Global Tuberculosis Programme

The Global Tuberculosis Research Initiative: Research to Make a Difference

Dr Paul Nunn, Ms Jennifer Linkins
Global Tuberculosis Programme, WHO, Geneva

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CONTENTS

1. Executive Summary ................................................................. page 1
2. Introduction: the Global Tuberculosis Research Initiative ............... page 3
3. The background to the Global TB Research Initiative ........................ page 4
4. The aims of this paper ............................................................. page 5
5. The epidemic: current status and future trends .............................. page 5
6. Controlling the epidemic ........................................................ page 7
7. Why does the burden of TB Persist?  
    An analysis of research needs ................................................. page 9
8. TB research today ................................................................. page 11
9. Conclusions and next steps .................................................... page 15
   Figure 1 ................................................................. page 17
   Figure 2a, Figure 2b ....................................................... page 18
   Figure 3 ................................................................. page 19
   Table 1 ........................................................................ page 20
   Figure 4 ................................................................. page 21
   Annex 1 ................................................................. page 22
   Annex 2 ................................................................. page 24
   References ................................................................. page 28
1. Executive Summary

Tuberculosis kills more adults than any other single infectious disease, and the epidemic is worsening. As an international public health authority the WHO, through its Global Tuberculosis Programme (GTB), has a responsibility to promote the equitable and rational use of the world’s TB research resources to achieve the greatest possible health gains in TB control. In 1997, therefore, GTB set in motion a Global Tuberculosis Research Initiative (GTRI) to assess global research needs and identify priorities for reducing the epidemic. The initiative is a consultative exercise involving a broad range of external specialists. This position paper represents GTB’s initial contribution to the exercise.

Background to the Initiative

GTB set up the Initiative following publication of the report of the WHO Ad Hoc Committee on Health Research Relating to Future Intervention Options (4). The Ad Hoc Committee showed that funds for the world’s health research are often allocated in a non-rational and inequitable manner, with the major health problems of the poor majority attracting only minimal funding. The Ad Hoc Committee recommended an analytic process to help decision-makers to allocate resources rationally. This process consists of measuring the scale of the health problem; understanding why the disease burden persists (for example because of lack of tools or failure to use existing tools efficiently); and agreeing a new research agenda to meet the needs identified, taking account of what is being done already about the problem and how likely the proposed research is to result in a useful outcome. The aim of the GTRI is to begin applying similar logic to the specific problem of TB.

The status of the epidemic

Every year, 7 million to 8 million people develop TB. In contrast to most communicable diseases, the burden of TB is expected to grow in the next two decades with the risk that, with no extra effort to control it, there will be 10 million new cases per year by 2020. The spread of HIV-related TB and of multidrug resistant strains of Mycobacterium tuberculosis are particular causes for concern.

The impact of TB control efforts today and their potential for slowing the epidemic

WHO’s recommended strategy to control TB is known as DOTS: Directly Observed Treatment, Short-Course. This five-point strategy, described in section 6.1 below, brings together the results of previous decades of work into a practical approach to TB control that represents current international best practice. In studies in Asia and Africa, DOTS has been shown capable of curing 80 to 90 per cent of patients, and is also highly cost-effective, costing only $1 to $3 per year of life saved in low-income countries. Models developed by GTB suggest that the DOTS strategy has the potential to significantly reduce the size of the TB epidemic: if WHO targets for case detection and cure rates could be met by the year 2000, the global burden of this disease could be cut by more than one-third over the next two decades and 32 million deaths could be averted using the DOTS strategy alone.
Why does the disease burden persist?

However, despite the existence of the DOTS strategy, the TB epidemic remains. In line with the Ad Hoc Committee’s approach, GTB has made a preliminary analysis of the reasons, as a means of identifying research needs.

*Poor use of existing tools.* Clearly, a major factor is the failure to use DOTS, the principal existing tool, as widely as possible. Worldwide, DOTS is reaching only a fraction of those who need it. Ninety-four of the WHO's 212 member states have implemented DOTS, and within individual countries, implementation is often uneven. For example, of the total global estimate of TB cases for 1996, only 12 per cent were notified by DOTS programmes. These low coverage rates can be explained largely by the low political priority accorded to TB, and the consequent underfunding of efforts to control it. In addition, certain technical limitations of DOTS, such as the length of the treatment period, may weaken patients’ adherence to therapy.

