.

Success requires invigorated control efforts, improved collaboration, and a special commitment to reach people living in poverty. A prerequisite to this success is to generate new knowledge, new strategies and new tools derived from research on tuberculosis. There are two general areas in which research should be applied in order for TB control targets to be achieved: research on programme implementation and development of new tools.

Research on implementation
Research on programme implementation is essential. Up to 60% of TB cases can be detected with smear microscopy, and nearly all can be cured with six months of treatment using existing regimens. However, the current shortfall in case detection suggests that we do not know how to optimize case detection.

Case detection and access to care
How can case detection be improved? Answers to this question will only derive from better understanding of the social and behavioural forces limiting case detection and from evaluations of new case detection strategies. Key factors to study are the barriers to accessing care, including transportation, user fees, hunger, work, gender discrimination and health system
infrastructure. Research on the factors limiting case detection at sites where TB screening occurs, including schools, workplaces, health and other centres providing HIV testing and care, and hospitals, will be necessary to identify appropriate outreach strategies. Operational research and tests of alternative design for detecting those with TB symptoms, and ensuring diagnosis and rapid entry into care, will be necessary to optimize case finding.

**Diagnostics**

To what extent can we optimize existing diagnostic methods – sputum smear microscopy, culture, and drug sensitivity testing – to increase identification of sputum smear-positive cases? Research on sputum concentration methods and fluorescence microscopy is essential to establish the optimal protocol for sputum-based diagnosis. In addition, improved mycobacterial culture systems need evaluating for their impact on case detection, including relating cost and performance to diagnostic yield. The role of drug sensitivity testing needs to be further examined. Finally, and perhaps most importantly, current diagnostic algorithms – which include both laboratory and empiric components (such as the use of empiric antibiotic trials to exclude TB) – need to be rigorously evaluated and improved.

**Treatment**

How can treatment outcomes be optimized with current drugs? Treatment adherence support strategies (such as directly-observed therapy and patient support systems) need to be assessed and optimized. The role of immunomodulatory drugs needs to be carefully assessed, with meta-analysis of existing data, and new trials are needed to assess the benefit of immunomodulators in conditions where benefit might accrue. Finally, the effect of treating HIV in patients co-infected with TB needs to be addressed. Ongoing studies should help identify optimum approaches for treatment of co-infected patients, but alternative co-infection treatment strategies need to be evaluated for improving clinical outcomes. Such clinical research would benefit from exploration of strategies to improve and integrate HIV care and TB treatment at national, district and health centre levels, as a means of overcoming infrastructural and manpower constraints and improving clinical outcomes – in keeping with HIV/TB policies. Social science research has a unique role to play in identifying the reasons for the successes and failures of current TB treatment and prevention efforts.

**Development of new tools**

The existing arsenal of diagnostic tests, anti-mycobacterial drugs, and bacille Calmette-Guérin (BCG) vaccine, is inadequate. New tools for TB diagnosis, treatment, and prevention are essential if long-term TB control targets are to be met.
New diagnostics
With at least 5 million cases of active TB unnotified each year, extra-pulmonary disease, paediatric TB and multidrug-resistant TB pose significant diagnostic challenges which are not addressed by sputum-smear microscopy. Diagnostics should be driven by the reality of the health system infrastructure; well-engineered, simple tests are needed at the point-of-care, at district hospital laboratories, and at central laboratories. The Stop TB Partnership Working Group on Diagnostics has articulated a focused research agenda for new diagnostics, including the detection of extra-pulmonary and paediatric TB infection and other forms of sputum smear-negative disease; the success of this programme will depend upon simple, sensitive and specific technology for diagnosis in the field, and appropriate funding.

New drugs
Short-course chemotherapy for TB consists of adhering tightly to six months of treatment with drugs with suboptimal toxicity profiles, but in patients co-infected with HIV these drugs are challenged by interactions with antiretroviral drugs used to treat advanced HIV disease. A simple regimen for simultaneous treatment does not yet exist. Strategic treatment goals include: developing a short and simple TB treatment regimen; developing improved treatment for multidrug-resistant (MDR)-TB; and identifying and developing drugs that can be safely co-administered with antiretroviral drugs in patients with TB/HIV co-infection. Such drugs will substantially improve treatment outcomes, simplify programme implementation, and accelerate TB control efforts. The TB Alliance has a comprehensive strategy and timeline to evaluate the promising pipeline of drugs and develop a better regimen within the next decade.

In addition to ongoing drug development efforts, research into clinical trial design and surrogate endpoints will greatly facilitate the development of more effective regimens.

Vaccines
An effective vaccine is the key tool for TB control and elimination. Development of this will require new insights into the immunopathogenesis of TB, advances in TB genomics and proteomics, and a better understanding of the deficiencies of the BCG vaccine. In addition to basic TB immunology, vaccine development will also require identification of immune correlates of protection which, if successfully developed, would greatly accelerate vaccine trials.

Research capacity strengthening
The research outlined above will require a significant investment in strengthening the research infrastructure in high-burden countries, without which progress will be delayed. Capacity strengthening efforts should focus on enhancing immunology laboratories, clinical trial
sites, and TB databases, as well as on integrating the overall research effort within national TB control programmes. Special efforts should be made to link TB research to vulnerable populations and to HIV clinical research programmes.

Research cannot be divorced from strengthening the research capacity of health systems within the resource-limited, high-burden countries most affected by the TB pandemic. Thus, the TB research agenda assumes that resources will be used to strengthen the health system’s capacity to cope clinically and programmatically with the anticipated increased burden of cases, as well as to participate in research.

**Regulatory process**

Finally, alternative strategies for clinical evaluation of anti-TB regimens, with harmonized, TB-specific regulatory guidance, as well as accelerated fast-track mechanisms for regulatory approval of investigational new drug applications, will need to be explored so as to match the urgent demand for new drugs and diagnostics. Once proven and approved for treatment, innovative approaches to implementation will be critical to expediting the rate at which new tools are brought into clinical use.
1. Background and objectives

Burden of tuberculosis

Tuberculosis (TB) remains a grave burden to public health (fig. 1 shows the incidence in 2004). Approximately two billion people worldwide are infected with Mycobacterium tuberculosis, the pathogen responsible for tuberculosis, which kills nearly 1.7 million people each year. Although most TB cases can be cured with six months of appropriate treatment, control efforts have been hampered by the challenges associated with sub-optimal case-finding and diagnosis, and a treatment regimen that requires multiple drugs for six or more months, with tight adherence. HIV co-infection has added additional challenges: in 2004 alone, 248 000 TB-related deaths were attributable to HIV.

TB is a disease of poverty. Low-income countries account for 95% of TB cases and 98% of TB deaths, including 4500 people each day. This link to poverty in the control of TB is an important component of the United Nations’ Millennium Development Goals; the major challenges for TB control lie in addressing case finding, case management and effective treatment of TB patients living in poverty. During the 1990s, a convergence of political, social and biological forces led to an escalation in the number of cases of TB. Inadequate TB control policies allowed the disease to spread and its societal impact to worsen. In resource-limited countries, lack of public health infrastructure, difficult access to health services for the most vulnerable people, inadequate prescribing norms, impaired drug

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**Figure 1. Estimated TB incidence rate 2004***

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a. Other closely related species, including *M. bovis* and *M. africanum*, are responsible for a small percentage of tuberculosis cases.
procurement systems, and a lack of patient support contributed to an ominous resurgence of TB. These factors coincided with the emergence of HIV, which buoyed the growing TB epidemic.

As a result of these factors and persistent poverty, the global incidence rate of TB is now growing at approximately 1% per year. The growth in global incidence is unevenly distributed around the world. There has been an explosion of TB in sub-Saharan Africa, fuelled by high HIV prevalence rates throughout the region. Thus, although the TB incidence rate was falling or stable in five out of the six WHO regions by 2003, the dramatic increase in HIV incidence rates in sub-Saharan Africa has increased overall growth in TB cases (fig. 2).

Global response and tuberculosis control
In response to the growing epidemic of TB, WHO launched its DOTS strategy for TB control in 1995. The Stop TB strategy has centred around five elements:
- Sustained political commitment.
- Access to quality-assured sputum smear microscopy.
- Standardized short-course chemotherapy for all cases of TB, under proper case management conditions.
- Uninterrupted supply of quality-assured drugs.
- Recording and reporting systems that enable outcome assessment.

Despite consensus around DOTS-based efforts however, there was slow scale-up of these efforts

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Figure 2. Trends in incidence rates of active TB, 1990–2004*

![Graph showing trends in TB incidence rates](image-url)}
towards achieving the global targets set by the World Health Assembly in 1991: detection of at least 70% of all infectious TB cases and cure of at least 85% of detected cases by 2005. The gravity of the situation resulted in coordinated action and the creation of the Stop TB Partnership, which was established in 2000 as a collaborative network of more than 400 organizations from the public and private sectors with the unified objective of achieving TB control targets by 2015 and ultimately eliminating TB as a public health problem later this century.

The Stop TB Partnership made the development of a unified global plan to control TB one of its priorities. The first Global Plan to Stop TB, for 2001–2005, achieved the majority of its objectives and led directly to the development of a second Plan focused on reaching both the World Health Assembly goals and the Millennium Development Goals, and increased funding for TB control and research has become available. Plans have been facilitated by the establishment of realistic objectives for short-term, medium-term, and sustained progress in each of the major areas of TB control. In addition, to accelerate control efforts, in 2000 a Global DOTS Expansion Plan was endorsed by the 22 highest burden countries, which represent 80% of global TB cases. Over the ensuing five years, rapid expansion of DOTS was achieved in several countries, notably China and India. By the end of 2003, roughly 77% of the world’s population lived in countries that had officially adopted the DOTS strategy. Estimates suggest that the proportion would have increased to over 90% by the end of 2005.

In 2005, the World Health Organization began to work with a wide range of stakeholders to build on the successes of the DOTS strategy while recognizing the additional needs and challenges posed by MDR-TB and HIV-associated TB, and to adapt the innovations in service delivery made in the past five years. A new expanded strategy underpinned the development of the second Global Plan of the Partnership and was launched by WHO in March 2006 as the Stop TB Strategy (table 1).

The Stop TB Partnership’s Global Plan to Stop TB (2006–2015) was developed as a working draft when the Scientific Working Group meeting on TB was convened in October 2005. During the time of writing this report however, the new global plan was launched. The Stop TB Strategy and the Global Plan acknowledge that more than a decade of DOTS programmes in countries with varied characteristics has offered two distinct lessons: the DOTS strategy is necessary to TB control, but the original five elements of DOTS are by themselves insufficient for global TB control. It also acknowledges the profound importance of poverty alleviation and socio-economic development for the long-term control of the TB epidemic. Thus, the Stop TB Partnership’s new Global Plan (GP2) incorporates the original DOTS strategy plus five additional elements, as outlined in table 1.

### Research and development of drugs, diagnostics and vaccines

Waksman’s discovery of streptomycin in the 1940s heralded the modern era of anti-TB chemotherapy. The 1959 discovery of a fungus, *Streptomyces mediterranei*, which produced a new antibiotic, rifamycin B, led to the development of a new anti-tuberculosis medication of remarkable potency, rifampicin. Two more TB drugs, pyrazinamide and ethambutol, followed shortly thereafter, in 1963 and 1967 respectively, enabling simplified, effective, multidrug treatment for tuberculosis.

Following the successful application of multidrug therapy, the death rate from TB dropped...
### Table 1. WHO’s Stop TB strategy

<table>
<thead>
<tr>
<th><strong>VISION:</strong> A WORLD FREE OF TB</th>
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<tr>
<td><strong>GOAL:</strong> To dramatically reduce the global burden of TB by 2015 in line with the Millenium Development Goals and the StopTB Partnership targets</td>
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<table>
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<tr>
<th><strong>OBJECTIVES</strong></th>
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<tr>
<td>- Achieve universal access to high quality diagnosis and patient-centred treatment</td>
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<td>- Reduce the human suffering and socioeconomic burden associated with TB</td>
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<tr>
<td>- Protect poor and vulnerable populations from TB, TB/HIV and multidrug-resistant TB</td>
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<td>- Support development of new tools and enable their timely and effective use</td>
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<th><strong>TARGETS</strong></th>
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<td>- by 2005: to detect at least 70% of new smear-positive cases and treat successfully at least 85% of these cases</td>
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<tr>
<td>- by 2015: to have halted and begun to reverse the incidence of TB</td>
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<tr>
<td>- by 2015: to have halved TB prevalence and death rates compared to 1990 levels</td>
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<tr>
<td>- by 2050: to have eliminated TB as a public health problem (&lt;1 case per million population)</td>
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1. **Pursue high-quality DOTS expansion and enhancement**
   - a. Political commitment with increased and sustained financing
   - b. Case detection through quality-assured bacteriology
   - c. Standardized treatment with supervision and patient support
   - d. An effective drug supply and management system
   - e. Monitoring and evaluation system, and impact measurement

2. **Address TB/HIV, MDR-TB and other challenges**
   - • Implement collaborative TB/HIV activities
   - • Prevent and control multidrug-resistant TB
   - • Address prisoners, refugees and other high-risk groups and special situations

3. **Contribute to health system strengthening**
   - • Actively participate in efforts to improve system-wide policy, human resources, financing, management, service delivery, and information systems
   - • Share innovations that strengthen systems, including the Practical Approach to Lung Health (PAL)
   - • Adapt innovations from other fields

4. **Engage all care providers**
   - • Public-Public, and Public-Private Mix (PPM) approaches
   - • International Standards for TB Care (ISTC)

5. **Empower people with TB, and communities**
   - • Advocacy, communication and social mobilization
   - • Community participation in TB care
   - • Patients’ charter for tuberculosis care

6. **Enable and promote research**
   - • Programme-based operational research
   - • Research to develop new diagnostics, drugs and vaccines
Tuberculosis rapidly in settings where diagnosis and treatment were available. Tuberculosis sanitoriums closed. Despite this early success, treatment costs, treatment duration, and poor implementation prevented people with TB living in conditions of widespread poverty from benefiting from multi-drug treatment.

Moreover, research into drugs, diagnostics and vaccines for TB stagnated; no new classes of drugs for TB have been developed in the past 40 years. The only available tuberculosis vaccine, BCG, which was developed at the beginning of the 20th century and has been in use since 1921, is largely ineffective in most countries. The main diagnostic technique – sputum smear microscopy – dates from the 1880s yet remains the mainstay of TB diagnosis and without improvement in more than a century of use.

With the rate of the current TB epidemic expected to climb over the next few years, it is clear that meeting the Millennium Development Goals for TB control and the elimination of TB as a global public health issue by 2050 will require new tools – new drugs, diagnostics and vaccines.

This is hardly a new refrain in tuberculosis research. The momentum for new drugs, diagnostics and vaccines has been building for more than decade. Working groups on new diagnostics, new drugs and new vaccines have been convened by the Stop TB Partnership and have set out strategies to develop new, improved tools for the detection, treatment and prevention of tuberculosis disease, drug resistance, and latent infection. Research supported by a number of organizations worldwide has led to the discovery of new compounds and new immune markers of disease, and several promising drugs, diagnostics and vaccines are currently in the developmental pipeline for the first time in 40 years. Strategies for the optimized implementation of new products – and to ensure delivery of existing drugs, diagnostics and vaccines to areas of need – have also been established. These achievements are the result of fruitful collaborations between public and private partners that have leveraged the scientific and clinical knowledge of industry, public health, and academic laboratories worldwide.

**Impact of HIV on tuberculosis**

The increasing number of new TB cases each year – propelled by the 10% annual increase in TB incidence in sub-Saharan Africa – is attributable largely to HIV infection (fig. 2). Co-infection rates in TB-infected patients in some countries are as high as 79% (fig. 3). The HIV epidemic is not merely increasing TB but is also driving a significant increase in the proportion of cases that are smear-negative pulmonary and extrapulmonary; these presentations of TB pose considerable challenges to currently available diagnostic methods and to clinical management. Even when diagnosed, HIV-positive, smear-negative pulmonary TB patients have inferior treatment outcomes, including excessive early mortality.

The HIV epidemic is now of such magnitude that meeting initial TB control targets for sub-Saharan Africa would only result in a marginal decline of the annual rise in incidence in the region – from 10% to 7% per year. In order to counter the HIV-driven TB epidemic, WHO and the Stop TB Partnership advocate a TB control strategy of expanded scope. These expanded efforts will be central to decreasing the burden of TB in HIV positive persons, and to reversing the alarming rise in African (and global) incidence rates. It is now widely recognized that collaboration between TB and HIV/AIDS disease programmes to provide patient-centred, integrated
care and services will be essential to controlling the TB epidemic.\(^1\)

In responding to the challenge of the synergistic HIV/TB pandemic, a key strategic objective of the Second Global Plan to Stop TB (2006–2015) is to scale up implementation of collaborative TB/HIV activities in all countries with a high burden of TB/HIV.

WHO’s *Interim Policy on Collaborative TB/HIV Activities*,\(^1\) the core essential guidance for countries in implementing and monitoring collaborative TB/HIV activities, suggested specific activities to address the dual epidemic including:

- Establishing mechanisms for collaboration.
- Decreasing the burden of TB among people living with HIV/AIDS through earlier detection of active TB by intensified case-finding, provision of isoniazid preventive therapy (IPT) for co-infected patients, and ensuring TB infection control in health care and congregate settings.
- Decreasing the burden of HIV among TB patients through provision of voluntary counseling and testing for people at risk of HIV, introducing HIV prevention methods and co-trimoxazole preventive therapy, ensuring HIV/AIDS care and support, and introducing antiretroviral therapy.
- Improving the care of people who are infected with both TB and HIV through cross-training and collaborative care initiatives.

In February 2005, an Expert Consultation Meeting was held to define the TB/HIV research priorities in resource-limited settings. The discussions of the Scientific Working Group for Tuberculosis affirmed the WHO HIV/TB

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**Figure 3.** Estimated HIV prevalence in new adult TB cases, 2004

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c. Major initiatives and partnerships are described in chapter 12.
Working Group and Expert Consultation recommendations.

There was emphasis on the promotion and support of operational research to establish evidence for global policy on collaborative TB/HIV activities (chapter 9). It is recommended that operations research be encouraged at country level to shape TB/HIV collaborative activities to country needs and develop national research capacity. The Scientific Working Group (SWG) highlighted the need for close collaboration with the drugs, diagnostics and vaccines working groups of the Stop TB Partnership to rapidly test and implement new diagnostics, treatments and vaccines as they are developed.

Notably, an investigational agenda was proposed for addressing the following major research areas: preventive therapy for TB (chapters 5, 6, 7, 9); research in co-trimoxazole prophylaxis, including interactions with antiretroviral treatment, and delivery strategies (chapters 7, 9); determination of efficacy of and optimal time for initiation of prophylaxis among people living with HIV/AIDS and TB (chapters 7, 9); timing of initiation of anti-retroviral therapy, and definition of immune reconstitution syndrome (chapters 7, 9); research to operationalize intensive case-finding (chapters 2, 3, 9); the development of new tools and algorithms to improve diagnosis of smear-negative TB in adults and children (chapters 5, 7, 9).

**Objectives of the Scientific Working Group**

Despite advances in TB control since the first TDR Scientific Working Group on Tuberculosis and the launch of the Stop TB Partnership in 2000, many of the same problems remain. There are old challenges, including how best to implement proven strategies for TB case detection, diagnosis and treatment. However, the escalating impact of the HIV pandemic on tuberculosis epidemiology, diagnosis and management constitutes a new challenge that will need new tools to combat the epidemic as it expresses itself in co-infected HIV/TB patients.

The TB research landscape has evolved since 2000. New research efforts are being undertaken in discovery of new drug targets, vaccines, and diagnostic methods for TB. Many of these efforts have been informed by rapid advances in TB genomics and proteomics, and a better understanding of the immunopathogenesis of TB infection, particularly immune factors that are distinctive to high-burden countries.

The main purpose of this report, therefore, is to determine global TB research needs in the context of the Second Global Plan to Stop TB (2006–2015). The objective is to provide guidance to TDR (and partners involved in tuberculosis research and control) by outlining general expert agreement on TB research priorities, and underlining the need for research capacity strengthening to support TB control efforts over the next five years (2006–2010).

This report reflects the consensus of the Scientific Working Group on Tuberculosis, which met in Geneva in October 2005.\(^d\) The report is structured as follows: chapters 3 to 8 provide detail within individual research areas, ranging from TB epidemiology, access to care and treatment, to diagnostics, drug and vaccine development. Chapters 2 and 9 serve as bookends to these research chapters, highlighting the importance of social, economic and behavioural research and implementation research across the entire spectrum of TB research activities. Specifically, the section on social, economic and behavioural

\(^d\) See annex 2 for a list of SWG members.
research (chapter 2) focuses on research issues of individuals and populations; it encompasses research questions on the social and economic forces that drive the tuberculosis epidemic and the public health response to it. The section on implementation research (chapter 9) focuses on research issues of health systems and operations; it encompasses research questions on the implementation of proven interventions to control the tuberculosis epidemic.

Chapter 10 reviews cross-cutting issues in TB research. Chapter 11 identifies the role TDR can play in supporting TB research, including strengthening TB research capacity, particularly in high-burden countries. Major partner organizations allied with TDR in conducting TB research activities and applying research findings to TB control efforts are described briefly in chapter 12. Finally, chapter 13 summarizes existing research gaps, and delineates specific TB research priorities and recommendations for TDR.
2. Social, economic and behavioural research

Social science research and tuberculosis control

Social science research for TB control refers to the contributions of the basic and applied social sciences to addressing fundamental social, economic, and behavioural questions related to TB. Social science questions arise in nearly every area of TB research. They include issues as identifying the constraints on health-seeking behaviour (constraints in accessing diagnosis and care); gender differentials in the epidemiology of the disease, in case detection and treatment success; and adherence issues related to treatment response, including the impact of user fees and treatment adherence support strategies.

The central focus of social science research is on identifying the barriers to timely case detection, diagnosis and treatment in the context of poverty and social inequality, and enabling interventions that would reduce these constraints.

Since there is a proven intervention for tuberculosis that remains poorly implemented, social, economic and behavioural research to understand the context and why there is poor implementation lies at the heart of many unanswered questions. Both social science and health systems research are thus integral to what we refer to in this report as ‘implementation research’, which addresses the challenges to implementing proven interventions. Although the two disciplines of social sciences and health systems research overlap, they are separated in this report to emphasize the importance of each to TB control efforts.

This chapter highlights central themes in social science research on TB. Four key domains of social science research as it relates to TB are identified, and key research topics that are further explored in other chapters in this report are introduced.

Key domains in social research for TB control

Four key domains are identified within which social science research on tuberculosis operates:

- Determinants of risk and vulnerability to TB.
- Impact of poverty on tuberculosis.
- Effects of gender inequality on disease risk, disease severity and case detection.
- Impact of community factors on TB control efforts.

Each of these domains is explored briefly below. Within each domain, key research topics are identified through which related questions of epidemiology, access to care, diagnosis, treatment and implementation can be further addressed. It should be noted that the social science research topics identified here focus on research that can inform TB control efforts, including providing input into the development of new tools and the implementation of existing control programmes, rather than on descriptive studies cataloguing risk and vulnerability.

Specific social science research questions are delineated in the appropriate place in subsequent chapters, and are cross-referenced here for convenience.

Determinants of risk and vulnerability to TB

Vulnerability to disease and ill health results from several major overlapping factors, including socioeconomic, biological and environmental factors. The links between TB and social inequality are well established; additional research defining the determinants of risk for and vulnerability to TB will help identify specific challenges to implementation and access to care, diagnosis and successful treatment.
Key research topics

- How do malnutrition and other co-morbidities (such as malaria and HIV) contribute to susceptibility to TB, and what interventions effectively reduce risk? (chapter 3)
- How does difficulty in access to food affect access to care and case detection? (chapter 4)
- How can TB programmes reach out to hard-to-reach populations? (chapter 4)
- How can community-based social research enhance the identification of the most vulnerable subgroups and define strategies to enrol them in quality TB care? (chapter 4)
- Why are technologies and resources for TB diagnosis and treatment not available where they are needed most? (chapter 5)
- How does difficulty in access to food affect treatment outcomes? (chapter 7)
- How can DOTS be enhanced through social and economic support mechanisms for vulnerable groups? (chapter 9)
- What can be learnt from polio eradication campaigns about reaching out to remote populations? (chapter 9)

Impact of poverty on tuberculosis

While TB is not exclusively a disease of the poor, the association between poverty and TB is well established and widespread. Impoverished communities and social groups are at higher risk of infection with Mycobacterium tuberculosis (MTb) compared to the general population due to overcrowded living or working conditions, poor nutrition, co-infections (such as HIV/AIDS), and migration from or to higher risk communities.

In addition, patients suffering from TB are less able to work and to generate income for themselves and their dependents. These factors pose significant additional economic hardships on patients and households, with a disproportionate impact on the poor, further limiting their access to care.

Key research topics

- What kind of financing schemes can enhance patients’ access to TB diagnosis and treatment? (chapter 4)
- What type of social and economic incentives for patients and DOTS workers can improve case-finding and adherence to therapy? (chapters 4, 9)
- How can health providers outside the public health sector, including private practitioners and traditional healers, contribute to case detection and access to care? (chapter 4)
- How can health providers outside the public health sector, including private practitioners and traditional healers, contribute to clinical management? (chapter 7)
- How can TB programmes respond to poverty related inequities which constrain patients’ ability to seek health care, cope with illness and suffering, and adhere to therapy? (chapter 9)
- How can communities in resource-poor settings with weak social cohesion be enrolled in TB control? (chapter 9)

Effects of gender on disease risk, disease severity and case detection

Both women and men face gender-specific barriers to TB diagnosis and care. These barriers, which vary in different settings, require thorough assessment and evaluation to identify interventions to reduce them. For instance, poor women access health care services less frequently than poor men, and may face financial limitations in accessing care. On the other hand, fear of job loss tends to discourage working men from seeking care, resulting in delayed diagnosis and treatment. As a result, under-detection of TB
may mask true incidence of the disease in both women and men.

Poor women with TB also tend to suffer from fear of rejection by their family and community, and it has been shown that the stigma of TB is often more pronounced among women than men. While men usually worry more about loss of wages and capacity for work, women worry most about social rejection – from husbands, in-laws and the community in general – if they have TB.

In many countries, women have to overcome a number of barriers before they can access health care. Where they undertake multiple roles in reproduction, production and child care, they may have less time to reach diagnostic and curative services than men. Also, concerning health needs, women may be given less priority than men, and generally have less decision-making power over the use of household resources. They often have less knowledge of TB, especially of its signs and systems, than men; this is related to the higher rate of illiteracy among women than among men worldwide.

**Key research topics**

- How do malnutrition and other co-morbidities (such as malaria and HIV) relate to women’s and girls’ susceptibility to TB? (chapter 3)
- In populations where women need to access health care accompanied by a man, what interventions would improve health seeking for women? (chapter 4)
- How can provider delays for women, men, and children be reduced? (chapter 4)
- What are the gender-specific barriers to TB diagnosis and care in different settings and how can they be translated into appropriate gender-sensitive interventions? (chapter 5)

**Impact of community factors on health services and DOTS programmes**

Community-based interventions have long been linked to TB control efforts. Effectively treated and cured patients living within their home communities are often the best advocates for TB services and may become the drivers of social mobilization to support TB control. While many community-based programmes have been developed by private nongovernmental organizations (NGOs), community approaches – particularly for active case-finding and TB treatment support – have been increasingly incorporated into public sector programmes. Evaluations of the most effective strategies for scaling up TB treatment, including DOTS implementation, through community-based programmes are needed.

Community studies are also useful for revealing people’s perception of health services. Findings from social and behavioural research in the community can then be used to eliminate practices that may discourage the poor and other vulnerable groups from seeking diagnosis and treatment.

One particular concern is stigmatization within communities. Stigma towards TB exists to differing degrees in most countries, and may be particularly problematic among hard-to-reach populations. Staff attitudes and behaviour can reinforce stigma through their own practices and interactions with TB patients. It is not uncommon, for example, to see health professionals wearing surgical masks in the presence of TB patients. During health education sessions, stigma can be reinforced by emphasizing the importance of safe disposal of sputum at the expense of conveying the message that modern treatment rapidly renders a patient non-infectious.
Key research topics

- How do effective TB therapy and support systems contribute to diminish fear and stigma? (chapter 4)
- How can case finding and case holding be improved by social research on TB- and AIDS-related stigma? (chapter 4)
- If health care workers stigmatize patients and each other, how can the stigmatization be overcome? (chapter 4)
- How can networks of people living with HIV mobilize to contribute to TB education, screening, and adherence to TB and TB-HIV therapy? (chapters 4, 7, 9)
- How can the quality of health care services and DOTS programmes become more responsive to the needs of the community? (chapter 9)
- How can community-directed interventions and community-based insurance schemes be designed to improve TB care? (chapter 9)

Application of social, economic and behavioural research to priority research questions

Throughout the remainder of this report, the key domains of social science research will be incorporated into research questions on access to care, diagnosis, and clinical management of TB-infected patients, and into questions related to implementation of proven interventions.

Given that so much is already known about the relationship between social forces and TB infection, the Scientific Working Group recommended that the focus of such future research should be on evaluating, informing and designing interventions that can enhance TB control.
3. Epidemiology of tuberculosis

Macroepidemiology of tuberculosis

Comprehensive assessments of global TB burden published in 2005–2006 review recent data on case notification and case detection rates, as well as available information on the prevalence of latent TB infection via tuberculin surveys.\(^1,3\), \(^8,13,14\)

Global prevalence of latent TB infection is estimated at 32% of the world’s population, some 1.86 billion people. The total number of new cases is estimated at 8.8 million per year, including 3.9 million cases of infectious pulmonary disease; point-prevalence estimates are more than 16 million cases of active disease. Eighty per cent of all incident cases of TB are found in 22 countries and more than half of the cases occur in five populous South-East Asian countries. Eleven of the 15 countries with the highest per capita rates of smear-positive disease are located in Africa.\(^1\) The prevalence of TB/HIV co-infection worldwide is estimated at 0.18%; some 656 000 new TB cases were co-infected with HIV in 2003. An estimated 1.7 million people died of TB in 2004. The global case-fatality rate is 23%, but exceeds 50% in some African countries with high HIV burden.

Although these staggering numbers represent a consensus among TB experts, the uncertainty surrounding incidence and mortality estimates is quite large due to poor quality of the underlying data. Uncertainty analysis for the 22 highest burden countries suggests that global incidence and prevalence could be as much as 21% lower or 40% higher; there could be 23% fewer or 47% more deaths each year.\(^14\)

Each of the two main approaches to calculating TB incidence rates – case notifications and the ‘annual risk of infection’ method – present methodological and data quality issues.\(^14\) Case notification approaches are beset by detection and reporting deficiencies. Tuberculosis cases are often underreported; case detection and notification is significantly less than 100%. The proportion of patients underreported is likely to be partially offset by over-diagnosis and double reporting of individual cases. Information on smear-positive cases is more reliable; however, in countries with low DOTS coverage, rates must be estimated from data on health systems coverage, drug availability, and patient condition. To calculate incidence rates based on the annual risk of infection, epidemiologists have used a ratio of 1:50, since an increase of one percentage point in the annual risk has been associated with an increase in 49 smear-positive cases per 100 000 population. However, this method was established on the basis of only six studies on incidence, prevalence and mortality, and computer simulation models used to validate the rule have determined its applicability only in situations where greater than 5% of TB cases are co-infected with HIV.\(^14,15\) Thus there is some degree of imprecision in global TB estimates within large populations, and better evidence is needed. Nonetheless, there is a high degree of confidence in the estimated range of TB incidence and prevalence worldwide.

A phenomenon which has important control implications and which highlights the difficulties in interpreting available epidemiological information is the case detection gap. Globally estimated case-detection rates under the DOTS strategy lag well behind geographic DOTS strategy coverage. Linear extrapolation implies that, with 100% geographic coverage, only half of all new infectious cases would be detected under the DOTS strategy. A similar comparison of geographic coverage vs. case detection under the DOTS strategy per country reveals that full geographic DOTS strategy coverage is paralleled by achievement of the 70% case-detection target in only a few settings. The likely reason for the
Tuberculosis

low case-detection rate is that many infectious patients do not have access to health facilities where tuberculosis care (diagnosis and treatment) consistent with the DOTS strategy is available. Strategies that improve case-finding and access for hard-to-reach populations have the potential to positively impact on the current case detection gap. Research activities in this area are further discussed in chapter 4.

A number of questions remain in relation to the timing of diagnosis and its potential impact on TB transmission. At present, it remains unclear how early diagnosis of TB needs to be in order to prevent transmission in different patient populations such as people living with HIV/AIDS, infants, pregnant women. For comprehensive TB and HIV prevention, care and support, there is a compelling need for research on specific elements of the interaction between HIV infection and TB, including on the epidemiology of co-infection, the timing of development of TB after HIV infection, and the effect of co-morbidity on TB susceptibility.

Lastly, additional work is needed to define the role of several important cofactors (such as tobacco, alcohol and diabetes) in the dynamics of the TB epidemic.

Microepidemiology of tuberculosis

The prevalence of TB can vary widely between neighbouring villages and within different parts of the same village. Both genetic and environmental factors are likely to contribute to these microepidemiologic variations. Genetic factors, including immune response genes, should cluster in households, and may contribute to differences in the prevalence of TB within a village. Environmental factors however, including social factors, probably play a major role in explaining these microepidemiologic differences between villages.

In addition, there is a growing body of evidence on the role of mycobacterial factors in local TB disease epidemiology. Both molecular genotyping techniques developed during the past decade and conventional epidemiological methods have been used to study the transmission and pathogenesis of TB, which has allowed tracking of strains of MTb as they spread through communities. It is clear that in certain geographic areas a restricted set of MTb strains is causing a disproportionate number of cases of the disease. Molecular epidemiologic approaches have also enabled an assessment of the transmission of drug resistant strains.

This information has the potential to influence TB control and prevention strategies in the future. However, there are still limitations in these techniques and their results. In the near future, the use of molecular epidemiology, bacterial population genetics, comparative genomics, immunology, and other disciplines will further our understanding of tuberculosis transmission and pathogenesis, and contribute to the development of effective drugs and a vaccine against this important human pathogen.

The importance of local variations in patterns of health and disease are increasingly recognized, but available methods for characterizing disease clusters in time and space are limited. There is a need for new quantitative bio-informatic approaches to study MTb microepidemiology at the level of the individual host and small community.

Challenges and opportunities

Increasing the quality of surveillance data will provide a more accurate picture of the epidemic, and illuminate the global impact of TB control efforts. There is a clear need to improve case notification reliability; however, it is recognized that, given current diagnostic limitations, certain
active cases, notably of smear-negative disease, will remain difficult to identify even in ideal circumstances.

Accurate estimates of the TB burden in selected countries can be obtained from special surveys of the prevalence of disease and infection. Unfortunately, good surveys are scarce and there are not enough resources to obtain survey information on a global scale. In addition, survey information becomes hard to interpret when countries have high rates of HIV/TB co-infection or declining rates of TB incidence. It is clear, though, that assessment of the impact of novel public health strategies for controlling TB will require higher quality epidemiological data from population- or community-level intervention studies.

The corollary is that baseline active TB prevalence surveys are needed to determine the accuracy of culture-positive prevalence estimates and to test sampling systems for outcome surveys. Furthermore, measurement of the baseline prevalence of TB infection will provide additional information to study communities. Measurements through tuberculin skin testing, however, are cumbersome and time-consuming; novel diagnostic methods for use in TB prevalence surveys are highly desirable.

An additional and promising element in TB epidemiology would be the ability to disaggregate data from national TB programmes. Further implementation of computerized databases at the district level promises to provide TB notification data that allow a closer, more detailed look at relevant local and district level microepidemiology, including data on poor, vulnerable, and hard-to-reach populations, as well as on other relevant determinants of the TB epidemic (such as tobacco, alcohol and chronic diseases).

**Research priorities**

<table>
<thead>
<tr>
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<tr>
<td>How early does diagnosis need to be to have an impact on TB transmission?</td>
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<td>How soon after HIV infection does TB develop?</td>
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<tr>
<td>What is the role of other cofactors (tobacco, alcohol, diabetes) in the dynamics of the TB epidemic?</td>
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<th>Microepidemiology</th>
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<td>Development of systems to disaggregate national programme data for use in studying local and hard-to-reach subpopulations.</td>
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| How do malnutrition and other co-morbidities (such as malaria, HIV, diabetes, alcoholism) relate to women’s and girls’ susceptibility to TB? |
4. Case-finding and access to care

Globally in 2004, DOTS programmes reached only 53% of the estimated 4.4 million sputum smear-positive TB patients. In addition, DOTS treatment success rates remain well below target in some regions, notably in Africa and Eastern Europe. The poorer and more vulnerable patients comprise a substantial proportion of those not served, face the greatest barriers to diagnosis and treatment, and are considered likely to be among the drivers of ongoing TB transmission. The HIV epidemic has increased poor people’s vulnerability and accelerated the spread of TB among the poor.

What accounts for the low case detection and cure rates? One key factor is access to TB care. People infected with tuberculosis must take several steps in order to receive effective care (fig. 4). Each step can be associated with significant costs and other potential barriers. At each step there may be some combination of the following costs:

- Charges for health services (user fees).
- Transportation, accommodation and subsistence costs.
- Lost income, productivity and time.

Certain social groups, such as women, the unemployed and the homeless, experience longer delays in achieving cure than TB-infected people in less vulnerable groups. These groups. These groups include larger numbers of poor people, who can ill afford the costs imposed by delays in diagnosis and treatment. A proportion of patients, particularly those from poor and vulnerable groups, may drop out completely at any stage on the path to successful treatment.

Barriers to accessing care have cascading effects on TB control: the longer the delay in case detection, the more opportunities for transmission, the lower the treatment success rates, and the more costs the patient has to bear.

Challenges and opportunities

Case-finding in vulnerable populations

Since roughly half of all cases of active TB currently go undetected, there is a compelling need to pursue research aimed at improving case-finding, particularly among hard-to-reach populations and for smear-negative disease. These populations include:

- poor populations in remote rural areas

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Figure 4. Simplified Piot model for case finding and treatment in tuberculosis control

Step 1, motivation: Patients with symptoms related to TB contact a health care delivery point.
Step 2, selection: The health professional suspects TB and requests a sputum examination (smear).
Step 3, examination: The sputum test is correctly carried out on the patient selected.
Step 4, sensitivity: The smear is positive if the patient has bacilli in the sputum.
Step 5, prescription: The newly identified case of TB receives the correct treatment prescription.
Step 6, treatment: The TB patient obtains the prescribed treatment.
Step 7, regularity: The TB patient takes his/her treatment regularly, as prescribed.
Step 8, effectiveness: The patient is cured with a certain probability if treatment is taken as prescribed.
• urban slum dwellers and other urban poor, including street children and other homeless people
• populations in conflict areas
• HIV-positive populations
• orphaned children
• migrant populations, internally displaced populations, refugees, and asylum seekers
• workers in exploitative employment situations, such as miners, plantation workers, factory workers, and sex workers
• drug-users
• incarcerated people and those released from prison.

User fees
Provision of anti-TB drugs free of charge is embodied within the enhanced DOTS strategy. Many programmes also offer reimbursement to patients for smear microscopy. But even under these circumstances, where services are ostensibly free, charges are often incurred: some providers may advocate additional drugs in addition to the free anti-TB drugs, especially if motivated by cost-recovery schemes. Thus, even where consultation, diagnosis and treatment are officially provided free of charge, patients may face unofficial (‘under-the-table’) charges imposed by hard-pressed or unscrupulous health providers. The extent to which user fees – charges for consultation, diagnostic tests and drug treatment, whether set by governments or imposed by providers – present significant barriers to care should be clearly established, and research should focus on the different kinds of financing scheme that can support access to care (chapter 4).

Transportation costs and opportunity costs
Payments for transport to and from health facilities for patients and caregiver(s) for several visits make up a large proportion of costs before diagnosis is established, and are likely to be a significant barrier to care. If treatment requires frequent travel (e.g. for observation of treatment), then these transport costs may continue to accumulate after diagnosis, even if the distances travelled are not very great. The time lost in repeat visits to health providers is also a cost borne by the patient through reduced productivity, lost earnings, and neglected household responsibilities. The impact of these indirect costs, and the effectiveness of interventions designed to reduce indirect cost-related barriers to TB control, should be investigated.

Private sector TB care
Little is currently known about the incentives, attitudes, practices, quality and performance of treatment providers in the private sector. It is important to conduct research that addresses how the private sector is integrated into case-finding and access to care.
### Research priorities

#### Table 3. Research topics in access to care and case-finding

<table>
<thead>
<tr>
<th>Category</th>
<th>Research Questions</th>
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<tbody>
<tr>
<td><strong>Case-finding</strong></td>
<td>What factors lead to delays in establishing a diagnosis of tuberculosis? Where are the missing cases?</td>
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<td></td>
<td>Which factors contribute to the low global case detection rate (‘diagnostic gap’)?</td>
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<td></td>
<td>What is the role of active case-finding, especially in hard-to-reach populations and areas of high HIV prevalence?</td>
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<tr>
<td><strong>User fees</strong></td>
<td>How do user fees affect access to care, case detection, diagnosis and treatment?</td>
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<tr>
<td><strong>Community-based research</strong></td>
<td>How can community-based social research enhance identification of the most vulnerable subgroups and definition of strategies to enrol them in quality TB care?</td>
</tr>
<tr>
<td><strong>Transportation and other opportunity costs</strong></td>
<td>How significant are the barriers created by the indirect costs of care, such as transportation costs, and what are the most effective strategies to remove the barriers?</td>
</tr>
<tr>
<td><strong>Case-finding and access to care in the private sector</strong></td>
<td>What are the most effective, easy-to-leverage, private sector capacities to achieve TB control goals?</td>
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<tr>
<td><strong>Diagnostics in support of case-finding</strong></td>
<td>What are the implications of changing the current symptom-based and laboratory-based diagnostic algorithms for case-finding?</td>
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<td>What are the sensitivity and specificity of the various thresholds for chronic cough (e.g. 2 vs. 3 weeks) as screening tests for tuberculosis?</td>
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<td>How do malnutrition and other co-morbidities (such as malaria and HIV) relate to women’s and girls’ susceptibility to TB?</td>
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<td>Is there a gender differential in TB case-finding? What factors contribute to such differentials?</td>
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<td>How does difficulty in access to food affect access to care and case detection?</td>
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<tr>
<td><strong>Implementation research: health systems and operations</strong></td>
<td>Assemble available data on implementation and outcomes of case-finding and detection.</td>
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<td>Which financing schemes enhance patients’ access to TB diagnosis and treatment?</td>
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<td>Determine the impact of including culture in the case-detection strategy.</td>
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<td></td>
<td>Evaluate different models/strategies for case-finding especially in hard-to-reach populations.</td>
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<td></td>
<td>Evaluate different models/strategies to optimize configuration of laboratory systems for case detection.</td>
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<td>How can health providers outside the public health sector, including private practitioners and traditional healers, contribute to case detection?</td>
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5. Diagnosis of tuberculosis

Sputum smear microscopy

The microscopic evaluation of a sputum smear, first used in the diagnosis of TB in 1882, is still at the heart of TB diagnosis. Sputum smear microscopy alone, however, is inadequate for diagnosis of the majority of the 9 million cases of active TB annually. There are three reasons for this.

First, a significant percentage of active pulmonary TB cases have negative sputum smears (reflecting both the biology of TB and the technical limitations of the assay). Diagnosing sputum smear-negative cases requires slower, more complex and more expensive methods, including chest X-ray and mycobacterial culture.

Second, roughly one in three cases of active TB is extrapulmonary disease. In these cases, sputum smears are obviously of little use; diagnosis necessarily depends on biopsy, with pathologic examination and/or culture. The proportion of sputum-smear-negative pulmonary disease and extrapulmonary disease is substantially higher in HIV co-infected patients, exacerbating the problem with diagnosis in high-prevalence HIV settings.

Finally, even in the 4 million annual cases of diagnosable sputum-smear-positive pulmonary disease, sputum smear microscopy has proven to be surprisingly difficult to implement. The performance specifications of traditional sputum smear microscopy – low throughput, high technical skill – are suboptimal. Overall, sputum smear microscopy has a sensitivity of only 40% to 60% in high-burden countries, and even lower sensitivity in HIV co-infection. Figure 5 illustrates the distribution of TB cases by sputum smear category in 2004.

Other methods of diagnosis

Mycobacterial culture remains the gold standard for the definitive diagnosis of active disease. Few TB programmes in low-income settings, however, are able to support the use of existing culture methods at primary care level, and the delay of several weeks before interpretable results can be obtained limits the utility of culture as a diagnostic tool. Currently available serologic tests for TB lack sensitivity and specificity for active disease. Chest radiography, in addition to technical and cost concerns, can also be misleading, as diseases related to HIV (including Pneumocystis pneumonia, heart failure and bacterial pneumonia) may be misdiagnosed as TB. The use of responsiveness to an empiric trial of antimicrobials as a diagnostic decision point is fraught with concerns about antimicrobial resistance, partial treatment of TB (when fluoroquinolones are used), and delay in diagnosis. None of these diagnostic approaches can be used reliably to diagnose extrapulmonary and paediatric tuberculosis in a timely fashion.

Thus, particularly within the 22 high-burden countries that encompass 80% of the global TB burden, the absence of a simple and reliable diagnostic test for all active TB has created difficult choices for TB control programmes: the use of mycobacterial culture systems for diagnosis of active pulmonary disease; the use of chest radiography, biopsy and/or diagnostic algorithms focused on symptoms; or, worse, persistent under-diagnosis and misdiagnosis.

In addition to the need for better diagnosis of active pulmonary and extrapulmonary disease in adults, there is also a need for improved diagnostics in special populations. There is a particular need to improve paediatric TB diagnosis and to improve drug susceptibility testing for the diagnosis of multidrug-resistant TB (MDR-TB).
Given the limited advances in TB diagnostics for more than a century, the development of new diagnostics has become a central part of the TB research agenda in recent years. Many organizations have acknowledged the urgent need for improved TB diagnostics, and have advocated for additional research. Several promising TB diagnostic tests, that vary according to the level of health system where they could be introduced, are currently in development. Unfortunately, tests that would have the greatest impact on TB control – point-of-care tests – are only in early development. New diagnostics that increase the sensitivity or simplicity of diagnosing active disease are in later development. These diagnostics would only be implemented at district or central referral laboratories; nonetheless, they are expected to have a measurable impact on TB control. Rapid implementation of proven new technologies will also be critical to meet the urgent public health need and TB control targets.

Figure 5. Breakdown of TB cases by sputum smear category, 2004

(a) Smear-positive

Proportion of estimated new smear-positive (a) and new and relapse cases (b) notified under DOTS (dark grey portion of bars) and non-DOTS (light grey portion of bars), 2004. Figures indicate the number of cases, in thousands, represented by each portion of each bar.

AFR = African region
AMR = Americas region
EMR = Eastern Mediterranean region
EUR = European region
SEAR = South-East Asia region
WPR = Western Pacific region

(b) New and relapse

Figures indicate the number of cases, in thousands, represented by each portion of each bar.
Challenges and opportunities

New diagnostics for TB incidence and prevalence studies

Over the past years the quality of information on TB micro and macroepidemiology has increased substantially. There is, however, consensus on the need for more and better TB prevalence surveys. Tuberculin skin testing is still the method in use, despite its shortcomings. Novel diagnostic methods for use in TB epidemiological studies are highly desirable.

Optimization of existing tools

Sputum smear microscopy

• Existing tools should be optimized to diagnose specific categories of TB disease in specific settings. Despite the limitations of sputum smear microscopy, several areas of research could lead to better sensitivity and improved use in field conditions.  
  • Sample processing techniques to improve the diagnostic yield of standard sputum smears, including better methods of sputum collection, sputum transport, and sputum concentration, should be investigated.
  • The optimal use of fluorescence microscopy should be defined through implementation research studies.

Mycobacterial culture methods

To allow their adoption by TB programmes in low-income settings, existing culture methods need improving e.g. through producing timely results. Simplified or faster culture techniques are a priority for short-term improvement of TB diagnostics, before new tests that might replace point-of-care culture become available. Colorimetric solid media are among the promising strategies demanding evaluation.

Evaluation of existing diagnostic algorithms

Given the lack of a single, sensitive and simple test, the current approach to diagnosing active disease combines clinical assessment and laboratory tests in a complex algorithm (fig. 6).

Few studies have investigated the sensitivity, specificity and implementation of this algorithm, or of other algorithms used for paediatric diagnosis, extra-pulmonary disease, and MDR-TB.  

Development and evaluation of new diagnostics

The Foundation for Innovative New Diagnostics (FIND), a not-for-profit foundation established in 2003 with support from TDR, is the lead agency of the new TB Diagnostics working group of the Stop TB Partnership. FIND focuses on leveraging investment for new TB diagnostic tool development to ensure the implementation of affordable and high quality diagnostics in the public sector of high-burden countries. FIND shares a joint workplan with TDR and with the Stop TB Diagnostics working group, whose activities concentrate on supporting an enabling infrastructure for diagnostic development, evaluation and demonstration. Given the unique strengths and resources available to the two institutions, it will be important to delineate the specific responsibilities within TDR’s ongoing collaboration with FIND.

Diagnosis of TB in HIV co-infection

There are special challenges in the diagnosis of TB in MTb/HIV co-infected patients, in particular the need to develop new tools and algorithms to improve the diagnosis of smear-negative TB in adults and children.

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e. FIND Diagnostics (http://www.finddiagnostics.org/)
The danger signs include any one of: respiratory rate >30/minute, fever >39 °C, pulse rate >120/min and unable to walk unaided.

AFB – acid fast bacilli. AFB-positive is defined as at least one positive smear; AFB-negative as two or more negative smears.

CPT = Co-trimoxazole preventive therapy.

HIV assessment includes HIV clinical staging, determination of CD4 count if available and referral for HIV care.

CXR = chest X-ray. The investigations within the box should be done at the same time whenever possible in order to decrease the number of visits and speed up the diagnosis.

Antibiotics (except fluoroquinolones) to cover both typical and atypical bacteria should be considered.

PCP: Pneumocystis carinii pneumonia, also known as Pneumocystis jirovecii pneumonia.

Advising to return for reassessment if symptoms recur.

Figure 6. Algorithm for the diagnosis of tuberculosis in the ambulatory HIV-positive patient.
Other challenges include: identifying the optimal algorithm to exclude active TB in asymptomatic individuals with HIV infection; developing diagnostic tests for detecting latent TB infection in persons with HIV infection; evaluating the accuracy and utility of novel markers of disease activity (e.g. T-cell based interferon assays and cytokines) in individuals with HIV infection; determining the optimal approach for diagnosing HIV infection in patients presenting with active TB.

Diagnosis of paediatric TB infection
Children rarely have sputum smear-positive TB, and diagnosing TB in children is difficult. Studies are urgently needed to develop and validate adapted diagnostic algorithms in children. In addition, it is essential to evaluate the optimal models to integrate revised algorithms into the WHO Practical Approach to Lung Health, and Integrated Management of Adult and Adolescent Illness.

Diagnosis of MDR-TB
Delays in diagnosing MDR-TB result in increased morbidity, selection of drug resistant populations of bacteria, and continued transmission of MDR-TB. Improved resistance testing and surveillance is a fundamental element in tackling MDR-TB. New rapid and accurate tests for drug resistance are urgently needed. Further, there is a need to define the optimal diagnostic algorithm for persons with suspected MDR-TB. Accelerated efforts and streamlined evaluation are necessary.

Research capacity strengthening
In its support for research capacity strengthening, TDR should play a lead role in strengthening and improving microscopy, including quality assurance programmes of research laboratories. These efforts could then be leveraged to provide support for sputum smear microscopy in national TB programmes, and support for essential medical laboratory services in high-burden countries (see chapter 11).

Research priorities

Table 4. Research topics in diagnostics

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<th>Optimization of existing tools: smear microscopy</th>
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<tr>
<td>What is the value and role of sputum processing and concentration (e.g. through use of bleach, centrifugation, sedimentation and combinations) in improving the accuracy and yield of smear microscopy?</td>
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<tr>
<td>What is the role, feasibility, and applicability of fluorescence microscopy in routine field conditions? Is fluorescence microscopy more sensitive in HIV-infected populations compared to conventional microscopy?</td>
</tr>
<tr>
<td>What is the clinical and public health significance of a ‘scanty smear’, particularly in HIV-positive patients?</td>
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Continues...
| What is the optimal cut-off point for declaring a smear examination positive? Is one positive out of three smears adequate for initiating anti-TB treatment? |
| What is the impact of introducing the two-smear strategy in high-burden settings? |

### Optimization of existing tools: mycobacterial culture methods
| What is the optimal use of mycobacterial culture systems, including automated systems, in TB diagnosis in resource-limited settings? |

### Evaluation of diagnostic algorithms
| What is the existing evidence base for the current diagnostic algorithms for TB diagnosis? |
| What is the optimal diagnostic algorithm for establishing a diagnosis in smear-negative patients, including patients with HIV co-infection? |
| What is the optimal diagnostic algorithm for persons with suspected extra-pulmonary TB? |
| What is the role of therapeutic antimicrobial trials in the diagnostic algorithms for smear-negative tuberculosis? |
| What is the impact of widespread use of fluoroquinolones on the utility of therapeutic antimicrobial trials in the evaluation of smear-negative tuberculosis? |

### Development and evaluation of new diagnostics
| What are the specifications of new diagnostics that can be pursued to increase case detection at each level of the health system? |
| Develop a programme to independently evaluate new diagnostics in field trials, including nucleic acid amplification, antigen, and antibody detection methods. |

### Diagnosis of TB in HIV co-infection
| What is the optimum algorithm to exclude active TB in asymptomatic individuals with HIV infection? |
| What is the optimal diagnostic test for detecting latent TB infection in persons with HIV infection? What are the accuracy and utility of novel markers of disease activity (e.g. T-cell based interferon-gamma assays, cytokines, etc.) in individuals with HIV infection? |
| What is the optimal approach to diagnosing HIV infection in patients presenting with active TB? |

### Diagnosis of paediatric TB infection
| What is the optimal diagnostic algorithm for children with suspected tuberculosis? |

### Diagnosis of MDR-TB
| What is the optimal diagnostic algorithm for persons with suspected MDR-TB? |
| Evaluation of rapid tests for drug resistance. |
| What is the role of rapid rifampicin resistance tests in the management and control of MDR-TB? |

### Social science and implementation research: health systems and operations
| How can the uptake of proven new diagnostic tests be accelerated in both public and private settings? |
| What measures will be helpful in shortening the duration of TB work-up (diagnostic pathway) and the number of consultation visits before a diagnosis is made? |
| How can laboratory workload be reduced in high-burden countries? |
6. Drugs for tuberculosis (including immunomodulators)

In the past five years, a robust portfolio of new drugs has been identified, assembled and managed for accelerated delivery. These are the first drugs to be assessed in clinical trials for 40 years.

Several factors account for this new impetus in TB drug development. Scientific developments in genomics and proteomics – including sequencing of the *M. tuberculosis* genome in 1998 – have revealed new targets for TB drug therapy. In addition, new technologies and methods, such as high-throughput screening, rational drug design and combinatorial chemistry, have transformed the drug discovery process.

A milestone in TB drug development was the creation of the Global Alliance for TB Drug Development (TB Alliance) in 2001. The TB Alliance is a public-private partnership with the priority of developing new agents to shorten the duration of chemotherapy from the current 6–8 months to two months or less. Several pharmaceutical companies have also committed funds and launched new programmes to develop drugs for TB and other infectious diseases, and there is collaboration with the Stop TB Partnership’s Working Group for New Drug Development, which is composed of approximately 80 members and led by the TB Alliance. The Working Group’s recent strategic plan summarizes the global portfolio for TB drug development and includes all known projects as of September 2005 organized according to stage of development – discovery, pre-clinical or clinical.

A review of the current pipeline shows that there has been initial progress towards major goals, including shortened and simplified treatment regimens, improved treatment for MDR-TB, and improved management of TB/HIV co-infection.

New drugs under development have the potential to influence more than one area: the fluoroquinolones and the new diarylquinoline (R207910) under development hold promise for management of drug-sensitive TB and MDR-TB, and for safe co-administration with antiretroviral agents. Although the majority of projects in the pipeline are in the discovery stage, it is encouraging to note that six products are already under testing in humans, and five more are in pre-clinical development.

Challenges and opportunities

Beyond the development of new compounds, there are two major challenges in global TB drug research and development. The goal of TB treatment is a simpler, safer and/or shorter multidrug regimen. It is not the development of individual drugs. Therefore the primary challenge is to create a streamlined process for identifying the best possible combination regimen for clinical testing. A second major challenge is to identify new drug targets for persistent and latent *M. tuberculosis* infection.

An additional challenge pertains to the realm of implementation research: how can we ensure that new, effective regimens are approved, registered and reach those in need?

Creating a streamlined process for accurately identifying the best drug combinations for human testing requires a significant paradigm shift for TB drug development, in both pre-clinical and clinical evaluation. The optimal regimen for simplified treatment will likely involve replacing all the current first-line drugs, given that each has shortcomings: isoniazid is associated with a relatively high prevalence of resistance, is a

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6. Drugs for tuberculosis (including immunomodulators). Drugs for tuberculosis (including immunomodulators) have been identified, assembled, and managed for accelerated delivery. These are the first drugs to be assessed in clinical trials for 40 years.

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f. These include AstraZeneca’s Bangalore programme for TB drug discovery and development; GSK’s Diseases of the Developing World programme; the Novartis Institute for Tropical Diseases in Singapore; and initiatives from J&J/Tibotec, Otsuka, and Sequella Inc.
factor in hepatic toxicity in some patients, may decrease efficacy in combination with other first-line drugs, and likely does not contribute to treatment-shortening; ethambutol appears to add little in terms of potency to the current regimen; pyrazinamide is only effective in the first two months of treatment and has significant associated toxicity, especially arthralgias; and rifampin and rifapentine both have significant cytochrome P450 interactions that make them difficult to administer simultaneously with antiretroviral agents.

Current timelines for phase I, II and III testing dictate that identifying a new regimen containing four novel drugs substituted for present first-line drugs will require approximately 14 years to complete, or twice what it would have taken in 1964. This timeline results from the stringency of drug approval standards (which may be more stringent than is socially optimal) as well as from the current practice of adding or substituting one new drug at a time to the standard regimen. A new clinical testing paradigm that uses a novel combination regimen as the unit for evaluation could streamline this entire process, making it much shorter, particularly for serious diseases. Close consultation with regulatory authorities will be key to accomplishing such a paradigm shift.

Use of immunomodulators
Immunomodulators – including corticosteroids, therapeutic vaccines, and other drugs and biologics – have the potential to shorten TB treatment by modulating the host response and helping the immune system eliminate persistent organisms. Immunotherapy is a novel approach to treatment shortening. Strategies studied to date in mouse models have been found to reduce the T-helper 2 (Th2) inhibitory effect on the protective T-helper1 (Th1) response either by inhibiting interleukin-4 (IL-4) production or by down-regulating the Th2 response. In animal models, impressive treatment shortening times have been observed, and further testing in humans under appropriate study designs are warranted.

In addition to shortening treatment, immunomodulation might improve treatment outcomes using existing treatment protocols. The current understanding of severe TB is that the host inflammatory response induces pathology that contributes to mortality. The use of novel immunomodulators or adjunctive corticosteroids could down-regulate this response. Adjunctive corticosteroids are widely used and have been shown to be beneficial in selected severe forms of TB. The level of evidence is incomplete for other forms of TB, and limited for HIV co-infected patients. Additional studies are warranted.

Surrogate markers of disease
A major challenge to drug (and vaccine) development is the length of time required for assessment of efficacy due to dependence on long-term clinical outcomes. Immunological biomarkers of treatment success would provide useful surrogates in drug regimen trials (and vaccine studies), reducing the costs and decreasing the long development timeline. Particularly important are surrogate biomarkers that can reduce the two-year follow-up currently used to monitor relapse.

Research capacity strengthening
TDR was considered uniquely positioned to interface with national TB programmes (NTP), national AIDS control programmes (NACP), research groups and stakeholders to identify and fill gaps in the process of new drug development, with involvement and coordination of implementation research activities to facilitate country evaluation and adoption of new regimens.
Research capacity strengthening in drug development needs to be enhanced, in particular clinical capacity for registration of quality clinical trials and pharmacovigilance activities. The key role of TDR in strengthening research capacity for TB is further discussed in chapter 11.

**Research priorities**

**Table 5. Research topics in new drug development**

<table>
<thead>
<tr>
<th>Development and evaluation of new drugs and new combination regimens</th>
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<tr>
<td>Evaluation of the use of new combination regimens of novel TB drugs</td>
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<th>Use of immunomodulators</th>
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<tr>
<td>Evaluation of the use of novel immunomodulators and adjunctive corticosteroids in treatment-shortening strategies.</td>
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<td>Evaluation of the use of novel immunomodulators and adjunctive corticosteroids in limiting immunopathology in TB disease.</td>
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<tr>
<th>Surrogate markers of disease</th>
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<tr>
<td>Development and validation of surrogate endpoints and specific biomarkers that can be used to shorten clinical trials of novel drugs and treatment regimens.</td>
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<th>Natural products</th>
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<tr>
<td>Independent evaluation of natural products developed for use in TB treatment.</td>
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<tr>
<th>Social science and implementation research: health systems and operations</th>
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<tr>
<td>Studies to define attributable benefit of new regimens (effectiveness, cost-effectiveness).</td>
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<tr>
<td>Mathematical models, including simulation models, of resource needs, costs and impacts of new treatment regimens (to be used to inform clinical trial design).</td>
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7. Clinical management of tuberculosis

The principles of DOTS – directly observed therapy, short-course – 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 principles were adapted and promoted by WHO as DOTS, and adopted in programmes around the world.

By the early 1990s, when asked to describe the optimal approach to 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. Thus, the basic principles of the strategy were not new. The crucial innovation was the addition of the human element – health-care workers or volunteers forming a close bond with 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 with the modification of the commonly used DOT acronym to include another key element of the strategy – the short-course treatment regimen.

The Stop TB strategy has been evolving since its creation, and countries have adapted the strategy to suit their local circumstances. New strategies that address some of the major barriers for TB control are all built on the core foundations of DOTS.

An essential new element in current TB clinical management is the integration of HIV and TB care. The global HIV epidemic is fueling an unprecedented increase in TB cases, and in the number of patients co-infected with both diseases. Management of TB/HIV co-infected patients is often fragmented, with little coordination of care between TB and HIV treatment programmes in many areas at many levels. As referred to earlier, care is further hampered by limitations of current TB diagnostic methods, limited access to and underutilization of HIV counselling and testing services, drug interactions between first-line TB and HIV regimens, and a paucity of data regarding optimal regimens and optimal timing of initiation of antiretroviral therapy. Collaboration between TB and HIV programmes and integration of services is strongly advocated. Collaboration is, however, hindered by a history of independent structures and functions in established national TB programmes and newly established HIV programmes, by differential funding, and by, in many countries, inadequacies of the primary care and general health systems on which to build integrated care.

Challenges and opportunities

Current TDR research ‘streams’ already focus on two important elements in TB clinical management: treatment simplification and establishing the optimal time for treatment of HIV-TB co-infection. These streams are outlined below.

Treatment simplification

Poor compliance, especially among HIV-infected TB patients, is primarily due to an increased rate of adverse drug events, length of treatment, and pill burden for TB treatment. Within TDR, an important research stream explores the feasibility of shortening TB treatment from six to four months through the use of gatifloxacin, and in addition assesses the efficacy and safety of fixed-dose combinations of anti-TB medications versus ‘loose’ anti-TB medications in improving treatment compliance. The expected outcomes of
the work are not only to gather evidence on the efficacy and safety of gatifloxacin for shortening of TB treatment – thus reducing the pill burden, and improving compliance and TB treatment outcomes – but also to establish, through a blinded, randomized controlled trial, the efficacy and safety of the currently recommended four-fixed-dose combination therapy vs. ‘loose’ TB drugs in HIV negative and HIV-infected TB patients. In addition, through conducting this research, the work is building institutional and research capacity within national control programmes for TB clinical trials.

Patient support for standardized treatment
Adherence to therapy remains a central issue in determining the therapeutic effectiveness of tuberculosis treatment. There is a well-recognized need to evaluate ways to broaden DOT to include more effective strategies for providing adherence support. Examples include evaluation of:
• Patient ‘treatment-literacy’ preparation before initiation of therapy.
• Adherence support provided by health care workers and or community or family members.
• The most effective frequency and intensity of adherence support.
• Combinations of these interventions.
• The most effective method of supporting adherence in HIV-positive TB patients receiving antiretroviral treatment (ARV). Does the co-administration of TB and HIV therapies require different or expanded adherence support strategies compared to TB or HIV alone?

For these studies, outcome measures should include both standardized and validated measures of adherence and biologic and clinical measures for TB (sputum conversion, treatment completion, case-holding, relapse, resistance, etc), as well as adherence and biologic and clinical outcomes for HIV (adherence assessment through standardized measures, viral load, clinical disease progression, mortality).

Optimal treatment for TB/HIV co-infected patients
The frequent coexistence of TB and HIV, varying from 35%–70% in sub-Saharan Africa, implies the need to manage both diseases simultaneously. Managing TB alone in the absence of HIV treatment is associated with an increase in mortality during the treatment duration for TB. This research stream assesses the optimum timing for introduction of concomitant HIV and TB treatment in TB co-infected HIV patients. The research also determines the feasibility and effect of concomitant and early use of antiretroviral drugs and TB medications on TB treatment outcomes and survival and, through pharmacokinetic studies, establishes the impact of drug–drug interactions on plasma levels of highly active antiretroviral therapy (HAART) and anti-TB drugs. It is expected that the evidence from this study will inform the current guidelines for TB and HIV disease management. As the research is an integral part of control programme activities, it will also improve the delivery of both TB and HIV/AIDS prevention and care interventions.

Treatment needs of multiply-infected patients (across neglected diseases)
TDR is suitably positioned to address the specific research questions related to exposure to multiple diseases (notably, malaria/HIV/TB) and associated treatments. This was considered a high priority, leadership-filling role for TDR. Specifically considered was evaluation of pharmacokinetics, drug–drug interactions, safety/toxicity issues, and defining of optimal treatment regimens in multiply-infected patients.
Paediatric tuberculosis

An often neglected area of evaluation within TB research is paediatric tuberculosis. All elements that demand evaluation in the adult population also require attention in children.

There is a need to evaluate the efficacy/safety of drug formulations in use, and a need for information on: paediatric pharmacokinetics in different epidemiological contexts, co-trimoxazole treatment efficacy, incidence of side-effects, and how to manage complications in children.

Pharmacovigilance activities

TDR offers a powerful mechanism that can help both to conceptualize research strategies of relevance to disease control and to implement these strategies from an end-user perspective. Pharmacovigilance activities in disease-endemic countries fall into this special category in the transition phase between drug research/development and implementation. As a high priority, the SWG recommended that TDR take a leadership role in:

- Engaging the local TB and AIDS control programmes.
- Devising systems to generate, process and use pharmacovigilance data on both a local and global scale.
- Strengthening capacity to conduct pharmacovigilance studies, analyse, report and make decisions based on data.

Immune reconstitution inflammatory syndrome (IRIS) induced by antiretroviral treatment

This was identified as a priority research area by the WHO and Stop TB Partnership. Key areas are to develop a case definition, to identify an immunological signature, and to develop effective management strategies.
### Research priorities

**Table 6. Research topics in clinical management of tuberculosis**

<table>
<thead>
<tr>
<th>Treatment simplification</th>
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<tr>
<td>Evaluation of gatifloxacin in shortening TB treatment from six to four months.</td>
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<td>Assessment of the efficacy and safety of fixed-dose combinations of anti-TB medications</td>
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<td>versus 'loose' anti-TB medications in improving treatment compliance.</td>
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<td>Assessment of effectiveness of patient 'treatment literacy' programmes prior to treatment</td>
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<td>Evaluation of impact of DOT and other adherence support strategies (including site-based</td>
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<td>vs. community-based support, frequency and duration of support interventions) on treatment</td>
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<td>Evaluation of impact of DOT and other adherence support strategies on treatment outcomes</td>
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**Treatment of TB-HIV co-infection**

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<td>Evaluation of optimal treatment initiation (timing, dosing,</td>
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<td>specific drugs) for TB-HIV co-infected patients (including TB–</td>
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<td>HAART randomized trials).</td>
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<td>Evaluation of optimal duration of treatment using existing</td>
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<td>regimens for pulmonary and extrapulmonary TB in HIV-infected</td>
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<td>Pharmacokinetic and pharmacodynamic studies of treatment</td>
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<td>regimens in TB-HIV co-infected patients.</td>
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<td>Evaluation of optimal protocols for isoniazid preventive</td>
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<td>treatment in HIV-infected people with latent TB infection.</td>
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<td>Evaluation of optimal protocols for cotrimoxazole treatment in</td>
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<td>TB/HIV co-infection.</td>
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<td>Development and validation of case definitions for immune</td>
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<td>syndrome (IRIS) in TB/HIV co-infected patients under ARV</td>
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<td>Immunologic assessment of IRIS in TB/HIV co-infected patients</td>
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<td>Evaluation of clinical management strategies for IRIS in TB/HIV</td>
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<td>co-infected patients under ARV treatment.</td>
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**Treatment of multiply-infected patients**

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<td>Evaluation of safety and toxicity issues in defining optimal</td>
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<td>treatment regimens across neglected diseases.</td>
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<td>Pharmacokinetic and pharmacodynamic studies of treatment</td>
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**Treatment of paediatric tuberculosis**

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<td>Evaluation of safety and efficacy of current drug formulations</td>
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**Social science and implementation research: health systems and**

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<td>Studies to define effectiveness of HIV case-finding in TB</td>
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<td>programmes, including availability and uptake of HIV testing.</td>
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<td>Operations research studies (including mathematical and</td>
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<td>simulation models) of resource needs, delivery sites, care</td>
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<td>models, costs and impacts of TB/HIV programme integration.</td>
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<td>Assessment of training needs and training effectiveness for</td>
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<td>HIV and TB treatment providers.</td>
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<td>Development and validation of systems to generate, process and</td>
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<td>use pharmacovigilance data and impact on treatment outcomes.</td>
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Now entering its ninth decade of use, bacille Calmette-Guérin (BCG) remains the only available vaccine against tuberculosis. The use of BCG to prevent tuberculosis, however, is limited to the prevention of severe paediatric disease; its efficacy against adult disease wanes in high-burden regions where TB protection is most needed.

Nonetheless, with accelerating progress in deciphering the MTb genome and proteome, and new insights into the immunopathogenesis of tuberculosis infection, significant progress has been made in TB vaccine development over the past five years. At the time of this report in late 2005, there are promising indications of improvements in BCG efficacy; at least five vaccine candidates are in phase I clinical trials, and several more candidates are in pre-clinical development.44,45,46

Challenges remain. Many current vaccine candidates are based on modifications to BCG, yet our understanding of the immunobiology underlying BCG’s ineffectiveness remains incomplete. Indeed, our understanding of the distinction between protective immune responses and immunopathology, though improving, remains blurred. In vaccine evaluation, study design is impeded by the lack of known immune correlates of protection against TB infection. Thus dependence on immunologic endpoints for interpretation of vaccine efficacy is not reliable and difficult to interpret, whereas use of clinical endpoints delays assessment of vaccine efficacy and requires several years and/or tens of thousands of subjects. Collectively these gaps in our knowledge make the design of vaccine assessment strategies difficult. The need for both pre-exposure (‘prime’ strategies) and post-exposure (‘boost’ strategies) vaccination is widely accepted, but the specific timing and vaccine component design remains to be established.

Further research into the basic immunobiology of tuberculosis is therefore necessary to guide vaccine development, particularly in the context of the known discrepancies between immune responses in developed and developing countries. In developing countries, primed Th1 and Th2 responses evoked by environmental mycobacteria appear to interfere with vaccine immunity. Helminth infections can also trigger Th2 responses, particularly along the IL-4 pathway, which is known to be integral to TB pathogenesis. So, in developing countries with high helminth burdens, vaccine-mediated immunity may be further impaired. Elucidating the mechanisms underlying mycobacterial immunity remains central to vaccine development efforts.

One of the scientific challenges in vaccine research relates to the scientific uncertainty about protective immunity to TB and the current lack of experience with new TB vaccines in human populations. In spite of recent advances in our understanding of host responses to M. tuberculosis infection and TB disease, a lot of work remains to be done in determining the immune correlates of consistent protection against TB.

Challenges and opportunities

Immunopathogenesis of MTb infection

Competing hypotheses have been offered to explain the poor efficacy of BCG vaccine in high-burden countries.47,48 The interplay between exposure to environmental mycobacteria, to helminths, and the level of IL-4 appears to be central to TB immunopathology (figs. 7 and 8). These issues have significant implications for vaccine design, the selection of animal models, and the design of vaccine efficacy trials, particularly site selection.
Identification of immune correlates of protection for vaccine studies

*Protective immune responses to MTb and mycobacterial latency and dormancy leading to long-term survival and mycobacterial reactivation*

One third of the world’s population is latently infected with MTb, and in areas of low endemicity, many cases of active tuberculosis arise out of reactivation of latent bacilli. MTb can persist intracellularly in lung tissue without histological evidence of tuberculous lesions.⁴⁹

In most individuals with latent MTb, the infection is kept under control by the immune system and in only 10% of cases does it lead to disease. There is ample circumstantial evidence from observation of the natural history of tuberculosis in humans and experimental animals that *Mycobacterium tuberculosis* is capable of adapting to prolonged periods of dormancy in tissues, and that these dormant bacilli are responsible for latency of the disease itself. Furthermore, the dormant bacilli are resistant to killing by antmycobacterial agents. A systematic evaluation of the mechanism of dormancy, and of attempts to abrogate latency, will require better understanding of the physiologic events that attend the shift-down into dormancy.⁵⁰,⁵¹,⁵²,⁵³,⁵⁴ There are probably two or more stages in the shift-down of MTb from active replication to dormancy as bacilli in unagitated cultures settle, through a self-generated oxygen gradient, into a sediment where oxygen is severely limited. One step involves a shift from rapid to slow replication.⁵⁵ The other involves complete shutdown of replication, but not death. Presumably this last step includes completion of a round of DNA synthesis. The shift-up on resumption of aeration includes at least three discrete sequential steps, the production of RNA, the ensuing synchronized cell division and, finally, the initiation of a new round of DNA synthesis. Three markers of the process of shift-down of MTb to dormancy have been described, namely the change in tolerance to anaerobiosis, the production of a unique antigen, and the ten-fold increase in glycine-dehydrogenase production. Additional markers represented in the shift-up and shift-down processes may yet be discovered, and determination of their specific functions should provide insights into the mechanisms of dormancy and latency in tuberculosis, and into strategies for preventing reactivation of the bacilli and development of disease.

MTb is a successful pathogen that overcomes numerous challenges presented by the immune system of the host.⁵⁴ This bacterium usually establishes a chronic infection in the host where it may silently persist inside a granuloma until a failure in host defenses leads to manifestation of the disease. None of the conventional anti-tuberculosis drugs are able to target these persisting bacilli. Development of drugs against such persisting bacilli is a constant challenge since the physiology of the dormant bacteria is still not understood at the molecular level.⁵⁶,⁵⁷ Some evidence suggests that the in vivo environment encountered by the persisting bacteria is anoxic and nutritionally starved. Based on these assumptions, anaerobic and starved cultures are used as models to study the molecular basis of dormancy. Research into the study of mycobacterial latency and dormancy is crucial for designing new drugs, treatment for latency, and new TB vaccines.

**MTb latency and T-cell-based assays**

A major challenge in tuberculosis control is the diagnosis and treatment of latent tuberculosis infection. Until recently, there were no alternatives to the tuberculin skin test (TST) for diagnosing latent tuberculosis. However, an alternative has now emerged in the form of a new in vitro test, the interferon-gamma assay.⁵⁷,⁵⁸ A systematic review to assess the performance
of interferon-gamma assays in the immunodiagnosis of tuberculosis was performed by Pai et al.\textsuperscript{56} By searching databases and contacting experts and test manufacturers, they identified 75 relevant studies. The results suggest that interferon-gamma assays that use Mycobacterium tuberculosis-specific region of difference 1 (RD1) antigens (such as early secretory antigenic target 6 [ESAT-6] and culture filtrate protein 10 [CFP-10]) may have advantages over the TST in terms of higher specificity, better correlation with exposure to Mtb, and less cross-reactivity due to BCG vaccination and non-tuberculous mycobacterial infection. However, interferon-gamma assays that use RD1 antigens in isolation may maximize specificity at the cost of sensitivity. Assays that use cocktails of RD1 antigens seem to overcome this problem, and such assays have the highest accuracy. RD1-based interferon-gamma assays can potentially identify those with latent tuberculosis who are at high risk for developing active disease, but this requires confirmation. There is inadequate evidence on the value of interferon-gamma assays in the management of immunocompromised individuals, children, patients with extrapulmonary or non-tuberculous mycobacterial disease, and populations in countries where tuberculosis is endemic. Current evidence suggests that interferon-gamma assays based on cocktails of RD1 antigens have the potential to become useful diagnostic tools. Whether this potential can be realized in practice remains to be confirmed in well-designed, long-term studies.

**Geographical variation in immune responses and identification of immune correlates of protection for vaccine studies**

Known discrepancies have been identified in immune responses in developed and developing countries.\textsuperscript{47} In developing countries, primed Th1 and Th2 responses evoked by environmental mycobacteria appear to interfere with vaccine immunity.

**Figure 7. Potential value of immunomodulatory treatment**

Geographical distribution of tuberculosis patients in whom interleukin-4 (IL-4) production was massively increased (i.e. detectable by simple ELISA [enzyme-linked immunoabsorbent assay] or equivalent method [triangles], or required RT-PCR [reverse transcriptase polymerase chain reaction] or prestimulation and flow cytometry [circles]). The dashed lines are drawn at approximately 30° North and South of the equator.\textsuperscript{60}

In spite of recent advances in our understanding of host responses to Mtb infection and TB disease, a lot of work remains to be done in determining the immune correlates of consistent protection against TB.

Further research in immunology is needed to support the development of evaluation criteria for vaccines in phase II/IIb trials and to identify correlates of immunity for eventual use in phase III trials.

**Figure 8. Potential vaccine targets**

This theoretical scheme suggests that an effective vaccine for citizens in developing countries might need to block the IL-4 response rather than induce a Th1 response that is already present. To achieve this, vaccines will need to modulate the function of regulatory T cells that control response mechanisms (preferably through the oral route).
Development and evaluation of vaccine candidates

Five vaccine candidates are presently under evaluation (see table 7). A vaccinia virus-vectored subunit vaccine based on a secreted antigen (Ag85A) of *Mycobacterium tuberculosis*, developed at Oxford University, underwent phase I clinical evaluation in 2004. Encouraging safety and immunogenicity results have been reported, especially when used as a ‘booster’ dose, on top of BCG vaccination, even when the BCG had been given decades previously. Additional phase I safety and immunogenicity trials have now been completed in The Gambia. Phase II studies in latently infected subject are currently ongoing in The Gambia and South Africa. A fusion protein (Mtb72f) vaccine developed by Corixa in Seattle, Washington, and delivered with an adjuvant formulation developed by GlaxoSmithKline, has completed a phase I clinical trial in the United States, and a phase I/II trial in Europe.

Table 7. New vaccines in the clinical trial pathway

<table>
<thead>
<tr>
<th>Vaccine name</th>
<th>Notes</th>
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<tbody>
<tr>
<td>rBCG30</td>
<td>Live, recombinant BCG Tice, over-expressing Ag85B from <em>M. tuberculosis</em>, produced by Dr. M. Horwitz’s group at the University of California, Los Angeles (UCLA), US. Intended to stimulate a stronger, longer-lasting response than conventional BCG. Clinical phase I trials have been completed at St. Louis University.</td>
</tr>
<tr>
<td>Ag85A</td>
<td>A recombinant BCG vaccine over-expressing Ag85A and developed at UCLA has just completed phase I trials in the United States.</td>
</tr>
<tr>
<td>rBCG: D ureC-lle+</td>
<td>Live, recombinant BCG, a urease-deficient mutant which expresses the lysteriolysin O gene from <em>Listeria monocytogenes</em>. Produced by Prof. S.H.E. Kaufmann’s group at the Max Planck Institute of Infectious Biology, Berlin, Germany. Intended to promote ‘leakage’ of antigens from the phagosome to improve CD8 responses via cross-priming. Currently scheduled to enter clinical trials in 2006.</td>
</tr>
<tr>
<td>MVA-85A</td>
<td>Live, recombinant, replication deficient vaccinia virus, expressing Ag85A from <em>M. tuberculosis</em>. Produced by Prof. A.V.S. Hill’s group at Oxford University, UK. Can stimulate a strong primary immune response, but intended primarily as a booster vaccine for individuals previously vaccinated with BCG. Clinical phase I trials have been completed in the UK and the vaccine is currently in clinical trials in the Gambia.</td>
</tr>
<tr>
<td>Ag85B-ESAT6</td>
<td>Recombinant protein, composed of a fusion of ESAT-6 and Ag85B from <em>M. tuberculosis</em>. Produced by Dr. P Andersen’s group at the Statens Serum Institute, Copenhagen, Denmark. Delivered in the IC31 adjuvant, a mixture of oligodeoxynucleotides and polycationic amino acids (from Intercell, AG of Austria). Can stimulate a strong primary immune response, but intended primarily as a booster vaccine for individuals previously vaccinated with BCG. Currently in clinical phase I trials in Leiden, the Netherlands. In one trial, the vaccine is being tested in a conventional parenteral vaccination strategy using IC31 as adjuvant. In a second trial, the antigen is being tested by the nasal route, using LTK63, a modified, heat-labile enterotoxin from <em>E. coli</em> (from Chiron) as adjuvant.</td>
</tr>
<tr>
<td>Mtb72f</td>
<td>Recombinant protein, composed of a fusion of Rv1196 and Rv0125 from <em>M. tuberculosis</em>. Produced by GlaxoSmithKline (GSK). Delivered in an oil-in-water emulsion containing the immunostimulant 3-deacylated-monophosphoryl lipid A and a purified fraction of <em>Quillaria saponaria</em> (Quil A), also produced by GSK. Can stimulate a strong primary immune response, but intended primarily as a booster vaccine for individuals previously vaccinated with BCG. Clinical phase I trials have been completed in the US, and currently recruiting for phase II trials in Lausanne, Switzerland.</td>
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</tbody>
</table>
A phase II safety and immunogenicity study in healthy purified protein derivative (PPD)+/TB-infected adults started in 2005.

Evaluation of vaccine candidates will require transition through a series of clinical trials of increasing size, complexity and cost to progressively evaluate their safety, immunogenicity and eventual efficacy.

Despite considerable progress, there is a need to expand discovery and translational research on vaccines. As discussed earlier, many current vaccine candidates are based on modifications to BCG, yet our limited understanding of BCG’s ineffectiveness heralds potential for failure. The early success of current clinical candidates does not signal an end to discovery research, but rather provides novel opportunities to link fundamental research to human studies. It is likely that experience gained as the current candidates move through clinical trials will contribute to the development of new sets of candidates in an iterative process of refinement.

**Research capacity strengthening**

The conduct of vaccine trials requires the availability of local expertise as well as baseline information on immunity in the populations who will participate in the trials. These prerequisites include local epidemiological information, development of community interaction programmes, development of protocols that are in compliance with legal and ethical requirements, coordination with national regulatory authorities and programmes, local proficiency in immunological assays and optimized diagnostic procedures, and infrastructure for delivery of the vaccine under evaluation. These activities provide important opportunities and challenges for training and capacity strengthening.
9. Implementation research

Given the needs of TB control programmes worldwide, TDR and its partners have also increased their efforts in ‘implementation’ research – defined as the application of a number of different research methods (social sciences research, health systems research, outcomes research, operations research) to address questions of how TB disease control can best be implemented, and how treatment and other programme outcomes can be optimized. TDR’s focus on implementation research is aimed at ensuring that existing tools are applied to their maximum benefit, and that once new tools and new strategies are shown to be effective, they can be readily adopted by control programmes. Thus, the overall objective of this research is to significantly improve access to efficacious interventions against tropical diseases by developing practical solutions to common, critical problems in the implementation of these interventions.

TDR disseminated its conceptual framework for implementation research in 2003. The practical realities in many resource-limited settings, as well as in developed countries, mean that many proven interventions fail to reach the people who need them most. Although not often considered part of traditional research, the implementation of proven interventions is in fact a critical area for research relevant to disease control. This is especially true for tuberculosis, where proven treatments exist but reach only a fraction of people with active disease. Thus, implementation research stands at the opposite end of the research spectrum from discovery research, and closest to the problems facing public health programmes.

Implementation research makes use of a number of different research methods. In addition to social science research (see chapter 2), implementation research encompasses policy research, health systems research, and operational research. All of these disciplines can address questions of how TB disease control can best be implemented, and how treatment and other programme outcomes can be optimized.

Policy research

Research under this rubric includes research on access to health care, health-care economics, health status and conditions, health insurance coverage, and disparities in health services provided to different populations, and methodological studies on data collection for public health policy. Research examines these issues in local and national terms, and also develops small area estimation techniques to provide statistical estimations for local geographic or epidemiologic areas most relevant to communities and policy-makers.

Health systems research

Rapid progress towards TB disease control targets in developing countries is greatly hampered by weak, poorly functioning or in some cases non-existent health systems. It is critical to know how best to approach health system strengthening, and what specific actions are appropriate in different settings. There is some information about the barriers or constraints to ‘scaling up’ health services. However, very little is known about how best to relax these constraints. How can knowledge of health systems be significantly increased and effectively applied to improve the health of the worst-off of the world’s population?

Some important insights have been gained in studying health policy and systems research:

- Health systems research can significantly contribute to health policies and programmes.
- Lack of research can lead to undesirable results.
- Research can contribute most when issues are formulated through clear and verifiable hypotheses.
Health systems research can develop a rich body of knowledge to support evidence-based policy-making.

Funding for health systems research in developing countries is far too low to ensure impact – 0.02% of health expenditure.

Only 5% of information on health systems worldwide focuses on developing countries.

Priorities can be harmonized to advocate for increased impact and funding.

Getting research to policy and practice can be enhanced through affordable interventions.

Research capacity has to be strengthened.

Operational research

Operational (or operations) research involves the use of advanced analytic techniques to solve optimization problems under conditions of uncertainty and constraints. Classic operational research has only recently been applied to public health problems. Applied to TB control, the research questions can be condensed to: how can TB interventions – case-finding, diagnosis, and treatment – be optimized, given the resource constraints? Operations research for TB control can greatly assist efforts to bring effective interventions to a greater number of people. As new tools are developed, operational research methods can also be used to guide implementation of new drug regimens, clinical trial design, and vaccine trial design.

Challenges and opportunities

Implementation and operational research bring important challenges. First, close collaboration between researchers, national TB control programmes, ministries of health, and other partners is essential to this research. Bridges between groups that do not traditionally work together need to be built. In addition to the challenges and opportunities in the areas of case-finding, diagnostics and clinical management of tuberculosis described in earlier chapters, several issues in TB control are uniquely suited to implementation research approaches. Examples are given below.

TB/HIV treatment integration

The high morbidity and mortality among TB/HIV co-infected patients demands a renewed focus on research to identify practical diagnostic tools for co-infected patients, appropriate treatment strategies, and new models of collaboration and integration between TB and HIV programmes and services.

Crucial issues to be addressed include:

- Availability and uptake of HIV counselling and testing in TB patients.
- Diagnosis of TB and latent tuberculosis infection in HIV-infected patients.
- Testing and implementation of clinical and laboratory algorithms effectively including best strategies to ensure uptake.
- Definition of the optimal time to start ARV therapy in a patient with active TB.
- Sites and personnel for HIV and TB care delivery.

While clinical trials will provide some answers to these questions, mathematical modelling, operations research and other implementation research methods should provide important, ancillary approaches.

Research capacity strengthening

The SWG report of 2000 emphasized the need to develop implementation research capacity. The need for and value of such a focus is even more urgent and important at this time. Linking the findings of operational research studies and other implementation research programmes with national TB and HIV programmes is essential to focus the research on relevant questions and rapidly bring research findings to bear.
### Research priorities

#### Table 8. Implementation research topics

<table>
<thead>
<tr>
<th>Case-finding and access to care</th>
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<tbody>
<tr>
<td>Assemble available data on implementation and outcomes of case-finding and detection.</td>
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<tr>
<td>Which financing schemes enhance patients’ access to TB diagnosis and treatment?</td>
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<tr>
<td>Determine the impact of including culture in the case-detection strategy.</td>
</tr>
<tr>
<td>Evaluate different models/strategies for case-finding, especially in hard-to-reach populations.</td>
</tr>
<tr>
<td>Evaluate different models/strategies to optimize configuration of laboratory systems for case-detection.</td>
</tr>
<tr>
<td>How can health providers outside the public health sector, including private practitioners and traditional healers, contribute to case detection?</td>
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<tr>
<th>Diagnostics</th>
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<tr>
<td>How can the uptake of proven new diagnostic tests be accelerated in both public and private settings?</td>
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<tr>
<td>What measures will be helpful in shortening the duration of TB workup (diagnostic pathway) and the number of consultation visits before a diagnosis is made?</td>
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<tr>
<td>How can laboratory workload be reduced in high-burden countries?</td>
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<tr>
<th>New drug development</th>
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<tr>
<td>Studies to define attributable benefit of new regimens (effectiveness, cost-effectiveness).</td>
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<tr>
<td>Mathematical models, including simulation models, of resource needs, costs and impacts of new treatment regimens (to be used to inform clinical trial design).</td>
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<tr>
<th>Clinical management of tuberculosis</th>
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<tbody>
<tr>
<td>Studies to define effectiveness of HIV case-finding in TB programmes, including availability and uptake of HIV testing.</td>
</tr>
<tr>
<td>Operations research studies (including mathematical and simulation models) of resource needs, delivery sites, care models, costs and impacts of TB/HIV programme integration.</td>
</tr>
<tr>
<td>Assessment of training needs and training effectiveness for HIV and TB treatment providers.</td>
</tr>
<tr>
<td>Development and validation of systems to generate, process and use pharmacovigilance data, and impact on treatment outcomes.</td>
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10. Cross-cutting issues

Poverty

As previously mentioned, TB is not exclusively a disease of the poor but the association between poverty and TB is well established and widespread. TB infection is transmitted more readily in the environmental conditions of poverty: overcrowding, inadequate ventilation, and malnutrition. Furthermore, there has been growing recognition that TB itself diminishes the livelihoods of those affected and that TB control therefore is a potential poverty alleviation tool.\(^{62,63}\)

A growing body of evidence shows that better health contributes to greater economic security and growth.\(^{64}\) Within the poorest 20% of the world’s population, communicable diseases represent the greatest burden (and in adults, the three leading causes of the communicable diseases burden are tuberculosis, HIV and malaria). Among this group, communicable diseases are responsible for 59% of deaths and 64% of DALYs lost. Among the richest 20% of the globe, the figures are 8% and 11% respectively.\(^{65}\)

Furthermore, there is an interplay between poverty and barriers to accessing diagnosis and treatment which supports non-adherence to TB treatment with consequent impact and challenges to TB control activities. Improvements in socio-economic conditions should lead to reductions in tuberculosis incidence. They should also lead to improvements in access to care, rational use of care, and quality of care.

In response to increasing evidence of the need for action to address TB and poverty, the Network for Action on TB and Poverty, and the TB and Poverty Sub-Group of the DOTS Expansion Working Group, were recently established. In 2005, the Subgroup together with the Network for Action on TB and poverty and the WHO Stop–TB department published a normative document outlining options for national TB programme managers to choose from in addressing poverty issues in DOTS implementation under the activities of the Global Plan.\(^{12}\) Six practical steps have been outlined in this document (see box 1).

Paediatric TB infection

Probably as a result of the fact that HIV-related TB remains largely an adult infection and that child infection with either TB or HIV contributes little to the spread of either disease, there is a clear gap in research for the paediatric population. In addition, all issues identified as priority research items for adults are a research element for children.

There is a clear need for evidence of the efficacy/safety of drug formulations in use, a need for information on paediatric pharmacokinetics in different epidemiological contexts, and a need to focus on the special challenges of diagnosis of TB in children.

As highlighted in TB/HIV research priorities in resource limited settings,\(^{31}\) there are a number of definite issues within the paediatric population including:

- The role of co-trimoxazole treatment including efficacy, incidence of side-effects, and how to manage complications in children.
- The need for improved methods to detect active disease among infants and children and to determine effectiveness of isoniazid preventive treatment programmes.
- Validation of diagnostic algorithms in children.

In addition, a number of other issues have been identified in paediatric TB, e.g. downstream adoption issues, notably the need for better evaluation of currently available fixed-dose combinations. There is also a clear need for evaluation
Step 1. Establish the profile of poor and vulnerable groups using:
- Government (or other) data on the prevalence and distribution of poverty and social vulnerability, and poverty-reduction plans.
- Information on which types of health care provider are used by poor and vulnerable groups.
- Locally conducted surveys on the socioeconomic status of TB patients and poverty-related disparities.
- Information on any adaptations already made in DOTS delivery to serve poor and vulnerable groups.

Step 2. Assess the barriers to accessing TB services faced by the poor and vulnerable under the following headings:
- Economic barriers: Does the organization of TB services simplify the health care pathway? Are diagnostic and treatment services for TB well integrated into general primary care facilities? Does treatment observation require patients to make multiple visits? Which services require patients to pay?
- Geographic barriers: Identify areas where patients have to travel long distances over difficult terrain to reach TB services.
- Social and cultural barriers: Identify areas and population groups where TB services are underutilized.
- Health system barriers: Assess staff attitudes towards poor patients and investigate whether decentralization leads to strengthening of TB services at primary care level.

Step 3. Take action to overcome barriers to access, for example:
- Address economic barriers by integrating TB services within primary care provision; encourage pro-poor public-private mix for DOTS expansion (PPM DOTS); promote TB control in workplaces; improve the coverage of smear microscopy networks avoiding user-fees but providing free smear microscopy and other diagnostic services.
- Address geographical barriers by extending diagnostic and treatment services to remote regions, providing free transport to patients from such regions, and promoting community-based TB care.
- Address social and cultural barriers by engaging former TB patients and TB support groups to advocate for services and encourage community mobilization.
- Address health system barriers by engaging in health services decentralization to ensure capacity strengthening in less well served areas, and by establishing TB control as a district-level priority.

Step 4. Work with situations and population groups requiring special consideration:
- Refugee communities, asylum seekers, economic migrants and displaced populations.
- Pockets of deprivation in wealthier countries, ethnic minorities, homeless people.
- Injecting drug users.
- Prison populations.

Step 5. Harness resources for pro-poor TB services from:
- Available strategies to engage in broad initiatives to improve access to health services (such as the Global Fund for AIDS, TB and Malaria, poverty reduction strategies).
- Technologies to enhance efficiency and effectiveness of services.

Step 6. Assess the pro-poor performance of TB control and the impact of pro-poor measures by:
- Harnessing the human and other resources required for equity monitoring through alliances with partners (such as universities).
- Including socioeconomic variables in routine data collection and analysis, ensuring that TB-related questions are included in district health surveys and other household surveys.
- Ensuring socioeconomic questions are included in TB prevalence surveys.
- Conducting periodic studies of care-seeking, diagnostic delay, and use of DOTS in health facilities, with linked socioeconomic data.
- Conducting qualitative assessments among community members and TB patients to see who benefits from TB services (including linked services for HIV) and who does not.

Box 1. Addressing poverty in TB control: six practical steps
of treatment regimens in MDR and evaluation of management strategies for MDR contacts.

**Multidrug-resistant tuberculosis**

Along with HIV/AIDS, MDR-TB is considered the most important threat to TB control. Strategies to combat resistance focus both on preventing the development of resistance through application and strengthening of DOTS and on appropriate treatment of resistant cases through DOTS-Plus.

Three rounds of surveys coordinated by WHO and the International Union Against TB and Lung Disease (IUATLD) between 1996 and 2002 have yielded data on anti-TB drug resistance among new and previously treated cases. The third round of surveys included new data from 77 settings or countries collected between 1999 and 2002 and provided a balanced appraisal of the available epidemiological evidence.

From this information, it is clear that MDR remains a locally severe problem. Although drug-resistant tuberculosis is present in all settings surveyed, the prevalence of MDR is high only in some settings.

The prevalence of resistance to at least one anti-TB drug (any resistance) among new cases ranged from 0% in some Western European countries to 57.1% in Kazakhstan (median, 10.2%). Among previously treated cases, the median prevalence of resistance to at least one drug (any resistance) was 18.4%, with the highest prevalence, 82.1%, in Kazakhstan (262/319).

With this information, a three-pronged strategy has been proposed for MDR-TB: widespread implementation of short-course chemotherapy (SCC), improved resistance testing and surveillance, and the careful introduction of second-line drugs following proper evaluation of cost, effectiveness and feasibility.

The SWG identified a number of priority areas for TDR collaboration with the Stop-TB Partnership. Current research areas identified by the DOTS-Plus Working Group include:

- Quality assurance of drug susceptibility testing (DST) to second-line drugs; resistance criteria for second-line drugs.
- Transmissibility and fitness of MDR–TB strains; effect of the HIV epidemic on the MDR–TB epidemic.
- Management of MDR–TB.
- Economic evaluation of DOTS–Plus.
- Availability of second-line drugs.

Presently seven studies are ongoing and three are under evaluation.

The SWG recommended the engagement of TDR and Stop–TB in defining and refining TDR’s role in the development of an early warning system for drug resistance, identifying and evaluating optimal treatment regimens, and in assessing management strategies of MDR contacts and special populations (HIV-positive patients, pregnant women and children).

In light of its linkages with national TB programmes, TDR’s involvement could facilitate early interaction of drug developers with: NTPs, WHO–HQ, and regional and country offices to help ensure adoption of new drug regimens following proper evaluation.

**Regulatory issues for diagnostics, drugs and vaccines**

In the development and registration of new tools for the diagnosis, treatment and prevention of TB, early and close consultation with regulatory authorities will be key to timely registration. TDR may be specially positioned to facilitate
the interface with regulatory agencies and foster regulatory harmonization. In 2000, TDR initiated dialogue with national regulatory agencies (NRAs) in order to standardize guidelines for the registration of new chemical entities effective against TB and for the new four-drug fixed-dose combinations. A meeting of NRAs from developed and developing countries with industry representatives, other government agencies, and academic establishments was convened in September 2000 at which NRA representatives agreed to the proposed guidelines and to lobby for their formal adoption by their respective agencies. Regulatory uniformity and agreement to expedited registration by national agencies would help remove some of the current disincentives to TB drug development.

TDR could also take a leadership role in promoting pharmacovigilance activities in disease-endemic countries, engaging local TB and national AIDS control programmes to devise systems to generate, process and, most importantly, to use and follow up on pharmacovigilance data at both local and global scale. Furthermore, TDR could focus on strengthening capacity to conduct pharmacovigilance studies, analyse, report and make decisions based on this information.
11. Research support

Research capacity strengthening in high-burden countries

Given its involvement in the spectrum of TB research efforts from discovery to implementation, and given its relationship with national TB programmes, TDR is in a unique position with respect to strengthening capacity for TB research in high-burden countries.

Since its inception, TDR has had among its objectives the fostering of self-reliance in research in disease-endemic, resource-limited countries. TDR has approached this goal through developing a critical mass of expertise, strengthening institutional research capacity, and supporting an environment conducive to research, while responding directly to public health research and programmatic needs.

Research capacity strengthening (RCS) is a cross-cutting programme area of TDR, with a basket of activities according to the needs of each country. For the least developed countries, there is a focus on training of individuals and strengthening of institutions, and on provision of information. For more developed countries, the focus changes to partnerships. For advanced developing countries, there is an emphasis on utilizing the capacity already developed in these countries, especially of training and certification in good clinical practices (GCP) and good laboratory practices (GLP). TDR works on the principle that successful long-term outcomes require comprehensive capacity-strengthening programmes that provide continuing professional development, support, and an enabling environment, rather than scientific training alone. To date, TDR has supported over 1400 postgraduate students and 400 research groups and institutions in roughly 80 disease-endemic countries.

During 2003–2004, TDR–RCS activities became more fully integrated into the programme’s research activities through its RCS-Plus initiatives. Following this change, RCS programme activities have increasingly been driven by TDR’s research agenda, and are becoming more pertinent to the research needs of each country’s population. RCS-Plus grants are intended to support projects based on targeted R&D-driven capability strengthening initiatives. Initiatives address priority issues ranging from laboratory-based research, through field intervention research, to social, economic and behavioural research.

The Scientific Working Group emphasized the need for research capacity strengthening in applied immunology, drug development, pharmacovigilance and implementation research, including social sciences research, health systems research and operations research.

With an expanding number of new drugs, vaccines and diagnostics at different phases of development, enhancement of clinical trials capacity in TB high-burden countries and especially within TB programmes is paramount. In this effort, there should be continued emphasis on training in and use of Good Practices, aimed to promote better conduct of research and the production of reliable, credible and internationally acceptable data, particularly in resource-poor environments.

Mechanisms were suggested to increase and sustain the use of scientific and institutional capacity already developed by TDR and others, which by now represents a critical mass with a comparative advantage for undertaking cutting-edge research in tropical diseases. Clinical trial sites either receiving TDR institutional grants or involved in the TDR-sponsored clinical trials should be continuously evaluated and monitored for possible involvement in other clinical trials and research
and development activities. Sites that cross therapeutic areas should be identified and enhanced. It was recommended that a catalogue of available sites should be created, enabling communication of this information to drugs, vaccines and diagnostics developers, which would promote these sites and their continual use, allow more adequate resource allocation to them, and thereby increase the number of researchers doing GCP trials in disease endemic countries.

Furthermore, the working groups recommended RCS activities should strengthen capacity to conduct pharmacovigilance studies, and to analyse, report and make decisions based on data generated. Another bottleneck area for future RCS activities would be to support and strengthen the drug, vaccine and diagnostics regulatory systems in developing countries.

**Ethical issues in tuberculosis research**

A number of TDR activities in the recent past have fostered discussion around research ethics and helped to establish bioethics as an integral part of health research in resource-limited settings.

TDR helped to set up a global Strategic Initiative for Developing Capacity in Ethical Review (SIDCER) to ensure that appropriate and competent ethics committees are established in countries where research is carried out. Already under SIDCER, six regional forums and more than 15 national forums have been established.

Guidelines for ethics committees that review biomedical research were developed by TDR (in 2000) and widely distributed. Guidelines were later established on surveying and evaluating ethical review practices. Latterly, guidelines on data and safety monitoring boards have been developed through coordination with local government to ensure political endorsement.

TDR has a specific role in sustaining momentum to ensure protection of the rights, safety and well-being of human participants in health research.

**Linking research with national tuberculosis control programmes**

The early involvement of national TB control programmes is a critical element to facilitate adoption of new drugs, tools and vaccines. Interventions need to be country-programme owned and sustainable. For that to occur, research activities and priorities should involve early consultation and collaboration with country programmes. Linkages between these control programmes and academic institutions should facilitate institutional capacity strengthening and research capacity development to ensure quality of the expected output. These links will facilitate the ready availability of research findings to national programmes and ensure that critical knowledge drives policy and practice. TDR would be specially positioned to interface with national TB control programmes and support this approach to ensure that the research activities planned are well conducted and attract the requisite resources.

**TB strain and specimen banks**

The WHO/TDR TB Specimen Bank and TB Strain Bank are precious resources that facilitate test development and evaluation, and support proficiency testing in laboratories around the world.

An important obstacle to the development of new diagnostics tests for TB has been the lack of access to reference materials. The WHO/TDR TB Specimen Bank addresses this need by providing an invaluable, growing resource of well-characterized clinical materials for use by academic and commercial test developers.
The WHO/TDR TB Specimen Bank was formally launched by TDR in June 2000. It contains samples from symptomatic respiratory patients with and without TB, from different areas of the world. Aliquots of sputum, serum, saliva and urine are frozen on site, and maintained at a central distribution site at –70 °C.

The specimen bank is intended to: stimulate commercial activity, set high standards of quality for tools in development, assist in quality control, limit the need for field trials, facilitate the approval process, and simplify direct comparison of new and existing diagnostic kits.

Some of the specimens are now out of stock; new specimens began to be collected in mid 2005. There are current plans to replenish the WHO/TDR TB Specimen Bank and expand its geographic diversity. A number of new sites have been selected and will be collecting aliquots of serum, sputum and urine.

The WHO/TDR Strain Bank has been established and will become operational at the end of 2006. Eight laboratories around the world contributed 239 specimens. The Bank is based at the Institute of Tropical Medicine in Antwerp. Continued expansion and availability of strains from different geographic locations is critical to support quality control and proficiency testing in endemic countries, promote the development of novel technologies for drug susceptibility testing appropriate for use in disease endemic countries, and facilitate laboratory evaluation of new and existing DST technologies.
12. Major initiatives and partnerships

Stop TB Partnership

The Stop TB Partnership was established in 2000 to realize the goal of eliminating TB as a public health problem. It comprises a network of international organizations, countries, donors from the public and private sectors, governmental and nongovernmental organizations, and individuals who have expressed interest in working together to achieve this goal.

The Stop TB Initiative was established following the meeting of the First ad hoc Committee on the Tuberculosis Epidemic, held in London, March 1998. The Stop TB Initiative produced the Amsterdam Declaration to Stop TB in March 2000, which called for action from countries with the highest burdens of TB. In the same year, the World Health Assembly endorsed the establishment of a Global Partnership to Stop TB and two targets for 2005: to diagnose 70% of all people with infectious TB, and to cure 85% of those diagnosed.

The First Stop TB Partners’ Forum was held in Washington D.C., October 2001, where the Global Plan to Stop TB was launched as the overarching framework of the Stop TB Partnership’s combined actions. The Second Stop TB Partners’ Forum, held in New Delhi in March 2004, produced the New Delhi Pledge which reaffirmed ministerial commitments to meet the 2005 targets and to frame a second global plan for guiding Partnership efforts to achieve the Millennium Development Goal targets for TB by 2015.

The Partnership involves all organizations and individuals committed to short and long-term measures required to control and eventually eliminate TB as a global public health problem. Partners have coalesced into working groups to accelerate progress in seven specific areas: DOTS expansion, TB/HIV, DOTS-Plus for MDR-TB, new drugs, new vaccines, new diagnostics, and advocacy, communications and social mobilization. The Partnership secretariat is hosted by WHO and supports a wide range of advocacy and coordination activities worldwide in the fight against tuberculosis.

The Partnership targets are:

- By 2005: 70% of people with infectious TB will be diagnosed and 85% of them cured.
- By 2015: the global burden of TB disease (deaths and prevalence) will be reduced by 50% relative to 1990 levels.
- By 2050: the global incidence of TB disease will be less than 1 per million population (i.e. TB will be eliminated as a global public health problem).

Global Alliance for TB Drug Development

The Global Alliance for TB Drug Development (the TB Alliance) is a public-private partnership, not-for-profit venture, designed to ensure that promising anti-TB drug candidates move quickly through all stages of development, receive rapid and appropriate regulatory approval, and are swiftly transferred into effective and accessible clinical use.

The TB Alliance was established in 2001 with initial grants from the Bill and Melinda Gates Foundation and the Rockefeller Foundation in response to the lack of major R&D breakthroughs in TB over the past thirty years. Although the market for anti-TB drugs is forecasted to reach US$ 700 million by 2010, the concentration of TB in poor countries had deterred any single industry player from pursuing the full development of an anti-TB drug.

The Stop TB Partnership’s Working Group on TB Drug Development, led by the TB Alliance, coordinates worldwide TB R&D activities. The activities of the working group’s members span...
the spectrum from basic research to discovery, clinical development, and registration.

The TB Alliance has built a portfolio of promising drug candidates and forged groundbreaking partnerships for their development. For the first time in 40 years there is a pipeline of promising compounds that are meeting development milestones. This recent progress is the result of new collaborations between public and private sector partners that have leveraged the potential of industry, the public health sector, and academic laboratories, largely spearheaded by the TB Alliance.

**TB vaccine initiatives**

Aeras Global TB Vaccine Foundation was established in 1997 to help develop new concepts and tools to control the global TB epidemic. Since 2003, the organization has focused solely on developing new vaccines against TB and ensuring their availability. It is the goal of Aeras to develop, test, characterize, license, manufacture and distribute at least one new TB vaccine within ten years.

Under the scrutiny of independent vaccine development experts, Aeras takes promising research and early development candidates through preclinical regulatory requirements, clinical phase I, II and III studies, process development, manufacturing and release. The aim of all of these activities is to license affordable, effective TB vaccines that Aeras or one of its partners will make available through a variety of distribution channels to people in the developing world.

In February 2004, Aeras received a five-year US$ 82.9 million grant from the Bill & Melinda Gates Foundation for new TB vaccine development and recently received additional funding from the US Centres for Disease Control and Prevention and the Government of Denmark.

**Stop TB Partnership Working Group on Vaccines**

In response to the current global TB problem and the shortcomings of the existing BCG vaccine, the WHO/UNAIDS Initiative for Vaccine Research (IVR) has established a Global TB Vaccine Forum. Building on previous WHO efforts in defining a global research strategy for TB vaccine R&D and fostering partnerships among the different players in the public and private sectors, IVR will be active in the following areas:

- Defining together with partners a global vaccine research strategy.
- Facilitating and coordinating vaccine development efforts among academia, industry, and regulators on the one hand, and the public health community as representatives of the end-user communities on the other.
- Supporting vaccine development approaches that are neglected by industry.
- Through innovative types of partnership, adding value to industry efforts in order to speed up vaccine development and availability.
- Performing an enabling function for conduct of clinical trials in developing countries using adequate ethical standards.

**Stop TB Partnership Working Group on Diagnostics**

The Working Group on Diagnostics was created to implement research, advocacy and/or operational activities in pursuit of the development of TB diagnostic tools. It also aims to collaborate with other elements of the Partnership so as to create synergy and add value to actions taken in pursuit of the aims of the Partnership.

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g. www.who.int/vaccines/intermediate/tuberculosis.htm
**Foundation for Innovative New Diagnostics (FIND)**

Launched in May 2003, FIND is a non-profit entity designed to speed the development, evaluation, and appropriate use of new and improved, yet affordable, diagnostic technologies for patient care and disease control.

FIND co-invests in promising new technology platforms and manages a portfolio of promising test systems, collaborating with TDR to support the ongoing enabling activities formerly managed through the TB Diagnostics Initiative (TBDI), and otherwise encourages R&D in TB diagnostics around the world.

FIND aims to develop diagnostic approaches that have been proven in principle and transform them into effective products, in partnership with academia, public and private research institutes and industry. Listed among FIND’s objectives are the comparison and evaluation of these products in coordinated laboratory and field trials and demonstration of the impact of improved tools on disease control, in close collaboration with WHO, TDR, TB control programmes and NGOs.

**Consortium to Respond Effectively to the AIDS/TB Epidemic (CREATE)**

The CREATE initiative was developed to organize, implement and evaluate epidemiologic interventions to reduce TB incidence and mortality in populations and communities with high HIV prevalence.

CREATE is presently conducting a series of population or community-level intervention studies of novel public health strategies for controlling HIV-related TB in resource-poor settings. The initiative relies on trials and interventions designed to assess the impact of new strategies for TB control at the population level, and to measure the endpoints of TB incidence and mortality over time.

Other approaches include parallel cohort studies, smaller randomized trials, and analysis of temporal trends. Determining the relative contribution of each of the proposed strategies to reducing disease burden is an essential step in formulating responsible TB control policies for heavily affected areas.

There are presently three ongoing CREATE trials:
- **ZAMSTAR** – a Zambia and South Africa tuberculosis and AIDS reduction study – in Zambia and Western Cape Province, South Africa.
- **Effect of community-wide isoniazid preventive therapy on tuberculosis among gold miners in Gauteng, North West and Free State Provinces, South Africa.**
- **Impact of TB preventive therapy for HIV/TB co-infected patients with access to HAART in Brazil: a phased implementation trial in Rio de Janeiro.**

**Global Drug Facility**

The Global Drug Facility (GDF) is an innovative mechanism to expand access to and availability of existing high-quality TB drugs to facilitate global DOTS expansion.

Today, insecure financing and frequent shortages of TB drugs in many parts of the world have hampered DOTS expansion. While poor drug supply is not unique to TB control, its impact may be especially severe. Access to drugs is essential to TB prevention and cure: inadequate supply can contribute to the emergence of MDR-TB.

Established by Stop-TB, the GDF provides procurement and financing services for qualified applicants thereby allowing governments and
non-governmental organizations to improve the coverage and quality of global TB control through the acquisition of quality TB drugs. It is designed to meet short-term needs for TB drugs to support DOTS expansion and thereby give countries time to develop and strengthen local drug procurement capacity.

In its first year, the GDF spent US$ 7.8 million on drugs for 16 countries with limited resources recommended for support. The international competitive bidding initiated by the GDF reduced TB drug prices by roughly 30 per cent; US$ 10 can purchase a full course of treatment, including regimens using four-drug fixed-dose combination tablets.
13. Research gaps and research priorities for TDR

One of the most important issues in tuberculosis research is the increasing burden of disease posed by rising HIV rates and failing health systems in resource-poor settings unable to cope with the increasing burden of both diseases. In order to increase the application of research results in control programmes and health systems, TB research needs to be integrated with HIV research within both TB and HIV control programmes. Health systems issues are at the heart of improved TB and TB/HIV control; the increasing number of new TB cases directly attributable to HIV infection, leading to high rates of co-infection, and increasing smear-negative pulmonary and extrapulmonary disease, mean that sequential diagnosis and co-management of both diseases must become the foundation of both programmes, irrespective of the patient’s point of entry into care. Consequently, research collaboration between TB and HIV/AIDS programmes, and a research culture that promotes collaboration at policy level and an integration of activities at point-of-care facilities, will facilitate the applicability of developed interventions and guidelines, and increase the production of research results relevant to the control of both diseases. By embedding research within control, the specific needs of country programmes and the cultural sensitivities of target populations can be addressed. Identification of research resources should form part of programme planning, and major funding agencies should be encouraged to provide meaningful funding for TB research and to support collaboration between TB and HIV researchers and control programmes.

Over the past five years, given the importance of HIV in the epidemiology of TB, TDR’s TB research portfolio has increasingly widened in scope to integrate and incorporate TB/HIV research, embed it within the context of constrained health systems in high burden countries, and build capacity for research within these health systems. TDR was instrumental in the creation and launch of FIND (see above), which is actively developing new TB diagnostic methods to replace sputum smear microscopy. TDR has also initiated a project to evaluate the impact of fixed-dose combination drugs on treatment outcomes. In a related project, the optimal timing of HIV treatment in the context of HIV/TB co-infected patients under TB treatment is being investigated. Recently TDR and partners presented compelling data demonstrating the impact on sputum clearance of adding fluoroquinolones to four-drug fixed-dose combinations (4FDCs); sputum clearance was improved compared to standard short-course chemotherapy. TDR also continues to play an active role in enhancing TB research capacity in high burden countries. The SWG felt that, in light of the changing epidemiology of TB, the global public health demands for TB control, and the extensive experience and networking developed by TDR, the organization should begin to focus on critical gaps that are not being extensively addressed in a systematic fashion. The following were considered high priority for TDR.

Treatment

Evidence for strategies to optimize the clinical management of patients dually infected with TB and HIV is limited. The optimal timing of antiretroviral therapy during tuberculosis treatment remains controversial. The current WHO guidelines for scaling up antiretroviral access in resource-limited settings are based mainly on best practices and require more validation, especially in high burden countries, therefore the following research areas were considered high priority for TB treatment:

- Research on programme implementation. This is essential; the current shortfall in treatment success rates suggests that we do not know how to optimize treatment, especially treatment...
in TB/HIV co-infected patients in sub-Saharan Africa. The optimal treatment and timing of treatment to improve treatment outcomes with current drugs in co-infected TB/HIV patients needs to be assessed.

- Treatment adherence support strategies. These need to be assessed and optimized.
- Development of short, simple treatment regimens, especially for use in co-infected patients.
- Identification of TB drugs (new and old) that can be safely co-administered with antiretroviral drugs (ARVs) in patients with TB/HIV co-infection, and that do not adversely affect dose/efficacy/bioavailability of ARVs (or vice versa).
- Identification and development of drugs to boost natural protective immune mechanisms for better response to TB infection – assessment of the role of immunomodulatory drugs that down-regulate inhibitory responses, or boost Th1 response.
- Improvements in design of clinical trials and identification of direct and indirect (surrogate) endpoints of clinical benefit so as to reduce the time to assessment of efficacy of new drug entities.
- Pharmacovigilance. Improve understanding of the frequency of adverse events (AEs) and serious adverse events (SAEs) in different populations, and support TB and HIV programmes to monitor AEs and SAEs and use the information generated to better manage treatment of patients.

Diagnostics

The current shortfall in case detection success rates suggests that we do not know how to optimize case detection and identify MDR–TB soon enough. There are special challenges in the diagnosis of TB in Mt/B/HIV co-infected patients, in particular there is a need to develop new tools and algorithms to improve diagnosis of smear-negative TB in adults and children.

- How can case detection of TB especially in poor areas, and of MDR–TB generally but especially in high HIV prevalence areas, be improved?
- To what extent can we optimize existing diagnostic methods – sputum smear microscopy, culture, and drug sensitivity testing – to increase the identification of sputum smear-positive cases?
- TDR needs to develop methods for early identification of TB (and smear-negative TB), especially simple methods that can be used at points of care within TB control programmes. There needs to be greater involvement of TB control programmes in the development of diagnostic methods, so that new diagnostic methods are relevant to TB control at the point of care, including at the periphery.

Optimizing the regulatory process

Dialogue with regulatory authorities is necessary to promote mechanisms for fast track approval and to optimize methods for registration of combination therapy submitted as investigational new drug applications. TDR can strongly support and/or lead this process.

Health systems and services optimization

The delivery platform for new interventions is critical to the success of the interventions. In settings with high HIV/AIDS and tuberculosis, the health system is challenged by the delivery infrastructure and mechanisms. The strategic vision of the Stop–TB Partnership’s TB/HIV working group is ‘To build a collaboration between TB and HIV programmes and communities to reduce the global burden of HIV-related TB and achieve the global targets for 2015 ….’. Developing a feasible mechanism for HIV/AIDS and TB programmes to collaborate at policy level and integrate activities at point-of-care facilities is important, and underlies the success of joint
management of the two diseases. Models for implementation of joint programme functions are therefore needed and this should be undertaken in a complimentary fashion jointly with identified operational research priorities of the Stop–TB department.

Social science research and implementation research in support of TB control

It was recommended that social science research should focus on interventions that can be developed to improve outcomes rather than on describing the problems related to risk factors for poor TB case-finding, adherence and treatment outcome. The following to be considered:

• Development of interventions that reduce risk and vulnerability to TB among poor populations and groups within these populations that are especially at risk (women) for disease and increased disease severity and have lower probability of case detection.
• Development and testing of interventions that can improve community ability to identify the most vulnerable subgroups and define strategies to enrol them in quality TB care.
• Can similar interventions to those of polio eradication campaigns be enabled so as to reach out to remote populations?
• What kind of financing schemes can be developed to enhance patients’ access to TB case-finding, diagnosis and treatment, and enhance treatment adherence?
• Can interventions be designed for people living with HIV to mobilize them to contribute to TB education, screening, and adherence to TB and TB/HIV therapy?

Research capability strengthening

• Invest to strengthen research infrastructure and develop clinical trials capacity: catalogue the available sites, promote these sites, allocate adequate resources, and increase the number of researchers conducting Good Clinical Practice trials at the sites in disease endemic countries.
• Improve research collaboration between TB and HIV programmes. Currently there are separate structures and separate budgets. TB has strong support for adhering to DOTS, and wide community-based experience which can be used to support adherence to ARV treatment given subsequently to TB treatment.

References


39. Brower V. Fast tracking drugs to patients. Drug approval agencies are frequently criticised for either being too slow or too fast. EMBO Reports, 2002, 3(1):14–16.
50. Demissie A et al. Healthy individuals that control a latent infection with M. tuberculosis express high levels of Th-1 cytokines and the IL-4 antagonist IL-4 delta 2. Journal of Immunology, 2004, 172:6938–6943.


Annex 1

AGENDA: Scientific Working Group on Tuberculosis
### Day 1, Monday 3 October 2005

<table>
<thead>
<tr>
<th>Time</th>
<th>Item</th>
<th>Speaker</th>
</tr>
</thead>
<tbody>
<tr>
<td>09.00–09.30</td>
<td>Welcome address and overview of general TDR research strategy</td>
<td>Dr R. Ridley, Director, TDR – ADG/CDS (Communicable Diseases) – ADG/HTM (HIV/AIDS, TB, malaria)</td>
</tr>
<tr>
<td>09.30–09.40</td>
<td>Overview of planned activities for the SWG meeting: objectives and expected outcomes</td>
<td>Dr P. Onyebujoh</td>
</tr>
<tr>
<td>09.40–10.10</td>
<td>Global TB burden: challenges and opportunities for meeting MDG targets</td>
<td>Dr C. Dye, WHO Stop TB (STB) Department</td>
</tr>
<tr>
<td>10.10–10.55</td>
<td>The WHO-proposed Global Strategy to Stop TB and the Stop TB Partnership Global Plan to Stop TB, 2006–2015</td>
<td>Dr D. Maher, Stop TB Department and Stop TB Partnership</td>
</tr>
<tr>
<td>10.55–11.15</td>
<td>Coffee break</td>
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### ISSUES AND CHALLENGES FOR TB RESEARCH

<table>
<thead>
<tr>
<th>Time</th>
<th>Item</th>
<th>Speaker</th>
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</thead>
<tbody>
<tr>
<td>11.15–12.05</td>
<td>TB research: a global overview of what is needed</td>
<td>Dr P. Godfrey-Faussett (30 min. + 20 min. discussions)</td>
</tr>
<tr>
<td>12.05–12.45</td>
<td>TB/HIV and MDR–TB: issues and challenges for TB research</td>
<td>Dr F. Scano and Dr M. Zignol (20 min. + 10 min. discussions)</td>
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<tr>
<td>12.45–14.30</td>
<td>Lunch break</td>
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<tr>
<td>14.30–15.00</td>
<td>Diagnostic and treatment challenges for TB in high HIV settings</td>
<td>Dr M. Perkins and Dr R. O’Brian (20 min. + 10 min discussions)</td>
</tr>
<tr>
<td>15.00–15.30</td>
<td>Social science, gender and health systems: considerations for TB research</td>
<td>Dr A. Castro (20 min. + 10 min. discussions)</td>
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<tr>
<td>15.30–16.00</td>
<td>Coffee break</td>
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<tr>
<td>16.00–16.30</td>
<td>The immunopathology of TB: developing new interventions</td>
<td>Dr G.A.W. Rook (20 min. + 10 min. discussions)</td>
</tr>
<tr>
<td>16.30–17.00</td>
<td>TB vaccines: new insights and current research activities</td>
<td>Dr D. Young (20 min. + 20 min. discussions)</td>
</tr>
<tr>
<td>17.00–17.30</td>
<td>New drug development: current research priorities</td>
<td>Dr A. Ginsberg (20 min. + 10 min. discussions)</td>
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<tr>
<td>17.30–18.00</td>
<td>Chairman’s review and summation of Day I activities</td>
<td>SWG chair</td>
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<tr>
<td></td>
<td>Closure – 1st day</td>
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### Day 2, Tuesday 4 October 2005

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<tr>
<th>Time</th>
<th>Item</th>
<th>Speaker</th>
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<tbody>
<tr>
<td>09.00–09.20</td>
<td>Current TDR TB research streams and strategic direction</td>
<td>Dr P. Onyebujoh</td>
</tr>
<tr>
<td>09.20–09.40</td>
<td>Current STB/WHO research streams and strategic direction</td>
<td>Dr M. Uplekar, STB/WHO</td>
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<tr>
<td>09.40–10.00</td>
<td>Introduction to working groups: objectives and expected outcomes</td>
<td>Meeting rapporteur</td>
</tr>
<tr>
<td>10.00–10.30</td>
<td>Working Groups I, II, III, IV</td>
<td>Rooms to be assigned</td>
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<tr>
<td>10.30–11.00</td>
<td>Coffee break</td>
<td></td>
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<tr>
<td>11.00–11.30</td>
<td>Working groups: continued</td>
<td>Working groups</td>
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<tr>
<td>12.30–14.00</td>
<td>Lunch break</td>
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<tr>
<td>14.00–14.40</td>
<td>Working groups: continued</td>
<td>Working groups</td>
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<tr>
<td>14.40–15.20</td>
<td>Working groups: continued</td>
<td>Working groups</td>
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<tr>
<td>15.20–16.00</td>
<td>Coffee break</td>
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<tr>
<td>16.00–16.40</td>
<td>Working groups: continued</td>
<td>Working groups</td>
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<tr>
<td>16.40–17.20</td>
<td>Working groups: continued</td>
<td>Working groups</td>
</tr>
<tr>
<td>18.00–19.00</td>
<td>Video or audio conference call: M. Raviglione, STB/WHO coordinators, Working Group coordinators and TDR secretariat</td>
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<td></td>
<td>Closure 2nd day</td>
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### Day 3, Wednesday 5 October 2005

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<tr>
<th>Time</th>
<th>Item</th>
<th>Speaker</th>
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<tbody>
<tr>
<td>09.00–9.15</td>
<td>Objectives and outcomes for Day 3</td>
<td>SWG Chair/meeting rapporteur</td>
</tr>
<tr>
<td>9.15–12.30</td>
<td>Finalization of WG recommendations</td>
<td>Working groups</td>
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<tr>
<td>12.30–14.00</td>
<td><strong>Lunch break</strong></td>
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<tr>
<td>14.00–14.20</td>
<td>Plenary presentation of WG-I recommendations</td>
<td>Working group rapporteur</td>
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<tr>
<td>14.20–14.40</td>
<td>Plenary presentation of WG-II recommendations</td>
<td>Working group rapporteur</td>
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<tr>
<td>14.40–15.00</td>
<td>Plenary presentation of WG-III recommendations</td>
<td>Working group rapporteur</td>
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<tr>
<td>15.00–15.20</td>
<td>Plenary presentation of WG-IV recommendations</td>
<td>Working group rapporteur</td>
</tr>
<tr>
<td>15.20–16.00</td>
<td>General discussions and final comments</td>
<td>SWG Chair/meeting rapporteur</td>
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<tr>
<td>16.00</td>
<td><strong>Closure</strong></td>
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### Day 4, Thursday 6 October 2005

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<tr>
<th>Time</th>
<th>Item</th>
<th>Speaker</th>
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<tbody>
<tr>
<td>09.00–10.30</td>
<td>Finalization of SWG report</td>
<td>Chair, rapporteurs/consultant</td>
</tr>
<tr>
<td>10.30–11.00</td>
<td><strong>Coffee break</strong></td>
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<tr>
<td>11.00–12.30</td>
<td>Finalization of SWG report</td>
<td>Chair, rapporteurs/consultant</td>
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<tr>
<td>12.30–14.00</td>
<td><strong>Lunch break</strong></td>
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<tr>
<td>14.00–15.30</td>
<td>Finalization of SWG report</td>
<td>Chair, rapporteurs/consultant</td>
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<tr>
<td>15.30–16.00</td>
<td><strong>Coffee break</strong></td>
<td></td>
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<tr>
<td>16.00–17.30</td>
<td>Finalization of SWG report</td>
<td>Chair, rapporteurs/consultant</td>
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Annex 2

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Annex 3
WORKING PAPERS:
Scientific Working Group on Tuberculosis

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BURDEN OF LATENT TB INFECTION

Globally, one third of adults are infected with Mycobacterium tuberculosis (MTB), with the greatest burden of tuberculosis (TB) infection occurring in the World Health Organization South-East Asia (46%), Western Pacific (32%), African (31%) and Eastern Mediterranean (27%) regions. This contrasts with a much lower prevalence of TB infection in the Americas (15%) and Europe (14%). The highest burden of human immunodeficiency virus (HIV) and MTB co-infection occurs in Africa (2.7%) compared to South-East Asia (0.3%) and Europe (0%). However, in sub-Saharan Africa there is a wide range in the prevalence of TB and HIV infection, from Benin with a low prevalence of TB and HIV to South Africa and Swaziland with a high burden of TB and HIV and an estimated prevalence of TB infection of 42% and 57% respectively.

Infection with HIV is one of the most potent risk factors for TB. HIV not only increases the risk of reactivation of latent TB infection but also results in rapid progression to disease. Countries with a high prevalence of HIV also have high rates of TB, most notably in East and Southern Africa. TB rates in Africa are increasing at a rate of 6.4% per year, with 31% of TB cases in adults attributable to HIV. Apart from HIV, there are a number of other well described risk factors for TB, such as recent TB infection, silicosis, evidence of lung scarring not previously treated for TB, increasing age, intravenous drug and alcohol abuse, immunosuppressive therapy, and diseases such as lupus and uncontrolled diabetes. As HIV is the major risk factor contributing to the growing burden of TB globally, particularly in developing countries, the focus of this paper will be on the treatment of latent TB infection in HIV infected individuals living in resource-poor settings.

RISK OF TB IN HIV-INFECTED INDIVIDUALS

HIV infection leads to an increased risk of active TB, which may result from reactivation of latent infection or rapid progression to disease following recent infection. The increased susceptibility to TB is evident following HIV seroconversion and becomes more pronounced as the degree of immunosuppression increases.

HIV-infected individuals with evidence of latent TB infection (i.e. tuberculin skin test [TST] positive) have a significantly higher risk of TB compared to those who are TST negative. HIV-infected individuals with evidence of anergy have a risk of TB which is intermediate to that of TST negative and positive individuals. In communities with a high prevalence of TB, reactivation of latent TB and recently acquired infection would both be important causes of TB in HIV-infected individuals. In low prevalence communities however, most HIV-associated TB would be the result of recently acquired infection, commonly the result of nosocomial or institutional transmission. Nosocomial and institutional transmission of TB is even more likely to occur in high TB prevalence communities affected by the HIV epidemic but would be more difficult to identify due to the high background incidence of reactivation TB and recently acquired TB from the community.

Exogenous re-infection, with a different strain of TB, may occur in HIV-positive individuals who have successfully completed TB treatment but are re-exposed.

The presence of other risk factors may further increase the risk of TB among HIV-infected individuals. However, there is a paucity of data on what the additional risk of TB associated with these factors is. Among HIV-infected South African gold miners, the risk of TB and death significantly increases with increasing age and silicosis. The combined risk of HIV and alcohol and drug abuse is unknown. This has important implications for decision analysis when comparing the risk of TB and death to the risk of isoniazid-associated hepatitis and death, both of which are associated with older age and alcohol abuse.

TREATMENT OF LATENT TB INFECTION AMONG HIV-INFECTED ADULTS WITH NO PRIOR HISTORY OF TB

To date four meta-analyses have been published on the efficacy of treatment for latent TB infection (LTBI) to prevent a first episode of active TB among HIV-infected adults. The most recent of these included ten placebo-controlled trials involving 8130 participants in Haiti, Uganda, Kenya, Zambia, Spain, USA and one multinational study (USA, Brazil, Haiti). The results of long-term follow-up were subsequently reported for the Ugandan and Zambian trials.
Efficacy

The combined efficacy of all treatment regimens for LTBI, regardless of TST status, was a 36% (relative risk [RR] 0.64, 95% confidence interval [CI] 0.51–0.81) reduction in TB incidence, compared to placebo. Isoniazid (H) alone reduced TB incidence by 33% (RR 0.67, 95% CI 0.51–0.87). Multidrug regimens (rifampicin with isoniazid and or pyrazinamide) were as efficacious as isoniazid alone. No trials compared the effect of different drug dosages or treatment frequencies and durations. The greatest reduction in TB incidence (62%) was observed among TST positive individuals (RR 0.38, 95% CI 0.25–0.57). Although TB incidence was reduced among individuals who were TST negative (17%) or anergic (33%), the results were not significant.

Durability of preventive therapy

The durability of preventive therapy remains unclear. In the Zambian trial which included all TST positive and negative individuals, the risk of TB in the isoniazid preventive therapy (IPT) and rifampicin and pyrazinamide (RZ) arms increased over time but remained significantly lower compared to the placebo arm in the first two and a half years, but not following this; whereas the long-term follow-up of TST positive individuals in Uganda showed continued benefit of rifampicin containing regimens (isoniazid and rifampicin [HR] and RZ) but not IPT.

Mortality

Overall treatment of LTBI was not associated with a reduction in mortality (RR 0.95, 95% CI 0.85–1.06), although among TST positive individuals there was a non significant reduction (20%) in mortality (RR 0.8, 95% CI 0.63–1.02). Of note however, treatment of LTBI using isoniazid and rifampicin was associated with a significant reduction in mortality (31%, in two trials, RR 0.69, 95% CI 0.5–0.95). In an observational study in Brazil, TST positive HIV-infected adults receiving preventive therapy had a significantly longer survival. Modelling the benefits of preventive therapy in Uganda suggests that life expectancy will be extended by the three regimens evaluated (6H, 3HR, 2RZ).

Progression to AIDS

Two randomized controlled trials of IPT showed no overall effect of IPT on progression to AIDS. However, the Haitian study showed a lower risk of and time to AIDS in purified protein derivative (PPD)-positive individuals.

Safety

Isoniazid was more likely to be discontinued than placebo due to adverse effects (RR 1.66, 95% CI 1.09–2.51). Hepatotoxicity is a serious side effect that may result in death if isoniazid is not withdrawn soon after symptoms of hepatitis occur. The risk of hepatitis and death from hepatitis has been best described for HIV-uninfected individuals. There is a wide range in reported rates of hepatitis (0.1%–6.4%) and death (0–58 per 100 000). In a more recent study in which patients were monitored clinically and isoniazid discontinued once symptoms of hepatitis occurred, the rate of hepatitis was 0.1% and there were no deaths. The risk of hepatitis increases with age and earlier recommendations excluded individuals over the age of 35 years. However, the current international guidelines do not exclude individuals over the age of 35 years who are at high risk of developing TB (National Institute for Health and Clinical Excellence [NICE] guideline, draft, September 2005). The risk of hepatitis also increases with alcohol use although in most studies this in not clearly defined. The risk of hepatitis appears to be lower in blacks than in whites.

In the clinical trials and compared to isoniazid, rifampicin-containing regimens were more likely to be discontinued due to side effects. Increased rates of hepatotoxicity and death have been reported for rifampicin and pyrazinamide, which led to the Centers for Disease Control and Prevention (CDC) and the American Thoracic Society (ATS) withdrawing their recommendation for the use of rifampicin and pyrazinamide as preventive therapy. However, the risk appears to be limited to HIV-uninfected individuals.

Adherence

Only five of the clinical trials reported on adherence. Adherence to shorter regimens in comparison to six or twelve months of isoniazid was better in some trials and similar in others. Among a cohort of South-East Asian refugees and migrants, individuals taking a multiple drug regimen compared to isoniazid alone were more likely to be non adherent and to discontinue therapy.

Adherence to IPT in the ProTest pilot sites in South Africa, Zambia and Malawi was low, and ranged from 24%–59%. Adherence was better when TST was included in the workup but resulted in a greater proportion of patients dropping out before completing the screening process. Poor adherence was associated with lack of money for transport and food, perceived and real side effects of isoniazid, non disclosure of HIV status, and perception that isoniazid...
was not effective;\textsuperscript{35} whereas good adherence was associated with support from health service staff, clinic groups and family, easy access to health facilities, and acceptance of HIV status. Modified directly observed therapy has also been associated with higher rates of adherence.

**Cost effectiveness**

There is a paucity of cost-effectiveness data for TB preventive therapy for HIV-infected individuals in resource-poor settings. One of the first estimates of the cost of providing voluntary counselling and testing (VCT) and IPT in a resource-poor setting was from Uganda (1995) and was estimated at US$ 60.19 per person treated, which included the cost of HIV testing and counselling (US$ 18.54).\textsuperscript{36} Although IPT was estimated to reduce the risk of TB by up to 62\%, the lack of VCT centres, logistical difficulties, and the cost of implementing IPT were considered to be important factors that would preclude the routine use of IPT.

A Markov model was used to determine the cost effectiveness of TB preventive therapy regimens (6H [i.e. 6 months of isoniazid], 3RH [i.e. 3 months of rifampicin and isoniazid], 2RZ [i.e. 2 months of rifampicin and pyrazinamide]) among HIV-infected TST-positive Ugandans.\textsuperscript{37} When the costs of medical care, the social costs, and the costs of treating secondary infections were considered, all three regimens resulted in savings in medical care and social costs. The cost effectiveness of IPT was modelled for HIV-infected Zambians.\textsuperscript{38} The benefits of IPT outweighed the costs if preventing one case of TB prevented five other secondary cases of TB. The costs and benefits of IPT over a period of eight years were modelled for 100,000 HIV-infected South Africans.\textsuperscript{39} Without inclusion of indirect costs, IPT resulted in significant net savings through averting healthcare costs. The cost effectiveness of TB preventive therapy (12H, 6H, 3RH, 2RZ, 3RHZ) has also been modelled for HIV-infected individuals who were TST positive with a CD4 count of less than 200 cell/mm\textsuperscript{3} in a resource-rich setting (United States).\textsuperscript{39} TB incidence was reduced by 27\% and life expectancy increased between 6.2 and 8.7 months, resulting in savings of between one and seven healthcare dollars for every one dollar spent on preventive therapy for all regimens apart from the 3HRZ regimen.

The total and incremental cost of providing IPT as part of the ProTest pilot projects was low and thought to be cost effective despite poor uptake and adherence.\textsuperscript{40} A recent study among South African gold miners demonstrated the cost effectiveness of IPT in a routine clinic setting.\textsuperscript{41} A six-month course of IPT reduced TB incidence by 46\% (RR 0.54, 95\% CI 0.35–0.83) in HIV-infected individuals with no prior history of TB. Treatment was discontinued due to hypersensitivity in 0.5\% (9/1655) of individuals because of a possible adverse event, eight due to skin hypersensitivity and one due to mild hepatitis (0.06\%). TB screening included a symptom questionnaire, chest radiograph, and two sputum samples for microscopy and culture. Despite the intensive screening process used to exclude active TB, IPT was cost effective (US$ 353 per TB case averted compared to the average cost of US$ 1736 per TB case treated).\textsuperscript{42}

**Feasibility**

The provision of TB preventive therapy is complex and requires HIV testing and counselling, screening for active TB, tuberculin skin testing to identify those who would benefit most, procurement and distribution of drugs, adherence support measures, long-term follow-up, and recording and reporting. The experience of the ProTest pilot projects demonstrated that it is feasible to implement IPT within the context of a TB/HIV collaborative framework although the uptake of IPT is generally low. In Northern Thailand it was demonstrated that it is feasible to integrate IPT into routine healthcare; completion rates were better when IPT was offered as part of a comprehensive HIV/AIDS package of care and when IPT was offered through or in collaboration with the AIDS units. The feasibility and acceptability of integrating IPT into a workplace HIV prevention and care programme has also been demonstrated.\textsuperscript{43}

**Implementation of IPT programmes**

Despite proven feasibility and cost effectiveness in resource-poor settings, joint UNAIDS/WHO guidelines for IPT for people living with HIV/AIDS,\textsuperscript{44} and endorsement by the Interim Policy on Collaborative TB/HIV activities,\textsuperscript{45} few resource-poor countries with a high burden of HIV and TB have implemented IPT programmes. Furthermore, the implementation of IPT in countries that have a policy of providing IPT has been limited, apart from Botswana which has national coverage.

There are multiple factors that may contribute to the low level of implementation in these countries.

**Two diseases, one patient, one community, BUT two programmes**

IPT requires both the national TB and HIV programmes for implementation. The HIV programme is responsible for identifying eligible individuals
Antiretroviral therapy reduces TB incidence by 80% or more,\textsuperscript{53-56} with the greatest effect among those with the lowest CD4 counts.\textsuperscript{5} Despite this, the rate of occurrence of TB among individuals on ART in settings with high rates of TB remains unacceptably high (2-10% per year).\textsuperscript{53,55,57} There is a higher incidence of TB among individuals who have previously been treated for TB compared to those without a history of previous TB (11.3 vs. 3 per 100 person years).\textsuperscript{53} For ART to significantly reduce the proportion of HIV-associated TB, it would have to be initiated early and with sustained high levels of compliance.\textsuperscript{58} The benefit of adding IPT to ART for reducing the risk of TB is unknown. As there is no evidence that IPT is contraindicated with ART, the World Health Organization interim policy on collaborative TB/HIV activities recommends that ART should not preclude the use of IPT.\textsuperscript{45} This position is supported by some authors.\textsuperscript{59} There is early evidence from an observational cohort study that previous or concomitant IPT reduces mortality by half during early ART treatment.\textsuperscript{60}

Screening for TB: the role of chest radiography

Screening for active TB disease prior to commencing preventive therapy is required to minimize the risk of developing drug resistance by treating active TB with an inadequate treatment regimen. The place of a chest X-ray in the screening process remains unclear. The WHO policy statement on preventive therapy against TB for people living with HIV/AIDS recommends a TB symptom review in all patients and a chest X-ray.\textsuperscript{44} The availability and cost of chest X-rays are important considerations in resource-poor settings. The available evidence on which to base recommendations for chest X-ray screening prior to initiation of IPT in HIV-infected individuals is limited. In support of symptom screening alone, only one case of TB (0.2%) was diagnosed on the basis of the chest X-ray among 560 asymptomatic HIV-infected Batswanaans screened for TB. However, 23 individuals had an abnormal X-ray that was not thought to be indicative of TB so no mycobacterial cultures were made. Thus the prevalence of active TB and the usefulness of the chest X-ray may have been underestimated. Symptom screening alone was also found to be adequate to exclude TB among 129 HIV-infected patients in WHO stage 3 or 4 (of the classification scheme for degree of clinical deterioration of HIV) in Cape Town. In contrast, chest X-rays were
found to be of value when combined with symptom screening in Kenya and in South African miners. Lack of on-site X-ray facilities adds to the costs and is a barrier to starting preventive therapy.

Drug resistance
Theoretically, if active TB is missed and the bacterial load is large enough, treatment with monotherapy or an inadequate regimen may generate drug resistance. The impact of widespread uptake of preventive therapy on the generation of drug resistance is unknown. Extensive use of preventive therapy in a low TB prevalence setting such as the US has not led to drug resistance. Botswana was considered to have a strong TB programme despite the more than four-fold increase in TB and is the only resource-poor country to implement a nationwide IPT programme. Drug surveillance from 1995 to 2002 showed an increase in overall drug resistance among new TB cases. Although the prevalence of isoniazid resistance with or without other drug resistance increased, isoniazid monoresistance did not increase. Continued surveillance will be important to determine the impact of the national IPT programme on isoniazid resistance.

The effectiveness of isoniazid preventive therapy in settings with high rates of drug-resistant TB is unknown. Although individuals known to be infected with isoniazid-resistant TB could be treated with rifampicin alone or rifampicin and pyrazinamide, this is not recommended in resource-poor settings.41

Children
There are clear guidelines for preventive therapy in infants and children under the age of 5 years who are exposed to adults with smear-positive pulmonary TB.61 These recommendations are based largely on studies in the pre-HIV era. HIV-infected children who are TST positive would also benefit from preventive therapy.

Pregnancy
HIV-infected pregnant women in resource-poor settings have high rates of undiagnosed active TB and would benefit from TB preventive therapy. The benefits are thought to outweigh the risk of isoniazid-associated hepatotoxicity and death during pregnancy and the post partum period. Current guidelines from the US Centers for Disease Control and Prevention (CDC) and The American College of Obstetricians and Gynecologists recommend that IPT be delayed until a few months after delivery.

TB control
In industrialized countries, TB control strategies have included evaluation of contacts of TB cases and treatment of latent TB infection among high-risk individuals. Widespread use of targeted IPT may have contributed to the decline in TB incidence in the US and other developed countries. The impact of the nationwide targeted IPT programme in Botswana on TB control is unknown.

Community-wide IPT was first investigated in a household randomized trial in the Bethel district of Alaska. A 69% reduction in TB incidence was seen among individuals receiving IPT. Following these results, all residents in the Bethel district were offered IPT, which, in conjunction with an ongoing TB control programme of passive case-finding and treatment, resulted in a sustained reduction in TB incidence. This study, when replicated in Greenland, had a modest effect only, largely due to the low dose of isoniazid used.

THE KNOWLEDGE GAP
Additional information is required to fill gaps in our knowledge in order to optimize TB preventive therapy programmes. The knowledge gaps are divided into two areas. Firstly those areas requiring further research to optimize existing practices, and secondly, new areas of research required to extend current practice.

Optimization of current practice

Uptake of IPT
The factors associated with poor uptake of IPT need to be identified at all levels (governmental, community, individual). What additional cost-effectiveness data are required to persuade policy-makers to allocate scarce resources to preventive therapy? What additional training for healthcare staff is required to support an IPT programme? Will community education and mobilization improve the uptake of IPT and decrease the associated stigma?

Drug regimen and duration
What is the optimal preventive therapy drug regimen? The optimal regimen should be safe, cost effective, short, intermittent, compatible with ART, durable and have a high threshold for generating resistance. Drug regimens currently under study include:

- Life-long isoniazid (3 years)
- Isoniazid and rifapentine weekly for 12 weeks
- Rifampicin and isoniazid twice weekly for 12 weeks
• Ethambutol and isoniazid for 24 weeks.

Will preventive therapy pulsed every few years be as effective, and cheaper and logistically easier, than life-long IPT in settings with high rates of TB transmission? Will drugs such as moxifloxacin, gatifloxacin and the new TB drugs in development have a role to play in TB preventive therapy?

**Safety**

There are limited data on the comparative risks of TB and isoniazid-related hepatotoxicity and death, which increase with age and alcohol use in resource-poor settings. If the uptake of IPT increases markedly, one would expect to see more cases of isoniazid-related hepatotoxicity. In order to better inform policy and practice, research is required to quantify the risks of hepatotoxicity in individuals over the age of 35 years who drink alcohol at least daily.

**Screening for TB**

What is the optimum method for excluding active TB prior to starting IPT? What is the value of adding chest X-ray and/or sputum examination (microscopy and culture) to symptom screening? What other methods could be used at the point of care to exclude TB?

**Diagnosis of infection**

What is the role of the new cytokine (gamma interferon) assays in determining infection, predicting risk of TB, and monitoring response to treatment?

**HIV/TB collaboration**

What is the most cost-effective model of collaboration between the HIV and TB programmes (separate, overlapping, fully integrated) that includes preventive therapy in the minimum package of care for people living with HIV/AIDS? What can be done to reduce the cultural differences (human rights vs. public health) between the HIV and TB programmes? How can we ensure that the IPT programme does not divert scarce human resources away from the national TB control programme? What additional healthcare training is needed to improve delivery of IPT?

**Cost effectiveness**

Additional cost-effectiveness data are required to persuade policy-makers to invest in preventive therapy programmes.

**Adherence**

Operational research is required to identify individual and health service factors associated with poor adherence, and to evaluate adherence enhancing measures.

**Drug resistance**

The Botswana experience will provide valuable insight into what impact widespread uptake of IPT will have on drug resistance.

**Extension of current practice**

**Antiretroviral therapy**

What is the additional benefit of IPT given concomitantly with ART to reducing the risk of TB and death? Will concomitant IPT and ART adversely affect or improve adherence to both? Will concomitant IPT adversely affect HIV treatment outcomes? What is the combined toxicity of IPT and ART (increased risk of hepatitis with nevirapine, of peripheral neuropathology with D4T, of neuropsychiatric disorders with efavirenz)? Should IPT be given concomitantly for six months, indefinitely, or stopped once the CD4 count rises above 350 or 500 cells/mm$^3$. Should IPT also be given to individuals who have previously been treated for TB?

**Secondary preventive therapy**

What is the cost effectiveness and feasibility of secondary TB preventive therapy among individuals who do not require ART and those who do? What is the optimum regimen and duration of secondary preventive therapy?

**Role of IPT in pregnancy**

What are the risks and benefits of IPT in HIV-infected pregnant women at high risk of developing TB?

**Role of IPT in HIV-infected children**

Is it cost effective and feasible to offer IPT to HIV-infected children over the age of five years who are TST positive? How will children be integrated into collaborative HIV/TB programme activities?

**TB control**

What is the role of widespread targeted and community-wide IPT in contributing to TB control in settings with a high prevalence of HIV and a high burden of TB? The Consortium to Respond Effectively to the AIDS/TB Epidemic (CREATE) is currently evaluating these strategies.

**RESEARCH PRIORITIES**

The World Health Organization hosted a meeting in early 2005 to establish TB/HIV research priorities in...
resource-limited settings. The following individual and population level research priorities were set for TB preventive therapy:

**Individual level**
- What is the optimum algorithm to exclude TB disease?
- What is the added benefit of IPT for people receiving ART?
- Should IPT be rationalized by targeting individuals with advanced HIV disease?
- Determination of the effectiveness among infants and children.

**Population level**
- Identification of macro-economic barriers to implementing IPT.
- What lessons were learnt from Botswana’s national IPT programme?
- What is the effectiveness of IPT in regions with elevated isoniazid resistance?

**References**
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WORKING PAPER 2.  
TUBERCULOSIS AND HIV: OPERATIONAL CHALLENGES FACING COLLABORATION AND INTEGRATION

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SUMMARY

The global HIV epidemic is fuelling an extraordinary increase in tuberculosis (TB) cases, and in the number of patients co-infected with both diseases. The management of TB/HIV co-infected patients is often fragmented, with limited coordination of care between TB and HIV treatment programmes in many areas and at many levels. Care is further hampered by limitations of current TB diagnostic methods, limited access to and underutilization of HIV counselling and testing services, and a paucity of data regarding optimal regimens and timing of initiation of antiretroviral therapy. Collaboration between TB and HIV programmes and integration of services has been advocated, but has been hindered by a history of independent structures and functions of established national TB programmes and newly established HIV programmes, and by the inadequacies of primary care and general health care services in many countries. The substantial morbidity and mortality among TB/HIV co-infected patients necessitates a renewed focus on operational research to identify practical diagnostic tools and treatment strategies, in addition to new models of collaboration and integration between TB and HIV programmes and services.

INTRODUCTION

Tuberculosis and human immunodeficiency virus (HIV) disease have been closely entwined since the early years of the HIV/AIDS epidemic. The two conditions interact synergistically in their epidemiologic characteristics and clinical manifestations and are clothed in stigma. Both conditions carry the broader risk of creating social, economic and political instability. The overwhelming share of the human toll of disease due to both TB and HIV is borne by resource-limited countries. In sub-Saharan Africa, HIV is fuelling the TB epidemic, with the incidence rate of TB increasing from 146 per 100 000 in 1990 to 345 per 100 000 in 2003. TB is now one of the leading causes of morbidity and mortality among persons with HIV disease and, in some countries, the percentage of patients with active TB who are co-infected with HIV has reached 60%. Even with appropriate management of TB, patients with HIV co-infection can have higher mortality, which may be due to concomitant conditions rather than lack of effectiveness of TB therapy.

The increased number of TB/HIV co-infected patients in Africa, where the co-epidemic has the greatest impact, as well as in other resource-limited areas has intensified the need to find solutions to diagnostic, therapeutic and management issues at the interface of both diseases. Knowledge and experience in the diagnosis and management of TB and HIV as separate diseases is extensive. In contrast, knowledge and experience in the diagnosis and management of co-existing HIV and TB is quite limited. While creating additional challenges, this nonetheless offers the prospect of enhancing the management of both diseases through collaborative and integrative efforts.

From a public health perspective, national TB control programmes (NTPs) and national AIDS control programmes (NACPs) need to develop mechanisms of collaboration which will promote interventions for disease control at a population level. The TB/HIV Working Group of the Stop TB Partnership has developed interim recommendations and policies. Several demonstration projects have been carried out to assess the feasibility of such collaborative and integrative efforts in urban and rural areas, and some programmes have begun to adopt the public health oriented strategies of TB care in newly developed HIV treatment programmes.

At the same time, health care delivery sites, especially primary health care centres, need to be able to provide appropriate care for the TB/HIV co-infected patient through integration of their often separated TB and HIV services. In some settings this has already occurred, such as when the same primary health care provider is responsible for TB and HIV services. In many others, the delivery of HIV diagnosis, care and treatment has remained separate from services for TB. However, successful integration of TB and HIV services will not reliably enable the primary health care system to provide satisfactory care.
Strengthening of the primary health care system beyond the TB and HIV services is also needed to allow for prompt recognition of HIV and TB related signs and symptoms with proper referral as appropriate for further diagnosis and management when and where necessary. Without general strengthening, efforts to control this co-epidemic are not likely to succeed.

Arguably, some of the greatest challenges in achieving effective programmatic collaboration and service integration are in the identification of practical approaches to diagnostic and therapeutic issues in the TB/HIV co-infected patient, with the goal of reducing morbidity, mortality and incidence of both active TB and HIV disease. To meet these challenges, interventions must be designed and then tested to determine their clinical and/or public health impact. Traditional clinical research strategies, such as randomized clinical trials, are a necessary part of the process of identifying answers to many questions. However, such strategies can be protracted and their results can have limited generalizability. The judicious and timely use of operational research (defined herein as the application of analytic techniques to available and modelled data to quantify or predict the impact of interventions on individual clinical outcomes, the benefits of interventions at a population level, and the ratio of benefit to cost for various interventions) is also needed to reach practical solutions to unanswered questions. An example of this is the mathematical modelling of different interventions and their impact on TB incidence which has been described, but more needs to be done with currently available data and data from new studies.

In this communication, we illustrate several of the treatment, diagnosis and management issues relevant to TB/HIV co-infection. Additionally, we describe the questions which need to be answered in order to achieve optimal patient outcomes through better collaboration between TB and HIV programmes and greater integration of TB and HIV services at the service delivery site with the net effect of promoting a decrease in the burden of disease created by the co-epidemic. Throughout, we recognize the need for flexibility since solutions may vary by setting depending upon prevalence of HIV and TB disease, local resources, history and current practice.

**DIAGNOSIS OF HIV IN PATIENTS WITH ACTIVE TB**

The availability and offering of HIV counselling and testing to patients with TB is an essential starting point for effective management of both conditions. However, it is not clear how best to provide this service. Barriers to delivering this exist at both the national and service delivery levels including programmatic, provider-based and patient-related barriers.

National programmatic barriers include the emphasis on stand-alone HIV voluntary counselling and testing (VCT) sites by some health ministries and a reluctance to provide access to HIV counselling and testing through other sites. Although access to HIV counselling and testing is increasing, with the establishment of HIV counselling and testing services in health care settings, its continued general lack has delayed or blocked TB patients’ access to HIV treatment. As access to HIV counselling and testing slowly expands, TB treatment sites face site-level programmatic barriers to providing this service to their patients including lack of space to provide confidential counselling and testing in most TB treatment sites and poor communication between TB treatment sites and off-site HIV counselling and testing services.

Provider-related barriers include the lack of appreciation of the importance of HIV status on their patients’ outcomes, lack of skills in the management of HIV disease, and a reluctance to discuss HIV, another stigmatizing disease, with their patients. TB providers who do not already provide HIV services need to be educated about the relationship between TB and HIV and involved in the delivery of these services through a multi-disciplinary team approach to care. On the other hand, barriers among patients with TB include the fear that, if HIV infected, they would face further discrimination and, until recently, in the absence of treatment for HIV disease, their perception of no benefit of knowing their status. As access to HIV care and treatment becomes more widely available in countries where HIV and TB prevalence is high, it is critical to address programmatic, provider and patient barriers to HIV testing in order for co-infected patients to benefit from the scale-up of HIV programmes. Box 1 highlights some of the unresolved challenges in the collaboration and integration of TB and HIV programmes and services.

Introducing HIV counselling and testing for TB patients in settings where antiretroviral therapy (ART) is available has been shown to be feasible with a high uptake of testing by TB patients, but other strategies to promote uptake of testing among TB patients need to be evaluated, especially in settings where ART is not yet available. Determining what measures will ensure the highest acceptability
and uptake of HIV counselling and testing by TB patients is a vital area of study. How to best implement HIV counselling and testing effectively on a wide scale at TB clinics remains unclear. For example, should TB programmes integrate HIV counselling and testing as a component of the services they provide, as has been advocated, or should patients be referred elsewhere for this service? Referring patients elsewhere can result in low uptake of testing, but in some settings, especially those without adequate counselling space or staff, this, along with increasing communication between TB and HIV service providers, may be the only feasible option. Operational research efforts that assess strategies to implement universally available HIV counselling and testing for all TB patients are needed.

If HIV counselling and testing is to be performed at TB treatment sites, should TB providers themselves be trained to provide counselling and testing to their patients or should national TB programmes or VCT sites provide specific counsellors for this particular service to take place at TB treatment sites? There may not be one answer to this question, with the best method varying depending on the volume of patients a site cares for and the number of TB and other staff available.

HIV counselling and testing through an ‘opt out’ as opposed to an ‘opt in’ strategy has been advocated in TB treatment sites. In ‘opt-in’ testing, patients are offered counselling and testing and must actively provide consent. In contrast, counselling and testing is part of routine care in ‘opt-out’ testing, and patients are informed of the right to refuse the test. A study of counselling and testing in antenatal clinics has demonstrated that an ‘opt-out’ strategy tests a greater percentage of patients. Despite this, some national TB/HIV coordinating bodies are not utilizing the ‘opt out’ approach, fearing possible infringement of individual human rights. In this case, the ‘opt in’ strategy may be the only choice and methods to maximize uptake of testing using this strategy need to be studied. Studies to assess HIV knowledge and attitudes among TB providers and patients, and the impact of different attitudes on utilization of these services, are also needed.

The components of care which follow a positive HIV test in a TB patient and how they are best delivered will need to be studied using operational research, including: when and by whom HIV clinical staging is best done, where the collection and measurement of CD4+ T-cell counts and HIV viral loads (if available) are completed, who begins the administration of cotrimoxazole preventive therapy and how is it continued after completion of TB treatment, and what mechanisms for referral into HIV care and treatment work best in which settings to minimize loss to follow-up. Outcomes research will be necessary to determine which of the possible service delivery methods of these components are associated with the greatest reductions in morbidity and mortality. This should be accompanied by cost-effectiveness research of the various programmatic components to determine if the components are within the resource capacity of the local health care delivery site and national programmes.

**DIAGNOSIS OF TB AND LATENT TB INFECTION IN HIV-INFECTED PATIENTS**

HIV co-infection complicates clinical presentations and diagnosis of active TB and limits the performance of the acid fast bacilli sputum smear, the most widely available TB diagnostic method in resource-limited settings. As a consequence of the high rates of sputum smear negativity, diagnosis of TB may be missed or delayed by health care providers at HIV treatment sites. This increases the risk of morbidity and mortality for individual patients as well as the risk of transmission of TB to other patients, staff, household and community members. Sputum culture, while useful in patients with smear negative disease is not routinely used in resource-limited settings due to cost constraints. In addition to the increased complexity of diagnosing active TB, HIV-infected individuals who have latent TB infection (LTBI) also have a higher risk of reactivation than HIV-uninfected individuals with LTBI due to the reduced sensitivity of the tuberculin skin test (TST), especially in those with lower CD4 T-cell counts, resulting in missed opportunities for providing preventive therapy.

Once diagnosed with active TB or LTBI, the difficulties do not end for the health care provider. To ensure treatment for the HIV-infected patient with newly diagnosed TB, a mechanism of referral to the TB treatment site must be in place with a strong communication system and contingencies for finding those patients lost to follow-up. Establishing methods to prevent loss to follow-up is essential and will vary depending on many factors including local geography and community structure. Similarly, treating the HIV-infected patient found to have LTBI will require programmatic support for the implementation of a new service requiring 6–9 months of therapy with isoniazid. Whether isoniazid preventive therapy (IPT) is best administered by the HIV care and treatment site or the TB treatment site is an open question and may vary depending on individual capabilities and resources. The timely answers
Generally speaking, current methods for diagnosis of TB and LTBI in patients with HIV disease are suboptimal and there is great need for new rapid, effective and affordable diagnostic methods. That said, there are major discrepancies between the technologies used in well-resourced as opposed to resource-limited settings; the former having access to culture and nucleic-acid amplification technologies and the latter dependant on smears. These differences are not only due to the prohibitive cost of some technologies but also, in part, reflect a lack of commitment on the part of health ministries and NTPs to introduce modern technologies and upgrade laboratory systems in general.

There have been some advances in diagnostics for active TB and LTBI including detection of TB-specific antigens or antibodies and tests based on interferon-γ production by T-cells when stimulated with TB specific antigens. However, research is needed to determine the utility and cost-effectiveness of these and other new TB diagnostic tests in resource-limited settings with high HIV seroprevalence. Progress in this area has been hindered by the fact that, to date, no internationally accepted guidelines for the assessment and evaluation of TB diagnostics are available. Until new tools are widely available, ways to maximize the effectiveness of old tools must be studied and then implemented. For example, the use of a screening questionnaire and sputum smear have been shown to effectively rule out active TB in HIV clinics. Despite these types of studies, little attention has thus far been paid to implementing active TB case finding by HIV programmes. Similarly, screening for LTBI and use of IPT is not a component of most HIV care and treatment programmes despite its proven clinical effectiveness and probable cost effectiveness. National programmes, with the exception of ongoing efforts in Botswana, have not embraced this intervention, often because of concerns about initiation of treatment for LTBI with isoniazid in patients who actually have underlying active TB disease, understandable given recent reports of high rates of subclinical TB in HIV-infected patients. The combined application of clinical and operational research is needed to determine what are the most efficacious and cost-effective TB screening algorithms in combination with new and old diagnostic tools as well as the methods for providing full access to IPT for HIV-infected patients found to have LTBI. These algorithms and tools then need to be modified to fit individual site circumstances.

TREATMENT OF HIV-INFECTED PATIENTS WITH TB

Concurrent treatment of TB disease and HIV disease presents practical and logistic questions including: 1) when in the course of TB treatment should antiretroviral (ARV) therapy, if indicated, be started; 2) what ARV regimen should be used; and 3) how should these patients be monitored for toxicity and clinical outcomes?

It is universally recommended that antituberculous treatment be promptly initiated upon diagnosis of TB in an effort to decrease mortality and risk of transmission of M. tuberculosis to others. Additionally, emphasis has been placed on starting ARV therapy, when indicated, during the TB treatment phase due to the high morbidity and mortality in patients with HIV-related TB co-infection even when receiving appropriate antituberculous treatment. WHO guidelines, based on expert opinion, indicate that the timing of initiation of ARV therapy in these patients should be based on the degree of immunosuppression as defined by CD4 cell count. Although the proposed algorithm provides a reasonable approach, data supporting the current guidelines are lacking regarding the risks, including drug toxicities, and the benefits of starting ARVs at different levels of immunosuppression.

Several factors may complicate concurrent use of antiretroviral (ARV) and antituberculous drugs including: additive toxicities of medications, drug interactions, risk of immune reconstitution events, and difficulty in adherence with multiple medications. The choice of ARVs is severely limited by the need for concurrent use of rifampin due to the latter’s effect on levels of protease inhibitors and non-nucleoside reverse transcriptase inhibitors (NNRTIs). Nevirapine-based regimens are the primary ones used in most national antiretroviral treatment programmes. The safety and efficacy of concomitant use of nevirapine-based regimens in conjunction with rifampin requires further study. Efavirenz-based regimens have been more extensively studied and are recommended in this scenario. However, the precise dose of efavirenz in this scenario remains to be determined due to rifampin’s effect on efavirenz metabolism.

Both pharmacokinetic and clinical studies are urgently needed in patients receiving concomitant antituberculous and antiretroviral drugs, particularly studies focused on antiretroviral drugs that are currently recommended and widely available in resource-limited settings. A few studies with limited numbers of participants have assessed...
co-administration of these agents with encouraging preliminary results.\textsuperscript{6,7,37} However, studies with larger numbers of participants are needed to evaluate the concomitant use of these various regimens and to assess their effects on laboratory and clinical outcomes.\textsuperscript{38} The feasibility and effectiveness of rifabutin in resource-limited settings needs urgent evaluation.\textsuperscript{39} Although the rifabutin dosage needs to be adjusted when administered with ARVs, its use does not preclude the utilization of many of the currently available ARV treatment options as does the use of rifampin.

**MANAGEMENT OF THE TB/HIV CO-INFECTED PATIENT**

Current national TB and HIV programmes remain largely separate with varying levels of interaction and communication. However, these programmes are often situated within the structure of the ministry of health. Thus, ministries of health can have an important role in ensuring communication and collaboration between the two programmes. Collaboration at the central programmatic level will facilitate similar collaboration and communication at the service delivery sites, resulting in better services for co-infected patients. Fig. 1 depicts stylized representations of two different paradigms for interactions between HIV and TB programmes and service delivery sites: an all too common paradigm and an alternative paradigm. The common paradigm is characterized by separate and distinct programmes with little coordination or overlap. However the alternate paradigm is focused on the co-infected patient rather than on the two diseases in isolation, which would improve the care and treatment of TB/HIV co-infected patients through increased collaboration and communication between programmes and integration of services. Achievement of this alternative paradigm requires intensive assessment of various models of collaboration and integration between TB and HIV programmes and services. These models may range from maintenance of separate programme services with enhanced communication and referral mechanisms to partial or full integration of programmes and the services they provide.

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**Figure 1. Common and alternative TB and HIV programme paradigms.** The alternative paradigm features increased communication and collaboration at national level, and partial, site appropriate, integration of services among TB, HIV and primary care services.

DOT = directly observed therapy; LTBI = latent tuberculosis infection; IPT = isoniazid preventive therapy; CT = counselling and testing; OI = opportunistic infection; Rx = treatment; Px = prophylaxis; HIV = human immunodeficiency virus.

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**A common TB and HIV paradigm**

**National TB control programme**

**TB services**
- Sputum collection
- DOT
- Treatment support
- Contact tracing
- LTBI screening
- IPT

**HIV services**
- CT
- Antiretrovirals
- OI Rx and Px
- Adherence support
- Community support
- HIV prevention

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**An alternative TB and HIV paradigm**

**National TB control programme**

**TB services**
- Sputum collection
- DOT
- Treatment support
- Contact tracing
- LTBI screening
- IPT

**HIV services**
- CT
- Antiretrovirals
- OI Rx and Px
- Adherence support
- Community support
- HIV prevention

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**Primary care services**
An example of a collaborative model is one where ARVs are initiated in eligible patients during TB treatment at the TB clinic with subsequent transfer of the patient to the HIV programme after completion of antituberculous therapy. This model would allow for reinforcement of the importance of adherence with ARV therapy through the use of directly observed therapy (DOT) services at the TB clinic and through utilization of other supportive and outreach efforts available through these programmes. Superior outcomes have been noted among patients with HIV-related TB who received their antituberculous treatment through DOT. Availability of the DOT infrastructure at TB treatment programmes allows for its use with ARVs and thus creates a unique opportunity to achieve high rates of adherence with ARV therapy and may provide patients with the skills to maintain self-administered lifelong adherence with ARVs once TB therapy is completed.\(^41\) In addition, close follow-up of patients through the frequent contact required for DOT allows for more careful monitoring of patients to promptly identify adverse effects of ARVs, particularly during the early phase after initiation of these medications. This approach will require training of TB programme staff on management of HIV and its complications, access to ARVs, and availability of laboratory assays such as the CD4 cell count and those needed for monitoring toxicity of the drugs used.

From the perspective of the HIV programmes, a focus on the co-infected patient also requires establishing models of collaboration. For patients with HIV who develop TB while in follow-up at HIV care and treatment programmes, these programmes may also need to expand their services to include provision of TB treatment and use of DOT. Similar to the scenario in the TB clinics described above, this approach requires training of HIV staff on TB diagnosis and management as well availability of antituberculous medications and other TB-specific resources.

Training of providers in both HIV and TB diagnosis and management can assist in the effective use of clinical staff. However, the scope of the HIV and TB epidemics requires assessment of the feasibility and effectiveness of new cadres of healthcare workers, particularly in settings with a paucity of nurses or physicians such as DOT workers and treatment supporters.\(^42\) Similar efforts are needed to determine how to provide community care models for the co-treatment of TB and HIV. The use of community care models for delivery of TB treatment to HIV-negative and HIV-infected patients has been studied and shown to be effective.\(^43,44\) In many resource-limited settings, patients’ families and communities provide resources not available to many HIV patients in developed countries,\(^45,46\) and some early data suggest that use of these facilitators may be associated with favourable clinical and virologic outcomes in patients with both TB and HIV disease in need of treatment.\(^7,47\)

Thus, in order to identify the optimal models and strategies for managing patients with HIV and TB, studies are needed to compare the feasibility, outcomes and cost effectiveness of specific collaborative and integrative approaches. It is however clear that one model may not fit all countries. Prevalence of HIV and TB, demographic characteristics of the
patients, available resources, existing programmatic structures, types of provider available and levels of expertise vary, and are all factors which influence the choice of model of care. Nor, for that matter, may one model fit each country, as differences in rural and urban sites of care, needs of special populations such as intravenous drug users, and varying levels within the healthcare system from primary to specialty clinics and tertiary care sites may require different degrees of collaboration and integration. Different models and strategies will need to be developed and evaluated, and their collaborative and integrative approaches compared.

MAKING IT HAPPEN

It would be naive to believe and argue that a collaboration strategy could be uniformly and rapidly accomplished throughout all areas in which HIV and TB epidemics overlap. Indeed it is important to recognize that, in most areas, TB programmes have insufficient structural and human resources in the face of rising caseloads driven by the HIV epidemic. Furthermore, national TB programmes in many cases do not have the authority to enforce high-level collaboration. Thus successful collaboration requires a commitment by national leadership in ministries of health and a devotion to achieving this goal. Infusion of resources is needed to strengthen the TB programmes, to expand the availability of trained TB providers and DOT supporters, and to improve facilities for diagnosis, treatment and integrated care for TB/HIV co-infected patients. Similarly, efforts must also focus on HIV programmes. These programmes are inundated with patients seeking care and treatment. They face enormous obstacles including the need for trained staff, extensive laboratory resources, and availability of ARVs, as well as the challenge of achieving excellent lifelong adherence with medications by their patients. Thus there is a specific urgency to undertake studies that address TB-related issues within HIV care and treatment programmes, lest in the understandable haste to establish these programmes, the opportunities to determine the most effective means for TB and HIV collaboration and integration are missed. Fundamentally, without a general strengthening of the primary healthcare system, the best intentioned efforts to improve collaboration and service delivery for TB and HIV co-infected individuals may fail.

Collaboration between HIV and TB care and treatment programmes has been hampered by their separate traditions and practices. TB programmes are characterized by their public health approach, with firmly established algorithms and standardized measures and outcomes. On the other hand, HIV care and treatment derives from a focus on the individual patient and is characterized by rapidly evolving treatment paradigms that must be rapidly incorporated into treatment guidelines. The nuances, subtleties and added complexities of TB diagnosis and treatment in the context of HIV co-infection must be recognized, as must the need for a large-scale public health approach for the management of HIV in resource-limited settings. Each discipline needs to accommodate the other. For the TB world, HIV should no longer be seen as an intruder and must be accepted as part of the current and future reality. For the HIV world, the accumulated experience acquired over the longer history of TB must be valued and can serve as source of important lessons. How best to harmonize these two basic approaches is at the core of the proposed research priorities delineated in this communication. Addressing the outstanding unanswered questions in the management of the two diseases in a spirit of accommodation and collaboration will greatly benefit patients with TB and HIV and establish a new paradigm for the future.

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References


INTRODUCTION

In 1966, rifampin was introduced for the treatment of tuberculosis (TB); this was the last time a novel class of drugs was added to the TB treatment armamentarium. From that notable landmark until the year 2000, TB drug development was devoted primarily to clinical trials for shortening and simplifying treatment, for example by identifying an orally bioavailable regimen to obviate the need for streptomycin, developing and testing various rifamycin analogues and regimens for intermittent delivery, and developing fixed-dose combination (FDC) formulations of current medications. The currently recommended treatment regimens are efficacious when administered and taken reliably, but despite the aforementioned efforts, their complexity and duration compromise their ability to ultimately control the global TB epidemic, particularly in the context of high HIV prevalence.

National TB control programmes and their patients therefore need novel therapies to shorten and simplify treatment of active TB (increasing compliance and freeing up valuable human resources), safely treat TB/HIV co-infected patients, improve the therapy of multidrug-resistant tuberculosis (MDR–TB), and shorten the treatment of latent tuberculosis infection (LTBI). A number of hurdles have hampered efforts to provide such regimens, including: 1) a dearth of available drugs with the potential to help shorten therapy; 2) a requirement for safe and effective drug combinations; and 3) a lack of TB-specific regulatory guidance to facilitate the drug development process.

By the year 2000, it was evident that worldwide far too few resources and too little effort were being focused on TB drug development to overcome these hurdles. The need to ensure affordability, adoptability and accessibility of any new regimen further discouraged TB drug development efforts in the private sector. The global pipeline of new candidate TB drugs was virtually empty and adequate efforts and resources to rectify the situation did not appear to exist, either in industry among pharmaceutical and biotechnology companies, or in the academic, governmental and non-governmental sectors.

CURRENT TB DRUG R&D ACTIVITIES

The TB drug R&D situation has changed dramatically in the last five years as a result of heightened focus on the TB epidemic and the associated critical requirement for improved treatment. A number of key events mark this sea change. In 2001, initial grants from the Rockefeller Foundation and the Bill and Melinda Gates Foundation supported the establishment of the Global Alliance for TB Drug Development (TB Alliance), a public-private partnership whose mission is to develop improved treatments for TB and ensure their affordability for the patients most in need. Also in 2001, GlaxoSmithKline (GSK) reaffirmed its commitment to a Diseases of the Developing World programme by opening a dedicated unit in Tres Cantos, Spain, focused on malaria and TB drug discovery, while AstraZeneca committed funds to open an institute in Bangalore, India, devoted entirely to TB drug discovery and development. In 2002, Novartis founded the Novartis Institute for Tropical Diseases in Singapore, aimed at discovering novel treatments and prevention methods for TB and dengue fever. In addition, efforts in a few other companies (J&J/Tibotec, Otsuka Pharmaceutical Co. Ltd., Sequella Inc.), and in the academic, governmental (e.g. the European Union’s European and Developing Countries Clinical Trials Partnership [EU/EDCTP], the US National Institutes of Health [NIH] and Centers for Disease Control [CDC], the Indian Council of Medical Research [ICMR]), and non-governmental organization (e.g. TDR/OFLOTUB – a consortium of ten partners from Europe and Africa initiated in 2002 to undertake phase II and phase III trials to test the safety and efficacy of a gatifloxacin-containing four-month treatment regimen for the treatment of TB) sectors have continued and, in some cases, received new or increased resources. In 2000–2001, the Global Partnership to Stop TB founded six working groups, three of which are focused on new tools development, including the Working Group for New Drug Development (NDDWG). This latter working group, which is composed of approximately 80 members (see appendix), has recently authored a 2005 Strategic Plan in which the global portfolio for TB drug development is summarized and includes all known projects as of July 2005 organized according to stage of development (discovery, preclinical or clinical; see table 1).
Table 1. Global TB drug pipeline July 2005*

<table>
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<th>Clinical testing</th>
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<td>• Nitrofuranylamides</td>
<td>• Diamine SQ-109</td>
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<td>• Synthase inhibitor</td>
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<td>AstraZeneca</td>
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*From the Stop-TB Working Group for New Drug Development

Although the majority of projects in the portfolio are in the discovery stage (i.e. the project is somewhere between target identification and preclinical candidate), six projects are already in human testing and five more are in preclinical development. This represents significant progress in building a robust pipeline of projects to ensure improved treatment for TB. However, additional projects will be needed in the coming years to build and maintain a steady state of development to ensure creation of needed regimens. (Several recent reviews have described preclinical and clinical-stage projects in detail, as well as novel classes and targets being explored in discovery projects that are not reviewed in detail here.)

Key considerations in adding projects to the portfolio must include technical feasibility and potential to fulfill unmet medical needs, or probability of successful registration of the product and its incorporation into global recommended practice. Summarized here are the process and criteria used by the TB Alliance (the organization currently responsible for more than one-third of the global portfolio) for selecting and prioritizing compounds within its portfolio.

The TB Alliance first established its fundamental R&D priorities by evaluating both potential impact and technical feasibility, resulting in the shortening and simplifying of treatment for active disease becoming a top priority. The TB Alliance’s near-term goal is to reduce the duration of first-line treatment to four months or less, its mid-term goal is to reduce the duration to two months, and the long-term goal to reduce it to two weeks or less. These were determined to be feasible goals in the designated timeframes based on available non-clinical and clinical data. The TB Alliance committed itself to tackling simultaneously with this top priority the additional priorities of developing safer, more efficacious treatments for MDR-TB and first-line regimens compatible with co-administration of antiretroviral agents. These goals are being accomplished, respectively, by early prioritization of compounds and projects with: 1) novel mechanisms of action relative to current first-line TB drugs, so that newly developed drugs will be equally effective against current MDR–TB strains and drug-susceptible strains; and 2) minimal or no interactions with cytochrome P450 microsomal enzymes, to minimize the potential for drug-drug interactions. The
TB Alliance’s fourth priority is to shorten effective treatment for LTBI. Achievement of this goal would likely have the greatest positive impact on eliminating the global epidemic by removing the reservoir of future TB cases represented by the estimated two billion people currently latently infected; but this is the most technically challenging of goals. It is possible that achieving the TB Alliance’s primary goal of shortening and simplifying treatment for active disease will also lead to improved treatment for LTBI if drugs efficacious against persistent bacilli (i.e. those phenotypically resistant to treatment for active disease) are also active against latent bacilli. This should be tested empirically once a treatment-shortening regimen is validated. However, because of the technical challenges involved, shortening treatment for LTBI may well be a more distant goal requiring a comprehensive understanding of latency’s fundamental mechanisms, relatively large and lengthy clinical trials (until improved diagnostics and validated surrogate markers of LTBI cure are available), and a regimen with an extremely clean safety record given the asymptomatic status of the intended recipients.

The TB Alliance has, in addition to setting these major priorities, established both relatively general criteria for accepting and prioritizing projects, and detailed, class or project-specific criteria for advancing compounds through the development pipeline. The relatively general criteria are presented in table 2, and focus on improving anti-TB activity, decreasing toxicity, and improving pharmacokinetic and/or pharmacodynamic properties. Compounds are selected that fulfil as many of the defined criteria as possible.

In addition to these technical criteria, the TB Alliance typically undertakes projects in which it can obtain non-blocking intellectual property positions. Appropriate intellectual property can be a key strategic tool used, if development is successful, to ensure availability and affordability of the marketed drug in developing countries.

At least two major challenges face TB drug R&D. Because the true unit of development in TB treatment is a safe and effective drug combination, not individual drugs, one key challenge is to create a streamlined process for accurately identifying the best possible combinations to take into clinical development. The second challenge is to identify new targets essential to M. tuberculosis persistence and latency, to serve as the basis for new discovery projects and help ensure an ongoing, robust pipeline of projects.

Creating a streamlined process for accurately identifying the best drug combinations for testing in humans will require a significant paradigm shift for TB drug development in both preclinical and clinical evaluation. A true paradigm shift is especially required because an optimal regimen will likely involve replacement of all the current first-line drugs, given that each has known shortcomings. Isoniazid is now subject to a relatively high prevalence of resistance, is a factor in hepatic toxicity in some patients, may decrease efficacy in combination with other first-line drugs, and likely does not contribute to treatment-shortening; ethambutol appears to add little in terms of potency to the current regimen; pyrazinamide is only effective in the first two months of treatment and has significant associated toxicity, especially arthralgias; and rifampin and rifapentine both have significant cytotoxicity andrifampicin toxicity, and improving pharmacokinetic and/or pharmacodynamic properties. Compounds are selected that fulfil as many of the defined criteria as possible.

In addition to these technical criteria, the TB Alliance typically undertakes projects in which it can obtain non-blocking intellectual property positions. Appropriate intellectual property can be a key strategic tool used, if development is successful, to ensure availability and affordability of the marketed drug in developing countries.

As illustrated in fig. 1 (top panel), current timelines for phase I–III testing would dictate that identification of a new regimen containing four novel drugs substituted for present first-line drugs would require approximately 24 years to complete. This long duration is necessitated by the present practice of adding or substituting one new drug at a time into the standard regimen. However, a new clinical testing paradigm that treats a novel combination as the unit for evaluation could streamline this entire process.

<table>
<thead>
<tr>
<th>Table 2. General compound selection criteria</th>
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**Primary:**
- Demonstrable whole-cell activity against Mycobacterium tuberculosis (Mtb) in suitable in vitro assay(s), with minimal inhibitory concentration (MIC) in the sub-μg/ml range.
- Novel mechanism of action (if known).
- Demonstrable structure–activity relationship(s) (e.g. for potency, selectivity, toxicity, P450 interactions), particularly for multiple compounds in a series.
- Therapeutic index (i.e. window between activity and cytotoxicity) of >10 as measured in suitable in vitro assay(s).

**Secondary:**
- Synthesis achievable in less than ten steps.
- Starting material readily available and inexpensive.
- Leads are amenable to combinatorial approaches, thereby maximizing the diversity of structures that can be synthesized and tested.
- Synthetic steps are scalable.
- Biochemical target well defined.
- In vitro functional assay available to simplify the optimization process, particularly if three-dimensional structural information can be used to guide synthesis.
- Active in a murine model of Mtb infection (although compounds that have been tested against other microbes, particularly other mycobacteria, will also be considered).
to take as little as six years, as seen in the lower panel of fig. 1. Close consultation with the regulatory authorities will clearly be key to accomplishing such a paradigm shift. The Stop TB NDDWG, the Bill and Melinda Gates Foundation and the TB Alliance co-sponsored an open forum in December 2005 to begin addressing this and other key, TB-specific regulatory issues. This and future meetings are planned to help catalyse the creation of harmonized, TB-specific guidance by the regulatory authorities.

Also key to effecting this shift and efficiently developing optimal new regimens will be the need for all drug candidates that have met pre-set criteria, e.g. successful completion of investigational new drug (IND)-enabling studies, to be available along with the present drugs for joint evaluation in vitro and in animal models to identify the most promising combinations for further development. Until now, in TB as in other therapeutic areas, individual sponsors have tested their own compounds for efficacy and safety independent of other sponsors’ ongoing projects. When monotherapy is the goal, and market considerations a priority, this approach is appropriate and feasible. However, when treatment requires combination therapy and the primary goal is solution of a public health emergency rather than profit, cooperation in the evaluation process is far more appropriate and, in fact, essential to accomplishing the goal in an acceptable timeframe. Without such joint testing, multiple sub-optimal regimens are likely to be registered for the foreseeable future, each containing only one novel agent, rather than a truly optimized regimen comprised of the safest, most efficacious drug combination. The current gatifloxacin and moxifloxacin development programmes are, by necessity, examples of this type of development, because they are clearly more advanced than any other candidates and share a common mechanism of action (so that combining them is unlikely to serve a useful purpose). They serve two important purposes, however: they have the potential to shorten therapy by at least two months in the relative near term and thereby contribute significantly to achievement of the TB Millennium Development Goals for 2015, and they are serving as trailblazers in a number of ways for the even more ambitious development programmes to follow with completely novel regimens – for example, by enhancing GCP-compliant clinical trial capacity, evaluating potential biomarkers, and helping to focus regulatory attention on important TB-specific development issues. However, as table 3 makes clear, within the next year there is the potential for as many as seven compounds to be in clinical testing, and this one-at-a-time substitution approach will no longer be a reasonable one to take. In preparation, the TB Alliance has begun establishing a streamlined, cooperative, preclinical testing process to facilitate joint evaluation in an environment that will enable individual sponsors to retain their intellectual property while working together to identify the most efficacious, safe combination regimen(s) for addressing the TB epidemic. The TB Alliance plans to issue a request for proposals in the near future in support of this process.

The second major challenge facing TB drug R&D is to identify new targets essential to persistent and/or latent M. tuberculosis to support the TB drug pipeline. A number of investigators and organizations are participating in this key activity, and one of the Bill and Melinda Gates Foundation-funded Grand Challenges is specifically focused on elucidating basic mechanisms and associated targets in TB latency.

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**Figure 1.** Conventional vs. alternative clinical development paradigms

**Conventional TB clinical development paradigm**

- **ABCD** → **BCDE** → **CDEF** → **DEFG** → **EFGH**
  - 6 years → 6 years → 6 years → 6 years → 24 years

**Alternative TB clinical development paradigms**

**#1:**

- **ABCD** → **EFCD** → **EFGH**
  - 12 years

**#2:**

- **ABCD** → **EFGH**
  - 6 years

- **ABCD** → **EFGH**
  - 6 years

---
Overcoming both these challenges is crucial to producing truly practical, safe and efficacious regimens that will: significantly shorten and simplify treatment of active TB, be safe and easy to administer for HIV-positive as well as HIV-negative patients, surmount the MDR–TB problem, reduce the duration and adverse effects of LTBI treatment, and ease resource-demsands on public health infrastructures in high burden countries. An adequate steady state portfolio must be maintained to create the improved regimens that will ultimately be combined with effective diagnostics and vaccines to eliminate tuberculosis as a significant public health problem.

ADDITIONAL DIRECTIONS FOR RESEARCH IN SUPPORT OF THE GLOBAL TB DRUG PIPELINE

Successful development and adoption of a safe, affordable, two-month and, ultimately, two-week, treatment regimen is a feasible but ambitious goal. Accomplishing it will require, in addition to the portfolio-building and development activities described above, a number of other actions. Streamlining clinical trials will be vital to moving forward expeditiously. Just as CD4 counts and viral loads have facilitated trials of potential AIDS drugs, identification of appropriate biomarkers would have a major impact on decreasing TB drug development timelines. Therefore approaches must be developed and executed to identify promising candidate biomarkers. Also, for the near term, sponsors must use TB drug trials to serve the additional purposes of elucidating an early efficacy biomarker useful in phase I/II clinical development to get a quick ‘read’ on a compound’s potential, and validating a surrogate endpoint to significantly shorten pivotal efficacy trials by abrogating the need for 6–24 months of post-treatment patient follow-up.

TB drug development remains significantly under-funded.15 Research to further explicate the benefit to be expected from a two-month or shorter regimen would be valuable both in helping to raise additional funding and in laying the crucial groundwork for ensuring the regimen’s adoption following regulatory approval. Ultimate elimination of MDR–TB as a significant problem is likely to require not only development of a safe, efficacious and affordable regimen containing several drugs with novel mechanisms of action relative to current drugs, but provision of these new agents in a fixed-dose combination

Table 3. Selected drugs in development: timetable towards registration*

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*from NDDWG 2005 Strategic Plan

D = discovery; PC = preclinical; NDA = new drug application; I, II, III = different phases of clinical trials
(FDC) to prevent new drug resistance from developing. Laying the groundwork for assessing the effectiveness of these FDCs in the community, addressing potential safety issues, and encouraging their adoption will also be important activities.

The status of TB drug R&D in 2005 is clearly more robust than it was even five years ago, and there is significant optimism that, by combining the efforts of public and private sectors, the drug development community will meet the sizable challenges ahead and successfully develop and deliver shorter, simpler, affordable TB regimens. Given that total funding for developing new tools for neglected diseases, including for TB, remains seriously inadequate compared to the urgent public health need, it is vital that each organization wanting to contribute to this arena identifies the niche or niches that best match its expertise, capacity and resources, and focuses its efforts. TDR is to be commended for tackling this crucial task through the current priority-setting exercise. It is impossible to imagine any organization of TDR’s size and resources being able to contribute in a meaningful way to development of drugs, vaccines and diagnostics for a total of ten diseases, the current TDR mission. Even the largest pharmaceutical companies do not attempt to meet so daunting a mandate. It is valuable, perhaps, to revisit the words of former TDR Director, Carlos Morel, in his introduction to the 2001–2002 TDR progress report (16): “TDR should concentrate its actions in areas where it can make a difference, where there are no other players, or where its leadership can mobilize the expertise needed for a given project.” TDR’s challenge remains to identify its unique niche in neglected diseases new tools R&D.

References

## Appendix

### STOP TB PARTNERSHIP WORKING GROUP ON NEW TB DRUGS:
MEMBERSHIP AS OF SEPTEMBER 2005

<table>
<thead>
<tr>
<th>Name</th>
<th>Organization/University</th>
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<tr>
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<td>Lupin Limited</td>
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</tr>
<tr>
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<td>National Institutes of Health (NIH)</td>
</tr>
<tr>
<td>Dr. Jaime Bayona</td>
<td>Socios en Salud</td>
</tr>
<tr>
<td>Dr. Mercedes Becerra</td>
<td>Partners in Health (PIH)</td>
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<tr>
<td>Dr. Niils Billo</td>
<td>International Union Against Tuberculosis &amp; Lung Diseases (IUATLD)</td>
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<tr>
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<td>Dr. Anne Fanning</td>
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<td>Dr. Bernard Fourie</td>
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Dr. Christian Lienhardt  Institut de Recherche pour le Development
Prof. Christopher Lipinski  Pfizer Global Research and Development
Dr. Nacer Lounis  Faculte de Medecine Pitie-Salpetriere
Dr. Stephen Matlin  Global Forum for Health Research
Dr. Francine Matthys  Médecins Sans Frontières (MSF)
Dr. John McKinney  Rockefeller University
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Dr. Edward Nardell  Partners in Health (PHI)
Dr. Andrew Nunn  Medical Research Council (MRC), United Kingdom
Dr. Rick O’Brien  Foundation for Innovative New Diagnostics (FIND)
Dr. Piero Olliaro  European and Developing Countries Clinical Trials Partnership (EDCTP)
Dr. David Olson  Médecins Sans Frontières, Doctors Without Borders
Dr. Philip Onyebujoh  World Health Organization (WHO), (TDR)
Dr. Ramesh Panchagnula  National Institute of Pharmaceutical Education and Research (NIPER)
Dr. Charles Pasternak  Oxford International Biomedical Centre
Dr. Mark Perkins  Foundation for Innovative New Diagnostics (FIND)
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WORKING PAPER 4.
TUBERCULOSIS DEATHS AMONG POPULATIONS WITH HIGH HIV PREVALENCE*

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Abstract
Death is the outcome of tuberculosis most feared by patients and their families. The development of antituberculosis chemotherapy in the 1950s led to dramatic reductions in tuberculosis deaths in populations with access to treatment. The emergence of HIV in the 1980s reinstated tuberculosis as ‘a captain of the men of death’ in countries with high HIV prevalence. The annual global toll of deaths among tuberculosis patients is currently about 2 million. Along with reducing morbidity and disease transmission, reducing tuberculosis deaths is one of the objectives of tuberculosis control. The world faces the challenge of reducing tuberculosis deaths by half by 2015, as part of achieving the United Nations Millennium Development Goals.

Since HIV increases the risk of death during and after tuberculosis treatment, and is related to the degree of immunosuppression, the total number of deaths among tuberculosis patients is increased in populations with high HIV prevalence. Sub-Saharan Africa is the region most badly affected by the HIV epidemic and therefore also with the highest proportion of tuberculosis deaths attributable to HIV. Improvements in the routine reporting of deaths by national tuberculosis programmes will increase the utility of tuberculosis deaths as an indicator of programme performance. Improved epidemiological surveillance of tuberculosis mortality depends on investment in developing vital registration systems. Decreasing deaths among tuberculosis patients in countries with high HIV prevalence depends on measures to decrease tuberculosis incidence (by implementing the World Health Organization expanded strategy to control HIV-related tuberculosis) and to decrease tuberculosis case fatality (e.g. health service improvements to decrease diagnostic delay, antiretroviral treatment, co-trimoxazole).

INTRODUCTION
Death is the outcome of tuberculosis most feared by patients and their families. The development of anti-tuberculosis chemotherapy in the 1950s led to dramatic reductions in tuberculosis deaths in populations with access to treatment. The emergence of HIV in the 1980s has reinstated tuberculosis as ‘a captain of the men of death’ in countries with high HIV prevalence. Reducing tuberculosis deaths is one of the objectives of tuberculosis control, along with reducing morbidity and disease transmission. Exacerbation of the tuberculosis epidemic by HIV has been most pronounced in sub-Saharan Africa, where HIV is now the single best predictor of tuberculosis incidence. As part of the impact of HIV on the tuberculosis epidemic, the risk of death during and after tuberculosis treatment, and therefore the total number of deaths among tuberculosis patients, is considerably increased in populations with high HIV prevalence. The focus of this review is on sub-Saharan Africa since, of the countries with high HIV prevalence (estimated adult HIV seroprevalence greater than 5%), 24 are in sub-Saharan Africa and one is in the Caribbean (Haiti).

The increase in tuberculosis deaths in high HIV prevalence populations in sub-Saharan Africa may change the popular perception of tuberculosis as a curable disease and threaten the reputation of national tuberculosis programmes (NTPs). This may have an adverse influence on the willingness of tuberculosis suspects to come forward for diagnosis and on the ability of the NTPs to ensure that tuberculosis patients complete treatment. NTPs face the challenge of not only ensuring the effective diagnosis and treatment of increasing numbers of tuberculosis patients, but also of trying to identify and implement ways of decreasing tuberculosis deaths. The annual global toll of deaths among tuberculosis patients is currently about 2 million. The world faces the challenge of reducing tuberculosis deaths by half by 2015, as part of achieving the United Nations Millennium Development Goals (MDGs). Achieving this global target through progress mainly in low and medium HIV prevalence countries would be a hollow victory without progress also in high HIV prevalence countries, which carry a disproportionate share of tuberculosis deaths.

This paper first clarifies the terminology regarding tuberculosis deaths, specifies the sources of data on tuberculosis deaths, and summarizes the global descriptive epidemiology of tuberculosis deaths.

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Concerning the impact of HIV on death during tuberculosis treatment, the main aspects then covered are the extent of increased deaths, the timing and cause of death, and the relationship with degree of immunosuppression. Next follows consideration of using the number of deaths among tuberculosis patients in countries with high HIV prevalence as an indicator in tuberculosis programme monitoring and epidemiological surveillance. Finally there is a review of ways of decreasing tuberculosis deaths among populations with high HIV prevalence.

**TERMINOLOGY**

‘Tuberculosis deaths’ refers to all deaths among tuberculosis patients, without specification of cause, as the cause of death can rarely be determined in the low-income, high tuberculosis incidence countries where the vast majority of these deaths occur. ‘Tuberculosis cohort deaths’ refers to the number and proportion of patients dying during treatment, as reported by NTPs. The tuberculosis case fatality, or as it is commonly but less accurately known, the case fatality rate (CFR), is the proportion of tuberculosis cases that die within a specified time. Tuberculosis mortality is the number of tuberculosis deaths in a defined population during a specified period, and the tuberculosis mortality rate is the number of these deaths per 100 000 population.

**SOURCES OF DATA ON TUBERCULOSIS DEATHS IN HIGH HIV PREVALENCE COUNTRIES**

Despite difficulties in analysing and determining the causes of death, tuberculosis deaths can be measured in several ways. The main sources of data are a) research studies that provide the CFR; b) routine NTP reporting that provides tuberculosis cohort deaths; and c) vital registration systems that provide tuberculosis mortality.

a) Research surveys of tuberculosis deaths in defined populations (including participants in clinical trials of the efficacy of anti-tuberculosis treatment) enable the calculation of tuberculosis CFR.

b) NTPs report tuberculosis cohort deaths as part of the system of recording and reporting tuberculosis cases and their treatment outcomes that is an intrinsic part of the DOTS strategy. As the number of countries implementing the DOTS strategy increases, routine NTP data on tuberculosis deaths are becoming more widely available.

c) Vital registration data are necessary to measure tuberculosis mortality and therefore also the mortality rate. The few countries which routinely report tuberculosis mortality are mostly in the industrialized world. Vital registration data are often not available or are of limited reliability in the developing countries which bear the brunt of the tuberculosis epidemic.

**GLOBAL DESCRIPTIVE EPIDEMIOLOGY OF TUBERCULOSIS DEATHS**

Tuberculosis case notification data reflect health service coverage and the efficiency of NTP case-finding and reporting activities. Often, poor performance of these programmes results in considerable under-detection and under-reporting of cases. Therefore World Health Organization (WHO) estimates of tuberculosis incidence are based on a variety of inputs, including surveys of prevalence of tuberculosis infection and disease, vital registration data, and independent assessments of quality of surveillance systems. Global tuberculosis mortality must also be estimated, drawing on these inputs along with the above sources of data on tuberculosis deaths.

Table 1 is a summary of tuberculosis incidence and mortality estimates for 2003 by WHO region. In 2003 the estimated global tuberculosis incidence was 8.8 million new cases. The estimated proportion of tuberculosis cases in adults attributable to HIV infection was 11% worldwide but 28% in sub-Saharan Africa. Sub-Saharan Africa bears the brunt of the burden of HIV-related tuberculosis: of the 2.4 million new cases in the region, 463 000 were attributable to HIV (28% of adult cases); and of 538 000 deaths from tuberculosis, 188 000 (35%) were attributable to HIV. Of the global total of 1.75 million deaths from tuberculosis, 227 000 (13%) were attributable to HIV.

**IMPACT OF HIV ON DEATHS DURING TUBERCULOSIS TREATMENT**

**Extent of increased deaths**

Since HIV testing has not generally been routinely available to tuberculosis patients in high HIV prevalence countries, routine NTP reporting of treatment outcomes has provided overall cohort deaths without a breakdown by HIV status. Clinical studies have yielded the tuberculosis CFR by HIV status in different settings.

Tuberculosis deaths with unspecified HIV status

Tuberculosis cohort deaths are closely linked to HIV prevalence, both within countries (i.e. in many countries tuberculosis cohort deaths have increased
as adult HIV seroprevalence has increased) and between countries (tuberculosis cohort deaths and national HIV seroprevalence in sub-Saharan Africa are strongly correlated).5 NTPs have generally reported routinely only on outcomes for patients with sputum smear-positive pulmonary tuberculosis, and so have generally provided cohort deaths for these patients, and not for patients with sputum smear-negative or extrapulmonary tuberculosis, or therefore collectively for all forms. An exception is a study in Zomba, Malawi, that reported tuberculosis cohort deaths of 31% (all forms) and of, respectively, 19%, 46% and 37% for patients with sputum smear-positive, sputum smear-negative and extrapulmonary tuberculosis.11

Tuberculosis deaths by HIV status

TUBERCULOSIS (ALL FORMS)

Among patients with tuberculosis (all forms), studies have generally shown a higher CFR in HIV-positive than in HIV-negative individuals, e.g. 27% vs. 9% in West Burkina Faso,12 16% vs. 8% in Mwanza, Tanzania,13 31% vs. 4% in Kinshasa, Zaire,14 and 35% vs. 9% in Lusaka, Zambia.15 Tuberculosis CFR was 2.5 times higher in HIV-positive than in HIV-negative patients in Zomba, Malawi.11 It is noteworthy that the tuberculosis CFR among HIV-negative patients is generally higher in populations with high HIV prevalence (e.g. Malawi, Zambia) than with low HIV prevalence (e.g. Mali, Comoros).10

SPUTUM SMEAR-POSITIVE PULMONARY TUBERCULOSIS

Among patients with pulmonary tuberculosis positive by sputum smear or culture, studies have generally shown a higher CFR in HIV-positive than in HIV-negative individuals, e.g. 6.1% vs. 0.4% in Abidjan, Cote d’Ivoire,16 18% vs. 10% in Zomba, Malawi,11 29% vs. 8% in Ntcheu, Malawi,17 14% vs. 3% in Kinshasa, Zaire, and 38% vs. 25% in Lusaka, Zambia.15 Among patients in Kinshasa, Zaire, for those with extrapulmonary tuberculosis, the CFR was 10% vs. 1% in HIV-negative patients and 29% vs. 8% in HIV-positive patients.14

Table 1. Summary of tuberculosis estimates for 2003 by WHO region*

<table>
<thead>
<tr>
<th>WHO region</th>
<th>Africa</th>
<th>Americas</th>
<th>Eastern Mediterranean</th>
<th>Europe</th>
<th>South-East Asia</th>
<th>Western Pacific</th>
<th>Global</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population (millions)</td>
<td>687</td>
<td>868</td>
<td>518</td>
<td>879</td>
<td>1 615</td>
<td>1 732</td>
<td>6 299</td>
</tr>
</tbody>
</table>

**New cases of TB, all forms**

<table>
<thead>
<tr>
<th>Number of cases (thousands)</th>
<th>2 372</th>
<th>370</th>
<th>634</th>
<th>439</th>
<th>3 062</th>
<th>1 933</th>
<th>8 810</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence rate (per 100 000)</td>
<td>345</td>
<td>43</td>
<td>122</td>
<td>50</td>
<td>190</td>
<td>112</td>
<td>140</td>
</tr>
<tr>
<td>Prevalence of HIV in new adult cases (%)</td>
<td>33</td>
<td>5.8</td>
<td>2.3</td>
<td>4.3</td>
<td>3.6</td>
<td>1.3</td>
<td>12</td>
</tr>
<tr>
<td>Attributable to HIV (thousands)</td>
<td>463</td>
<td>12</td>
<td>8.3</td>
<td>11.3</td>
<td>61</td>
<td>13</td>
<td>617</td>
</tr>
<tr>
<td>Attributable to HIV (% of adult cases)</td>
<td>28</td>
<td>5.2</td>
<td>2.1</td>
<td>3.9</td>
<td>2.9</td>
<td>1.2</td>
<td>11</td>
</tr>
</tbody>
</table>

**New smear-positive cases of TB**

<table>
<thead>
<tr>
<th>Number of cases (thousands)</th>
<th>1 013</th>
<th>165</th>
<th>285</th>
<th>196</th>
<th>1 370</th>
<th>868</th>
<th>3 897</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevalence rate SS+ TB (per 100 000)</td>
<td>220</td>
<td>25</td>
<td>100</td>
<td>31</td>
<td>155</td>
<td>106</td>
<td>109</td>
</tr>
<tr>
<td>% of prevalent SS+ cases HIV+ve (%)</td>
<td>6.4</td>
<td>1.1</td>
<td>0.3</td>
<td>0.8</td>
<td>0.5</td>
<td>0.1</td>
<td>1.7</td>
</tr>
</tbody>
</table>

**Deaths from TB**

<table>
<thead>
<tr>
<th>Deaths from TB (thousands)</th>
<th>538</th>
<th>54</th>
<th>144</th>
<th>67</th>
<th>617</th>
<th>327</th>
<th>1 747</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths from TB (per 100 000)</td>
<td>78</td>
<td>6.2</td>
<td>28</td>
<td>7.6</td>
<td>38</td>
<td>19</td>
<td>28</td>
</tr>
<tr>
<td>Deaths from TB in HIV+ve adults (thousands)</td>
<td>187</td>
<td>3.8</td>
<td>4.3</td>
<td>3.3</td>
<td>25</td>
<td>4.9</td>
<td>229</td>
</tr>
<tr>
<td>Adult (15–69 years) AIDS deaths due to TB (%)</td>
<td>11</td>
<td>4.1</td>
<td>14</td>
<td>9</td>
<td>7.8</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>TB deaths attributable to HIV (%)</td>
<td>35</td>
<td>7.1</td>
<td>3.0</td>
<td>4.9</td>
<td>4.1</td>
<td>1.5</td>
<td>13</td>
</tr>
</tbody>
</table>

* Data from estimates provided by WHO and from reference 2. The WHO African Region comprises sub-Saharan Africa and Algeria. The remaining North African countries are included in the WHO Eastern Mediterranean Region. For a list of countries in each WHO region, see reference 2 (annex 1).

TB = tuberculosis; SS+ = sputum smear-positive.

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0.5% in Johannesburg, South Africa, and 13% vs. 0% in Kinshasa, Zaire.

SPUTUM SMEAR-NEGATIVE PULMONARY TUBERCULOSIS

A study in Malawi in patients with sputum smear-negative pulmonary tuberculosis reported a higher CFR in HIV-positive (59%) than in HIV-negative (26%) individuals. For comparison, the corresponding CFRs in sputum smear-positive patients were 18% in HIV-positive and 10% in HIV-negative patients.

When deaths occur

Studies in South Africa, Kenya, Tanzania, and Zambia showed a stable probability of death in HIV-negative and an increasing probability of death in HIV-positive tuberculosis patients during and after treatment. In South Africa, the probability of death for both HIV-positive and HIV-negative patients was greatest in the two weeks following the start of treatment. The probability of death then remained stable for HIV-negative patients at around 1% per month, while it continued to increase throughout the treatment period in HIV-positive patients at an average of 3% per month. In Kenya, the difference in probability of death between HIV-positive and HIV-negative tuberculosis patients increased between the 2nd and the 6th month of treatment. In Zambia there were five more deaths in HIV-positive compared to HIV-negative tuberculosis patients two years after the start of treatment.

High cohort deaths continue after the end of treatment. In Zomba, Malawi, 42% of a large unselected cohort of patients with tuberculosis (of whom 77% were HIV-positive) died within 32 months of starting treatment. Cohort deaths by 32 months according to type of tuberculosis were 30% (sputum smear-positive pulmonary), 60% (sputum smear-negative pulmonary) and 47% (extrapulmonary). In Tanzania, 35% of HIV-positive patients died four years after the diagnosis of tuberculosis compared to 13% in HIV-negative TB patients.

Most studies have only followed patients up to the end of treatment, or often for 24 months after. In the one study of long-term outcomes of patients with tuberculosis in a high HIV prevalence country, 65% of a large unselected cohort of patients with tuberculosis died within seven years of starting treatment. Half the deaths occurred in the first year during treatment, and half in the remaining six years. HIV seroprevalence in the cohort was 77% and HIV was the main factor associated with death. Cohort deaths were higher among patients with sputum smear-negative or extrapulmonary tuberculosis than with sputum smear-positive pulmonary tuberculosis. Just over 10% of the HIV-positive tuberculosis patients were alive after seven years. Nearly half of the HIV-negative tuberculosis patients had died by seven years. This surprising finding probably reflects the consequences of co-morbid conditions associated with tuberculosis, including poverty, malnutrition, alcohol abuse and social marginalization.

Cause of death

Deaths among HIV-infected tuberculosis patients may be either deaths from tuberculosis (i.e. tuberculosis is the immediate cause of death), or deaths with tuberculosis (i.e. some other HIV-related disease is the immediate cause of death). HIV infection may lead to increased deaths from and with tuberculosis among tuberculosis patients co-infected with HIV. Increased deaths from tuberculosis may be due to: HIV-induced immunosuppression which increases the severity of tuberculosis disease and is in turn more likely to be fatal; decreased quality of care because the HIV epidemic increases the demand on already over-stretched and under-resourced tuberculosis services; or a failure of tuberculosis treatment, e.g. due to the adverse effect of HIV on the pharmacokinetics of some anti-tuberculosis drugs. Increased deaths with tuberculosis may be due to a failure to diagnose or treat other HIV-related diseases, and because tuberculosis may accelerate the rate of progression of HIV disease.

The explanation for the particularly high CFR among HIV-positive patients with sputum smear-negative pulmonary tuberculosis at least partly lies with misdiagnosis (a particular problem in countries with high HIV prevalence, where diagnostic services are often limited and hard-pressed). Firstly, new patients with sputum smear-positive pulmonary tuberculosis (for whom the currently recommended regimen includes rifampicin in both the initial and continuation phase) who have been misdiagnosed as sputum smear-negative may in the past have been undertreated with a regimen including rifampicin only in the initial phase. Secondly, since there is no gold standard diagnostic test for patients with sputum smear-negative pulmonary tuberculosis, the CFR in these patients represents a mix of deaths from tuberculosis and from other diseases misdiagnosed as tuberculosis (including diseases related to HIV, e.g. Pneumocystis carinii pneumonia, and diseases unrelated to HIV, e.g. heart failure).

Immunological and virological studies indicate that the host’s immune response to M. tuberculosis enhances HIV replication and might accelerate the
natural progression of HIV infection. Among HIV-positive patients, evidence that the lungs of those with tuberculosis have more signs of HIV replication than those without tuberculosis supports the hypothesis that pulmonary tuberculosis enhances local replication of HIV. cohort studies of HIV-positive patients reported shorter survival among those with, than among those without, tuberculosis. Thus tuberculosis accelerates the course of HIV infection and enhances the suppression of cellular immunity, which is strongly associated with death.

Unfortunately, few data are available on the proportions of deaths from and with tuberculosis in HIV-infected tuberculosis patients since establishing these is difficult. The routine performance of post-mortem is rare in most countries in sub-Saharan Africa, and even then they may not reliably determine the direct cause of death. A small number of post-mortem and clinical/microbiological studies have been carried out to determine the direct causes of death in HIV-positive tuberculosis patients, but in the published post-mortem studies only a few cases were examined, making it difficult to draw general lessons. The assumption is that early tuberculosis deaths probably represent deaths from tuberculosis, and deaths in the later part of treatment and after the end of treatment represent deaths with tuberculosis (i.e. caused by some other HIV-related disease).

### Relationship with degree of immunosuppression

HIV-induced depression of cellular immunity increases the susceptibility of individuals to develop tuberculosis through either reactivation of latent infection or rapid progression of a recent infection. The location and extent of tuberculosis in HIV-infected individuals depend largely on the degree of the immunosuppression, with an increased frequency of extrapulmonary and disseminated tuberculosis and lower field infiltrative pulmonary tuberculosis in the more severely immunocompromised. This may increase the difficulty of diagnosis and delay the initiation of treatment, resulting in an increased risk of death. Studies have shown a strong correlation between the severity of tuberculosis and high CFR, and also between severe immunosuppression and mortality. With increased immunosuppression, patients are at increased risk of dying from HIV-related conditions such as bacteraemia and pyogenic infections.

### TUBERCULOSIS DEATHS AS AN INDICATOR IN TUBERCULOSIS PROGRAMME MONITORING

As NTP coverage becomes more comprehensive, tuberculosis cohort deaths more closely approximate to the tuberculosis CFR, provided that the interpretation takes into consideration the limitations in accuracy. There may be problems with over- and under-reporting of deaths. Over-reporting of deaths occurs since the diagnosis of tuberculosis in NTPs is less reliable than, for example, in clinical trials of the efficacy of anti-tuberculosis treatment, with the result that a proportion of patients who are diagnosed as having ‘tuberculosis’ and who then die do not in fact have tuberculosis. This is a particular problem with sputum smear-negative pulmonary tuberculosis, since the specificity of this diagnosis is especially low in the presence of HIV. A study in Malawi established as far as possible the true diagnosis in patients initially registered by the NTP with a diagnosis of sputum smear-negative pulmonary tuberculosis. Among patients grouped according to certainty of diagnosis, cohort deaths were 31% for patients with bacteriologically confirmed tuberculosis, 35% for patients with possible tuberculosis (but without bacteriological confirmation), and 53% for patients who were found not to have tuberculosis. The problem of under-reporting of deaths may arise where a proportion of patients reported as ‘lost to follow-up’ have in fact died (as many as one third in a study in Malawi).

Routine NTP data on tuberculosis deaths are important in programme monitoring despite the above limitations in their accuracy. WHO has, since 1991, recommended the collection of data on tuberculosis deaths at district level as a key element of programme monitoring. The use of routine programme data as an indicator of programme monitoring is particularly important in countries with high HIV prevalence. Where HIV is driving the incidence of tuberculosis upwards, tuberculosis control depends not only on improved tuberculosis case-finding and treatment but also on the effectiveness of HIV interventions that limit the spread and mitigate the impact of HIV. Tuberculosis and HIV programmes share the responsibility for implementing the joint interventions that will help to decrease the burden of HIV-related tuberculosis. Irrespective of the proportions of deaths that are due to tuberculosis or to other HIV-related diseases, tuberculosis deaths in high HIV prevalence populations represent a failure of joint implementation of interventions by tuberculosis and HIV programmes and therefore a joint failure of tuberculosis and HIV programmes. NTPs and HIV programmes therefore face the joint challenge.
of identifying and implementing ways of decreasing tuberculosis deaths.\textsuperscript{42}

In particular, the prospect of dramatically scaled up access to antiretroviral therapy (ART) has considerable implications for tuberculosis control in high HIV prevalence populations.\textsuperscript{43,44} The initiative to provide 3 million people in developing regions with access to ART by the end of 2005 aims at considerable reduction of illness and deaths among HIV-infected people.\textsuperscript{45} Since NTPs can provide an important entry point for the treatment of HIV infection, an increasing proportion of HIV-positive tuberculosis patients will also receive ART.\textsuperscript{44} Routine NTP monitoring of tuberculosis deaths is therefore crucial to evaluate the expected impact of ART.

**TUBERCULOSIS DEATHS AS AN INDICATOR IN EPIDEMIOLOGICAL SURVEILLANCE**

In the pre-HIV era, Styblo described tuberculosis surveillance as dealing with two distinct subjects: i) assessment of the tuberculosis situation (i.e. the epidemiological evaluation of the overall extent of the tuberculosis problem and its trend over time), and ii) measurement of the impact of control measures and hence progress in achieving the epidemiological objectives.\textsuperscript{46} Since the overall objectives of tuberculosis control are to reduce deaths, morbidity and disease transmission, while preventing the development of drug resistance,\textsuperscript{1} the epidemiological indicators of tuberculosis control are those which reflect progress in achieving these objectives, including reduction of deaths.

Styblo suggested that tuberculosis deaths were important as an indicator of the impact of control measures, but less important in the descriptive epidemiology of tuberculosis because firstly, adequate chemotherapy reduced the CFR by the end of treatment to a low level, and secondly, few programmes at that time were routinely reporting data on tuberculosis deaths.\textsuperscript{46} These two reasons have now become less valid, since CFRs in countries with high HIV prevalence have now risen to very high levels despite adequate chemotherapy,\textsuperscript{2} and many countries now report systematically on tuberculosis deaths. However, problems with the routine reporting of tuberculosis deaths by NTPs limit the extent to which they reflect tuberculosis mortality and therefore their use as an indicator in the measurement of the impact of tuberculosis control measures. The three main limitations are: i) incomplete coverage of all incident tuberculosis cases by NTPs; ii) inaccurate routine programme reporting of deaths; and iii) the unknown contribution of deaths from and with tuberculosis to all deaths among patients with tuberculosis. For these reasons, determination of the impact of tuberculosis control measures on tuberculosis mortality depends on the use of vital registration data. Measuring progress towards the MDG target of reducing tuberculosis deaths by half by 2015 will therefore require substantial investment in improving national vital registration systems for more accurate determination of tuberculosis mortality.

**WAYS OF DECREASING TUBERCULOSIS DEATHS**

Global tuberculosis mortality is the product of the global tuberculosis incidence and the tuberculosis CFR. Therefore reducing tuberculosis mortality depends on reducing tuberculosis incidence and the tuberculosis CFR. In sub-Saharan Africa, where HIV prevalence and therefore the tuberculosis CFR are much higher than in other regions, reducing tuberculosis mortality depends much more on reducing the CFR than in other regions, where HIV prevalence and therefore the tuberculosis CFR rate are much lower.

Reducing tuberculosis incidence in sub-Saharan Africa requires implementation of the expanded strategy to control HIV-related tuberculosis.\textsuperscript{41} This comprises measures directly against tuberculosis, e.g. full implementation of the DOTS strategy, intensified case-finding with high cure rates, isoniazid preventive treatment, and measures against HIV (and therefore indirectly against tuberculosis) e.g. condoms, treatment of sexually transmitted infections, and ART.\textsuperscript{41} Recent assessment of the status of efforts to control tuberculosis in high HIV prevalence countries indicates a generally low level of implementation of the essential measures that comprise the expanded strategy.\textsuperscript{47}

Implementation of the expanded strategy is likely to contribute to reducing the tuberculosis case fatality, depending on the extent to which the quality of tuberculosis care may improve as tuberculosis incidence falls and NTPs face a decreased burden. In addition, several measures have a specific impact on the tuberculosis CFR.\textsuperscript{42} These include operational measures to shorten diagnostic delays, adjunctive treatments such as co-trimoxazole,\textsuperscript{48-50} antiretroviral treatment,\textsuperscript{51,52} the development of new diagnostic tests for all forms of tuberculosis that are more sensitive, specific and user-friendly than the current approach involving mainly sputum smear microscopy and chest radiograph,\textsuperscript{53} and improved preventive\textsuperscript{54} and therapeutic\textsuperscript{55} anti-tuberculosis drugs.
CONCLUSIONS

Urgent action is necessary to reduce the global toll of tuberculosis deaths in high HIV prevalence countries. In order for NTPs to make better use of the routinely reported data on tuberculosis deaths in measuring their performance, a better understanding of the causes of these deaths and improved accuracy of recording and reporting of tuberculosis cases and deaths are required. Measuring progress towards the MDG target of decreased deaths will require substantial investment in improving national vital registration systems for more accurate determination of tuberculosis mortality.

Acknowledgements

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References


1. THE THINKING BEHIND THE CURRENT VACCINE CANDIDATES

Immunity to *M. tuberculosis* is associated with Th1 activity and the production of tumour-necrosis factor (TNF). Genetic defects in receptors for cytokines, such as IL-12 or interferon-γ (IFN-γ) that promote Th1 differentiation or are produced by Th1 cells, lead to increased susceptibility to progressive mycobacterial disease, while neutralizing TNF with therapeutic monoclonal antibodies can lead to reactivation of latent disease. Therefore the predominant view has been that vaccines should create the largest possible IFN-γ response (CD4+ but also CD8+ T cells) to selected antigens, but this view now seems flawed. We reviewed elsewhere the evidence that it is the quality not the quantity of the Th1 response that determines protective efficacy, so only brief notes are given here.

The evidence that the size of the IFN-γ response does not correlate with immunity comes largely from five sources:

- **Experiments with vaccine candidates in mice**
  There is a minimum level of IFN-γ that is needed for protection, so it is easy to design experiments with suboptimal vaccines or protocols where subsequent boosting of IFN-γ appears useful. However the requirement for IFN-γ rapidly reaches a plateau, and procedures that increase IFN-γ further do not increase protection (C. Locht, personal communication).

- **Genetically modified strains of *M. tuberculosis***
  Studies with strains lacking transcription factors or associated components of *M. tuberculosis* (such as SigH, rpoV and WhiB3) indicate that relatively few Th1 cells are sufficient to control bacterial proliferation, and that the remaining 90% that accumulate in lesions may be more concerned with immunopathology.

- **Latent TB**
  Little immune activity or cellular infiltration is required to maintain *M. tuberculosis* in the latent state.

- **The way that *M. tuberculosis* causes disease**
  Although there is evidence of suppression of Th1 responses in the peripheral systems of TB patients (considered later in relation to regulatory T cells), we are unaware of evidence that this is so in the lungs. When lung responses have been studied, these have been vigorous. It is possible that *M. tuberculosis* needs a vigorous Th1 response in order to generate the immunopathology that leads to cavitation and so facilitates spread of the disease via coughing. It is unlikely therefore that suppression of Th1 is a major strategy of pathogenesis.
• Immunopathology and the Koch phenomenon

In the 1890s, Robert Koch first demonstrated that tuberculous animals and humans mount a necrotic reaction to components of M. tuberculosis. Wilson et al. then proved that those animals in which the Koch phenomenon could be elicited with minute quantities of antigen were more susceptible to subsequent intramuscular infection with small numbers of virulent M. tuberculosis than were unimmunized controls or animals with much weaker skin-test responses.\(^\text{18}\)

In summary, it is unlikely that the efficacy of protection is directly related to the size of the IFN-\(\gamma\) or Th1 response. Why, then, does BCG fail, particularly in developing countries, and will the current vaccine candidates do any better?

2. DIFFERENCES BETWEEN TB IN DEVELOPING AND DEVELOPED COUNTRIES

2.1 TB in developed vs. developing countries

BCG vaccination is most likely to fail to protect from TB in developing countries, perhaps especially in those close to the equator.\(^\text{19–25}\) Also, death rates from TB during the first two months of standard treatment with antibiotics and chemotherapeutic agents are unusually high in developing countries.\(^\text{22–24}\) There are potential confounding factors, such as co-infection with HIV, distance from healthcare centres and the severity of disease at diagnosis, but death rates remain high even when these factors are taken into account.\(^\text{22,25}\) Death in these patients is probably due to a systemic Koch phenomenon,\(^\text{17}\) recently mimicked in the mouse.\(^\text{25}\) But why might patients in developing countries be more prone to this syndrome, and less easily protected by BCG?

First we consider recent points to emerge from studying differences between animal models in rich vs. developing countries.

2.2 Effects of previous exposure to environmental mycobacteria in mice

In laboratories in Europe or the USA, fatal progressive infection of mice with M. tuberculosis can be achieved with 50–200 organisms. In contrast, to achieve progressive infection in the same mouse strains housed in Mexico or Brazil,\(^\text{27}\) it is necessary to give a much higher infecting dose (10\(^6\)–10\(^8\) colony-forming units [cfu]); the small doses used in Northern laboratories fail to cause infection, and even 3000–4000 organisms merely cause stable latent infection in Mexico.\(^\text{26}\) This latent infection shows a pattern of mycobacterial DNA detectable by in situ PCR in apparently normal tissues that is similar to that seen in healthy tissues from humans with latent TB.\(^\text{10}\) It has recently emerged that the animals, or the breeding pairs from which they are derived, in both Brazil (D.B. Lowrie and C. Silva, personal communication) and Mexico (Y. Lopez Vidal and R. Hernandez Pando, personal communication) are exposed to heavy loads of environmental mycobacteria. This is easily demonstrated by measuring antibody to mycobacteria (Brazil) or by sampling the environment of the breeding room, or the water supplies used (Mexico).

Interestingly, in animals exposed to environmental mycobacteria in this way, at doses in the range of 10 000–50 000 cfu of M. tuberculosis, a percentage of the animals develop progressive disease, while in the remainder the disease stays latent. This mimics the human pattern, and provides important new ways to screen vaccine candidates that will be discussed later.

A final point is that the response evoked by contact with environmental mycobacteria in mice is largely Th1, and clearly protective, but nevertheless there is some priming of a Th2 component, and large doses of an environmental saprophyte cause a switch in the balance towards Th2.\(^\text{28}\) This is a known effect of large doses of particulate antigen,\(^\text{29}\) and applies also to BCG and to M. tuberculosis itself.\(^\text{30}\)

2.3 Background immunization by mycobacteria in humans

In developing countries, even healthy individuals have, like Mexican and Brazilian BALB/c mice, a background response to mycobacteria that is cross-reactive with M. tuberculosis as a result of contact with environmental mycobacteria (fig. 1). The mycobacteria consist of 100 or more saprophytic environmental species that are common in soil and untreated water. Skin-test studies with reagents prepared from these species show that in developing countries almost everyone is skin-test positive to many mycobacterial antigens,\(^\text{31}\) whereas in developed countries at higher latitudes this is increasingly unusual, presumably because of changes in lifestyle and chlorination of water supplies. Inevitably, most community controls in developing countries already respond well to one or more of the antigens used in the current candidate vaccines.\(^\text{32,33}\) If four recombinant antigens are used (ESAT-6, Rv2031, Ag85A, TB10.4), individuals who do not respond to one antigen will usually be found to respond to others, or to purified protein derivative (PPD) (VACSEL and VACSIS projects; unpublished data).
However, this background response in developing countries is not a ‘pure’ Th1 response. Rather it resembles that seen in mice exposed to high doses of environmental mycobacteria, as described in the previous section. This was shown in blood samples from Malawians, in which PPD (antigens precipitated from *M. tuberculosis* culture supernatant) induced secretion of the Th2 cytokine IL-5, whereas little IL-5 was seen in samples from the UK run in parallel. BCG vaccination failed to downregulate this IL-5 response to *M. tuberculosis* in Malawians (Dockrell HM, Black GF and Weir RE, personal communication). In addition to the possibility that the Th2 component is due to high-dose exposure to cross-reactive mycobacteria, the Th2 component of this response might be attributable to the exposure of mother and child to helminths, which commonly exert Th2 adjuvant effects. BCG induced a Th2-biased response in babies that had been sensitized in utero to antigens of the Th2-inducing helminths *Wuchereria bancrofti* or *Schistosoma haematobium* as a result of maternal infection. This effect of helminth infection in the mother is of particular interest, and needs to be investigated thoroughly. These helminth-mediated effects will also modulate the response to cross-reactive environmental mycobacteria in the babies, so it is inevitable that populations in developing countries have background mixed Th1 and Th2 responses to mycobacteria.

### 2.4 Other mechanisms enabling *M. tuberculosis* to induce IL-4 responses

In addition to dose effects, and to the adjuvant effects of helminths outlined earlier, several other factors lead to induction of IL-4 responses by *M. tuberculosis*. These are reviewed elsewhere. It is of particular interest that hypervirulent Beijing *M. tuberculosis* strains cause human monocytes to express IL-4, and a number of hypervirulent Mexican strains, that are not Beijing, have also been shown to evoke exaggerated IL-4 responses (R. Hernandez-Pando and D. Aguilar-Leon, personal communication).

### 2.5 IL-4 in TB patients in developing countries

We have pointed out that people living in developing countries have mixed Th1 and Th2 responses to cross-reactive mycobacterial antigens. Under some circumstances this mixed response can be protective. However, when individuals are exposed to high doses of *M. tuberculosis*, the tendency for particulate antigens at high dose to evoke IL-4 responses might allow *M. tuberculosis* to exploit the pre-existing IL-4 component, increase it, and use it to undermine the efficacy of the Th1 response, as demonstrated in mice similarly exposed to environmental mycobacteria.

If this were correct, we would expect unusually high levels of IL-4 to be present in TB patients in developing countries. Indeed, this is what we find.

Briefly, early studies (mostly before 2000) sometimes failed to show raised IL-4 levels in TB cases in Northern countries, and there is a technically flawed and certainly incorrect claim that IL-4 is absent from infected primate lungs. More recent data indicate that these findings might be attributable to the technical difficulties of working with a cytokine that is expressed with a very low mRNA copy number, with a very short mRNA half-life, that is further confused by the simultaneous presence of a splice variant that was ignored by all previous workers. Using a carefully validated quantitative real-time reverse transcriptase-polymerase chain reaction (RT-PCR), the copy number of mRNA encoding IL-4 present in unstimulated bronchoalveolar lavage (BAL) cells from TB patients in the UK is almost 2 logs higher than in BAL from matched controls.

However, in developing countries where BCG is most likely to fail, and where environmental mycobacteria are abundant and helminth infections common, IL-4 levels can be still more striking in TB patients. Free IL-4 can be detected easily in the patients’ serum or in supernatants of patients’ peripheral blood mononuclear cells cultured with tuberculosis antigen in vitro. The presence of free IL-4 in serum, that can be assayed by ELISA, represents an extraordinarily high level of IL-4, which is almost never detectable in the serum, even of asthma patients, in the UK. Interestingly, the half life of the mRNA encoding IL-4 is greatly prolonged in the blood of TB patients (Dheda et al., in preparation).

### 2.6 IL-4δ2 in healthy latently infected individuals in developing countries

Additional evidence for the importance of IL-4 in tuberculosis has come from a study of a splice variant of IL-4, known as IL-4δ2. This variant lacks exon 2, and is therefore 48 base-pairs smaller than IL-4 and is usually not recognized by researchers analysing IL-4 mRNA levels. Recombinant IL-4δ2 is a competitive antagonist of IL-4, though interestingly production of IL-4δ2 by CD8+ T cells is said to contribute to pulmonary fibrosis in patients with systemic sclerosis, implying that IL-4δ2 is an agonist on fibroblasts (in TB there are CD8+ cells that secrete either IL-4 or IL-4δ2; the methods used did not distinguish between the two cytokines).
TB, the expression of IL-4 and IL-4Rα tend to increase in parallel.\textsuperscript{50} This is different from asthma (a Th2-mediated disorder), where the expression of IL-4 increases 1000 times more than the expression of IL-4Rα.\textsuperscript{50} The expression of IL-4Rα mRNA is increased in unstimulated peripheral-blood mononuclear cells from healthy donors who have latent TB compared with non-infected individuals or patients in The Gambia, Denmark and Ethiopia.\textsuperscript{51,52} This indicates that blocking the effects of IL-4 through increased production of IL-4Rα might have a protective function, though prospective longitudinal studies are now needed (fig. 1). So why might opposing IL-4 be useful? Can we relate the IL-4 levels to failure of BCG and to immunopathology and increased mortality in developing countries?

### 2.7 Detrimental functions of IL-4

#### i) Susceptibility

Although knocking out the IL-4 gene has minimal effects on bacterial counts following challenge with \textit{M. tuberculosis} in some mouse strains housed under specific-pathogen-free conditions in a Northern climate,\textsuperscript{53} preimmunization such that there is an IL-4 response before challenge with \textit{M. tuberculosis} increases pathology and mortality in BALB/c mice.\textsuperscript{28,41,54,55}

#### ii) Impairment of effector functions

The increased susceptibility is likely to be due in part to impairment of effector functions.

**A) REGULATION OF INDUCIBLE NITRIC OXIDE SYNTHASE**

In addition to its roles in the toxicity of TNF and fibrosis, IL-4 also downregulates the expression of inducible nitric oxide synthase (iNOS)\textsuperscript{56} and drives an alternative form of macrophage activation with diminished antimicrobial efficacy,\textsuperscript{57} and so is potentially a regulator of the ability of macrophages to maintain \textit{M. tuberculosis} in the latent state.\textsuperscript{58} This might also explain the observation that apparently healthy healthcare workers whose CD8+ and γδ T cells produced IL-4 in response to \textit{M. tuberculosis} developed progressive TB within 2–4 years.\textsuperscript{59}

**B) INHIBITION OF APOPTOSIS**

Macrophages, alveolar macrophages\textsuperscript{60} and the THP-1 monocytic cell line\textsuperscript{61} infected with \textit{M. tuberculosis} can undergo apoptosis. TNF-α is involved in this process both in human macrophages\textsuperscript{62} and in macrophages from BALB/c mice.\textsuperscript{63} Since the apoptosis tends to be accompanied by killing of the contained organisms\textsuperscript{64,65} (whereas necrosis is not), this explains why treatment with neutralizing antibodies to TNF-α can cause reactivation of tuberculosis.\textsuperscript{3} Virulent \textit{M. tuberculosis} strain H37Rv induces substantially less macrophage apoptosis than the attenuated strain H37Ra.\textsuperscript{66} Low-level infection of human monocytes reduces the usual spontaneous apoptosis.\textsuperscript{67} Virulent \textit{M. tuberculosis} seeks to evade apoptosis by causing infected macrophages to release increased levels of IL-10, and increased levels of soluble TNF-α receptors, leading to formation of inactive TNF-α-TNF receptor complexes.\textsuperscript{66}

This strategy used by \textit{M. tuberculosis} to avoid apoptosis is likely to be enhanced by IL-4, because IL-4 downregulates expression of TNF-α in human monocytes/macrophages\textsuperscript{68,69} and increases the release of soluble TNF receptors.\textsuperscript{69}

**C) DOWNREGULATION OF TOLL-LIKE RECEPTOR 2**

IL-4 downregulates expression of, and signalling via, Toll-like receptor 2 (TLR-2).\textsuperscript{70} This TLR appears to be the dominant TLR in recognition of mycobacteria by the innate immune system.

**D) ENHANCEMENT OF TH1-INHIBITORY REGULATORY T CELLS**

A recent report suggests that IL-4 can preserve CD25+ regulatory T cells (T_{reg}), and enhance their function. If excessive regulatory T cell activity is blocking T cell effector function in TB, this function of IL-4 could be important.\textsuperscript{71} T_{reg} are discussed in greater detail below.

#### iii) Fibrosis

Moreover, despite modest effects on bacterial load even in BALB/c mice, knockout of the IL-4 gene markedly reduces fibrosis in a BALB/c model of pulmonary TB.\textsuperscript{75,76,77} Globally tuberculosis is the major cause of pulmonary fibrosis, and this needs explanation because IFN-γ downregulates fibrosis.\textsuperscript{73} On the other hand, IL-4 promotes fibrosis. This is a well-documented effect of IL-4, and has led to the ‘Th2 hypothesis’ of fibrosis in human pulmonary disease.\textsuperscript{73}

#### iv) Toxicity of TNF-α

Knockout of the IL-4 gene also markedly reduces the toxicity of TNF,\textsuperscript{72} which is another crucial but often ignored aspect of human TB. TNF is essential for protection,\textsuperscript{3} but has toxic effects in patients with progressive TB, in whom symptoms are alleviated by reducing TNF levels.\textsuperscript{74} In BALB/c mice, we have shown that the toxicity of TNF during tuberculosis depends on the presence of IL-4.\textsuperscript{72} The involvement
of IL-4 in the toxicity of TNF in inflammatory lesions dominated by Th1 cells has been observed in other infectious disease models, such as schistosome-induced fibrosis, *Trichinella* infection and fungus-induced pulmonary mycosis, and could explain the high mortality during treatment of TB in developing countries, where the IL-4 component is most prominent.

### 2.8 Regulatory T cells

Ultimately the balance between different effector mechanisms is likely to be controlled by the various subsets of regulatory T cell. These are involved in the regulation of Th1 and of Th2 responses, and of both protective and immunopathological mechanisms. There is evidence that background regulatory T cell activity is likely to be higher in citizens of developing countries.

There are many different types of regulatory T cell, probably with some overlap:

- CD25+ Foxp3+ Treg that usually require cell–cell interactions to inhibit
- Tr1 cells, that secrete high levels of IL-10
- Th3 cells that secrete high levels of transforming growth factor-beta (TGF-β), common in gut
- Th1-like Thet+, Foxp3+, interferon(IFN)-γ+, IL-10+ (suppress Th2)
- Cells generated in vitro in the presence of glucocorticoids and vitamin D3
- Regulatory forms of other cell types such as CD8+ and natural killer T cells (NKT) (+ regulatory cells that are not T cells, such as regulatory dendritic cells and regulatory macrophages).

There are almost no data on these cells in TB, whether in developing or developed countries, but there are a few provocative snippets of information.

The lymphoproliferative responses of blood lymphocytes from TB patients are often depressed, and there are ‘anergic’ TB patients who are tuberculin skin-test negative and whose T cells secrete the regulatory cytokine IL-10 but release little IL-2 or IFN-γ in response to *M. tuberculosis*. These IL-10-secreting cells could be TR1 regulatory T cells.

Meanwhile there are not yet any published data on CD25+ Foxp3+ Treg in TB, though several papers are in preparation or submitted at the time of writing.

However, whatever may be happening in the peripheral system, responses in the lungs of patients seem to be strong, implying that excessive regulation might not be the problem. Moreover many believe that the characteristic immunopathology of TB is mediated by the immune response, in which case the problem might be too little regulation (or the wrong type of regulation) rather than too much. Interestingly there is a report of T cells in the lungs of TB patients that secrete IFN-γ and IL-10, indicating that they might be the recently discovered regulatory T-cell subset that expresses both Th1 (a Th1-promoting transcription factor) and Foxp3 (a transcription factor associated with CD25+ Treg), rather than true Th1 cells. These Th1/Treg cells suppress Th2 responses, and might be beneficial in TB.

Logically, all we can say at this stage is that in TB there might be:

- The wrong type of regulatory function, leading to inappropriate activation of Th2: immunopathology due to Th1+IL-4+TNF-α as described earlier.
- Insufficient regulatory activity: immunopathology due to excessive Th1.
- Excessive regulatory activity that compromises essential effector mechanism: immunopathology due to a property of uncontrolled *M. tuberculosis*.

We cannot distinguish between these possibilities at present, and opinions differ strongly. In the figure we show putative helpful regulatory T cell downregulating Th2, and putative detrimental regulatory T cell downregulating Th1. We do not attempt to specify what type of regulatory T cell these might be. The data are not available. But when designing vaccines we clearly need to know what we are doing to regulatory T cell function.

### 2.9 Summary of differences between rich Northern countries and developing countries: a hypothesis

The development of better assays has led to the realization that IL-4 in the lungs is likely to be an important component of the pathogenesis of tuberculosis. This is evident with appropriately studied material from patients in the UK, but more importantly, the levels of IL-4 in tuberculosis patients in the countries where BCG fails are very high indeed, and can also account for other paradoxes such as early deaths, fibrosis, failure of Th1-mediated effector functions, and toxicity of TNF-α.

We suggest that in developing countries a background mixed Th1/Th2 response (section 2.3), attributable to environmental mycobacteria and, in some environments, to helminths, protects against low-dose challenge but not against high-dose challenge.
High-dose challenge can exploit the pre-existing IL-4 component (especially if Beijing strains are involved) and so corrupt the Th1 effector response for the reasons outlined above (section 2.7). In some individuals this corrupting effect is blocked by IL-4δ2 (section 2.6). This model leads to several conclusions:

- A vaccine that only boosts the Th1 response might not work in developing countries because progressive disease is not due to lack of Th1 but rather to high dose infection in the presence of Th2.
- A vaccine that is effective prophylactically will also be effective as a therapeutic vaccine because requirements for the two types of vaccine are similar.
- Controlling regulatory T cell activity is likely to be fundamental to solving the problem because T\textsubscript{reg} control not only the size of the response but also its nature.

3. THE SCREENING PROCEDURE USED TO SELECT VACCINES FOR CLINICAL TRIALS

Does the screening select candidates that will do what is required of a vaccine in a human popula-
tion? There are major differences between what we look for in mice when we screen vaccine candidates, and what we expect the vaccine to do in humans. This is worrying. Similarly, the immune status of the mice we use does not resemble that of the target human population. Finally we have been neglecting the mucosal route, and therapeutic vaccination.

3.1 Protection from disease vs. temporary attenuation of disease

When humans are infected with \textit{M. tuberculosis}, about 90% develop a latent infection (or no infection at all), with no apparent clinical consequences. The remaining 10% develop progressive disease. In countries where BCG vaccination is most protective, this 10% is reduced to 2% in vaccinated individuals, which constitutes 80% protection.\textsuperscript{20,21} In other words, 80% of the 10% who would have developed the disease, no longer do so after vaccination. This is true protection, but it is not how we screen vaccines in mice. We infect vaccinated and control mice with a dose of \textit{M. tuberculosis} that causes 100% of the animals to develop fatal disease, and then we hope that the vaccine candidate prolongs life, or reduces bacterial load. Even with the most effective vaccines, all of the animals die. Is this the right way to select...
a vaccine that will block the initiation of disease in humans?

3.2 The use of hypersusceptible immunologically naive mice

Vaccine candidates are tested using immunologically naive specific-pathogen-free (SPF) laboratory mice. These animals have few, if any, mature dendritic cells, and few memory T cells. As discussed in section 2.2, mice housed in equatorial countries and allowed microbial exposures similar to those of the people living in the same areas (discussed in section 2.3) are resistant to low-dose infection. They only develop progressive infection if challenged with high numbers of cfu, and this progression is always accompanied by striking expression of IL-4. Importantly, this sequence of events mimics human disease in the same latitudes (section 2.4).

3.3 Lack of partial immunity to a live vaccine that needs to replicate

The use of SPF mice introduces a further problem. The degree of immunity that mice in Brazil or Mexico have gained from their environment might be sufficient to impair replication of a live vaccine, and so diminish its efficacy. This provides one of the candidate explanations for the failure of BCG vaccine in developing countries (discussed in 86). This point is not addressed using SPF mice, despite its obvious relevance to a vaccine that will be given to subjects exposed to environmental mycobacteria, to BCG or even to subclinical TB.

3.4 The use of other animal models

The use of other models such as guinea pigs and monkeys is of some help, but similar objections can be raised. First, it might be a problem that all vaccines are first screened in inappropriate mouse systems. We cannot be sure that the right vaccines have gone on to further study. Secondly, the points raised in sections 3.2 and 3.1 apply equally to guinea pigs. Finally, it must be remembered that to do a statistically valid test of a protective vaccine, using Fisher’s Exact test to prove efficacy, a minimum of 12 monkeys must be used (6 per group), and all controls must develop disease, while all vaccinees must be protected. This result just achieves significance, but significance is lost if there is a single exception in either group.

3.5 Route of vaccination: improving efficacy by avoiding needles

In view of the obvious problems surrounding use of needles in the countries worst affected by tuberculosis and HIV, more emphasis should have been placed on models of vaccination via the gut or respiratory tract. The lungs are unusual, and receive T cells from both the systemic and mucosal immune systems. Therefore intradermal or intramuscular immunization clearly can result in increased immunity to tuberculosis. Nevertheless, there is evidence that a mucosal route could be more effective and safer.

**Oral**

Oral BCG is probably effective in man, but tends not to induce long-lasting delayed hypersensitivity, and this might have been seen as an indication of unreliability. Recently a recombinant fusion protein of Ag85B and ESAT-6 was given by gavage directly into the stomach in a mouse model. This was effective, particularly when used as a booster vaccine.

**Aerosol**

BCG administered by aerosol to guinea pigs was an effective vaccine.

**Intranasal: via the airways?**

Intranasal BCG vaccine is effective in mice. A single dose of BCG given intranasally protected better than subcutaneous vaccination in counterparts at both 3 and 6 months postvaccination. Similarly a recombinant adenovirus-based vaccine expressing Ag85A caused greater numbers of antigen-specific CD4+ and CD8+ T cells to appear in the airway lumen when administered intranasally. A recent study suggests that the BCG does not need to be living if given intranasally with a suitable adjuvant. However there may be a granulomatous response in the lungs that gives rise to worries about safety.

**Waldeyer’s ring**

It is not clear that intranasal vaccines always go to, or act via, the lungs. Much of the vaccine will go to the gut and to the ring of lymphoid tissue (‘Waldeyer’s ring’) that includes the tonsils and adenoids and ‘guards’ the gastrointestinal and respiratory tracts. The notion of a ‘common mucosal immune system’ is no longer acceptable. Priming an immune response in the gut, for instance, is a relatively poor way to prime a response in the airways, and vice versa. By contrast, responses evoked via Waldeyer’s ring home in on the airways and gut.

3.6 Therapeutic vaccines

As discussed in section 2.9 and in fig. 1, a successful vaccine might need to have therapeutic properties, but there has been little emphasis on seeking
such vaccines. Most vaccine candidates are inactive or even dangerous when administered therapeutically.\(^8\) As reported by Koch, injection of \textit{M. tuberculosis} antigens into infected animals can induce tissue damage.\(^{17,25}\) This is partly due to release of TNF-\(\alpha\) into lesions rich in both Th1 cytokines and IL-4.\(^{22}\) (A claim that DNA vaccines expressing mycobacterial antigens can also induce immunopathology\(^{39}\) is now thought to have been due to contamination with endotoxin.)

Three vaccine preparations have been found to be active therapeutically in mouse models without causing immunopathology: \textit{M. vaccae},\(^{100}\) a DNA vaccine encoding hsp65,\(^{101}\) and a liposome preparation of the cell-wall skeleton of \textit{M. tuberculosis} designated RUTI.\(^ {102}\)

Of these three, only \textit{M. vaccae} has yet gone into clinical trials, though the hsp65 DNA vaccine and RUTI are both ready for trials that might begin within one year in Brazil and Spain respectively. \textit{M. vaccae}, after failing in clinical trials of single doses, might have been effective as multiple intramuscular doses\(^ {103,104}\) and is now a licensed TB drug in China.\(^*\)

A major component of the mode of action of \textit{M. vaccae}\(^ {105}\) and of the hsp65 DNA vaccine\(^ {27,101}\) appears to be downregulation of IL-4. This recent increase in understanding also explains the variable efficacy of the hsp65 DNA vaccine in different studies. It may be most active in those models where the pathogenesis of the disease involves a large IL-4 component, and this is most frequent in mouse models in Brazil and Mexico (section 2.2). We are informed that the hsp65 DNA vaccine has never failed in mice in Mexico or Brazil.

In summary we suggest that vaccines that exert a therapeutic effect by downregulating Th2 responses (in addition to enhancing IFN-\(\gamma\) responses, which might or might not be necessary) should be a priority area for research. This might involve an understanding of regulatory T cell function, and the design of vaccines that manipulate one or more kinds of regulatory T cell.

4. WILL THE CURRENT TRIALS YIELD DATA THAT WILL ENABLE RATIONAL SELECTION OF A SUBSET OF CANDIDATES FOR FURTHER STUDY?

The status of current trials has been extensively reviewed by others.\(^ {106,107}\) We do not have access to the details of protocols that are being used or planned. However the information analysed above suggests that if the current phase I studies indicate safety and show boosting of the IFN-\(\gamma\) response to the antigens released by, or encoded by, the vaccine, this will indicate the \textit{possibility} of protective efficacy, but will not provide evidence for it. We suggest alternative strategies for monitoring trials in section 5.7.

5. SUGGESTED RESEARCH EMPHASIS AND NEW RESEARCH STRATEGIES

5.1 The study of geographical variation

(See sections 2.1–2.9 for background information.) In view of the geographical variation in immune status of the ‘at risk’ population (Dockrell HM, Black GF and Weir RE, personal communication) and of the patients themselves,\(^ {37}\) it is remarkable that few studies compare individuals in different environments using exactly the same methods. Such studies, comparing patients with healthy populations, should be a priority. It is unwise to design new vaccines without first understanding the nature of the problem and the reasons for the failure of BCG in the important target countries.

5.2 Screening of vaccines

(See sections 3.1–3.4 for background information.) Vaccines should be screened for their ability to protect from disease, not for their ability to attenuate disease. This now appears to be possible using mouse models where the breeding mothers are exposed to environmental mycobacteria (if required, the mothers could be exposed to helminths as well). This mimics the situation in the target countries. High dose challenge is required in these animals, and can be adjusted so that only a percentage of the animals develops progressive pulmonary TB. Relevant vaccines should increase this percentage. At present the microbiological aspects of these models are poorly characterized. The precise mycobacterial exposures that are taking place in animal houses in Mexico and Brazil need to be documented and standardized.

5.3 Route of vaccination

(See section 3.5 for background information.) Avoidance of needles should be a priority. There should be intensive study of the mucosal route, with particular emphasis on dissecting out the relative merits of:

- the airway
- the gut
- Waldeyer’s ring.

Strategies to differentiate experimentally between

\(^*\) http://www.longcome.com/longcome/english/index.htm?class=100&serial=English
Waldeyer’s ring and the other routes will need to be devised. Differences between human and murine Waldeyer’s ring function will need to be considered.

5.4 Is there a need for multiple vaccines?
(See sections 2.1–2.9 for background information.) Data from studies of geographical variation are likely to reinforce the view that several different vaccines will be required. In addition to the often-discussed need for ‘pre-exposure’, ‘post-exposure’, ‘pre-BCG’ (or BCG-replacing), and ‘post-BCG’ vaccines, we make the following points:

- **A vaccine for ‘mycobacterially naive’ subjects**
  This is the situation in Northern countries. The current vaccine candidates might be suitable for this purpose, though it is doubtful whether they will replace BCG.

- **A ‘booster’ vaccine for people with pre-existing IFN-γ responses**
  The current candidate vaccines for developing countries are likely to boost IFN-γ responses, but we do not know if this will increase the rates of protection. Similarly and for two reasons, we do not know if such a vaccine will benefit the small percentage of the population in developing countries that does not already have an IFN-γ response:
  - Some of these rare people belong to the subset who eliminate *M. tuberculosis* without developing T cell memory. This is presumably a result of an innate immune mechanism, and for this reason these people should be studied, but they do not need to be immunized.
  - Others in this group have immunological defects or polymorphisms and it might not be possible to vaccinate them.

- **A therapeutic vaccine for people with pre-existing IFN-γ and IL-4 responses**
  It was argued in section 2, that a vaccine that only boosts the Th1 response might not work in developing countries because progressive disease might not be due to lack of Th1 but rather to high dose infection in the presence of Th2. Vaccines that have the ability to downregulate existing Th2 responses are feasible, and this property can be combined with the boosting of Th1. This is expanded in the next section.

It is possible to envisage vaccination regimens that are tailored to the target population.

5.5 Therapeutic vaccines
(See section 3.6 for background information.) Three therapeutic vaccines have entered, or are about to enter, clinical trials. The advantages of this approach include:

- Efficacy trials relatively simple and quick.
- As discussed above (section 2.9) and illustrated in fig. 1, theoretically these might also be the most effective prophylactic vaccines.

Since candidates are ready for trial, WHO should attempt to encourage and facilitate the initiation of these studies.

5.6 Understanding and then harnessing regulatory T cells
(See section 2.8 for background information.) There is currently almost no knowledge of regulatory T cells in TB. Research in this area is lagging behind research on regulatory T cells in other diseases. This is tragic because immunology is ultimately about immunoregulation. We need to know:

- Which types of regulatory T cell are beneficial in TB, and which are detrimental.
- Whether TB is due to too much, too little, or the wrong type of regulatory T cell activity.
- If the ‘high-IL-4’ TB seen in developing countries where BCG fails is due to a disorder of regulatory T cell balance.
- Whether there are distinct subsets of antigens in *M. tuberculosis* with a tendency to drive particular types of regulatory T cells. If so, this will influence the choice of antigens for inclusion in vaccines.

In normal people and contacts, the research can use peripheral blood. For patients, lung cells should be used because suppression in the peripheral system is not necessarily matched by suppression in the lungs.

Adjuvants that enhance specific types of regulatory T cell are beginning to emerge from work on chronic inflammatory disorders such as allergies and autoimmunity that are common in rich countries. TB research can benefit from this work, and such adjuvants are likely to be integral components of future successful TB vaccines that will need to upregulate some arms of the response to *M. tuberculosis* while downregulating others.

5.7 Parameters to be studied in human vaccine trials
A major problem for ‘proof-of-principle’ trials in man is our poor understanding of the effector mechanisms that control TB. All we have is the belief that they are associated with Th1 responses. Attention is turning away from oxygen reduction products, and towards bactericidal peptides and obscure side
effects of apoptosis of infected macrophages. This ignorance makes it very difficult to devise definitive correlates of protection. The studies of IFN-γ production we are currently using are unlikely to be reliable for this purpose. Other issues that will need to be studied include:

- **Memory and effector T cells**
  There is little understanding of the significance of ‘effector memory’ cells (EM) or of ‘central memory’ cells (CM) in relation to immunity to TB. The new IFN-γ assays using ELISPOT or ELISA after short incubation with ESAT-6 and CFP-10 might be measuring EM, but even this is not proven. It is thought that EM are relatively short lived in the absence of a continuing source of antigen, so long-lived immunity will probably rely on CM, but this is not certain either, and these cells are more difficult to quantify.

- **CD4 versus CD8**
  The importance of CD8+ cells in immunity to TB in man is unknown, but probable.

- **CD1-restricted cells that recognize non-protein antigens**
  Again the importance of these cells is unknown. In view of our current lack of certainty about the crucial effector mechanisms, this area should be pursued.

- **Regulatory T cells**
  Eventually we might be able to look at the pattern of regulatory T cell response to *M. tuberculosis*, and this might indicate the type of effector response that will dominate after challenge. This should include screening for release of IL-10, TGF-β, etc.

- **IL-4/IL-4R**
  Screening for disappearance of the IL-4 response (sections 2.5 & 2.7), or its replacement with IL-4R (section 2.6), might be important, but this remains speculative.

**Strategy**

Clearly this is an area of ongoing, rather early-stage, research, and we do not yet have the appropriate tools. It might be useful to think in terms of one or more standardized microarrays that would indicate the ex vivo state, and the pattern of response after challenge of peripheral blood cells in vitro, preferably with live *M. tuberculosis*. Such technology could be applied to phase I or phase I/II studies in a standardized manner.

**5.8 Conclusions**

It is not yet certain that we have made progress towards designing vaccines that will work in places where BCG vaccine fails. Boosting IFN-γ responses might be useful in a few localities, but will not be sufficient. We need to place much more emphasis on:

- geographical differences
- screening models that mimic the immune status of human populations most in need
- the rapidly growing knowledge of immunoregulation (regulatory T cells).

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