*Lack of tools.* Another reason for the persistence of TB is the simple lack of more effective tools, such as better drugs and vaccines. DOTS alone cannot prevent the development of TB in those already infected with *Mycobacterium tuberculosis*. Even if the WHO global targets for case detection and cure rates are met by the year 2000, it will take two to three decades for incidence to fall to a rate of 2 million people per year.

*Lack of knowledge.* Finally, some of the burden of TB persists because of a lack of knowledge. For example, the impact of drug resistance on treatment is not fully understood; nor is it clear exactly what constitutes immunity to TB in humans, a factor that may delay the development of a TB vaccine. More knowledge may be needed, therefore, before new or better interventions can be developed.

**Research needs identified**

From this preliminary analysis, the following research needs are apparent:

- research to widen the implementation of DOTS, using health policy research to understand the current constraints better and, according to what is learnt, operational research to improve delivery;
- the development of new tools to control TB--specifically tools that will be appropriate for the needs of poorer populations;
- research to provide the knowledge base for further or better interventions.

**Existing research**

The WHO Global TB Programme has set out to determine what research is being done on TB already and whether, and to what extent, this research fits the needs identified above. The Programme conducted a preliminary survey of the major research agencies to determine how much they spent on TB research in one year. Using the findings of the survey and drawing also on analyses conducted by the Ad Hoc Committee, the programme found that:

a) global resources for research on tuberculosis are disproportionately small compared to the share of the global disease burden;
b) within existing funds for TB research, the areas of activity that attract most resources are (i) the expansion of the biomedical knowledge base and (ii) the development of certain classes of new biomedical tools; the area that attracts least resources is research to improve existing tools, in the health policy sciences and operational research.

Conclusions

The Global TB Programme concludes that:

1. The TB epidemic is among the world’s greatest health problems and is worsening.
2. The DOTS strategy has the potential to reduce the TB burden by more than one-third in two decades if properly and rapidly implemented. However, at present only 12 per cent of those who develop TB are being notified by DOTS programmes.
3. According to the preliminary analysis of research needs conducted by GTB, a significant portion of the burden of TB persists because of failure to use DOTS as widely as possible. A further portion of the remaining burden may be attributed to a lack of new tools, and a further portion to a lack of knowledge needed to develop further, or better, tools. This suggests the need for several new research agendas:
   a) research to improve the implementation of DOTS;
   b) the development of new tools specifically geared to the needs of low-income countries; and
   c) strategic research to provide the knowledge base for further and better interventions.

4. Resources for TB research overall are disproportionately small compared to the burden of the disease. An overall increase in resources will be essential to expand research and development activities to meet the needs identified.
5. Using this position paper as a basis for discussion, the participants in the Global Tuberculosis Research Initiative should discuss and reach agreement on unmet research needs, on the relative priority to be accorded to each of those needs, on the rationale for formulating a new research agenda, and the process for doing so.

2. Introduction: the Global Tuberculosis Research Initiative

Tuberculosis is the leading infectious killer of adults worldwide. As an international public health authority concerned with TB control and research on a global level, the WHO, through its Global TB Programme, has a responsibility to the resource-poor populations where the majority of the disease burden is concentrated. That responsibility includes working with the agencies that invest in TB research to promote the most equitable use of their resources for improving health by TB control.

Therefore, the Global TB Programme has during 1997 set in motion a Global Tuberculosis Research Initiative (GTRI) to identify priorities for reducing the burden of TB worldwide. The initiative is a consultative exercise involving a wide range of external specialists, including researchers and practitioners in public health and industry, health authorities in high-prevalence countries, such as national TB
programme managers, and representatives of funding agencies. The first meeting to discuss the process for this initiative will take place in March 1998.

The aims of the initiative may be summarised as follows:

- to establish a process to develop and sustain a focused and prioritised global research agenda that takes account of the needs of populations at risk from TB and national TB programmes;
- to set up the framework of analysis and discussion of TB research which will be required to support this agenda;
- to make the best use of resources, to coordinate the efforts of stakeholders, and to increase financial support for tuberculosis research worldwide.

3. The background to the Global TB Research Initiative

Within the past few years, there have been a number of attempts to review global health needs and priorities for health research. The reviews emerged from the observation that the world’s health research funds are allocated unevenly, with approximately 95 per cent of resources being devoted to health problems that primarily affect the rich populations of the world, and only 5 per cent being devoted to the health problems of the poor majority (3).

The most recent review was conducted between 1994 and 1996 by the WHO Ad Hoc Committee on Health Research Relating to Future Intervention Options (4), referred to in this paper from here on as the Ad Hoc Committee. The Ad Hoc Committee attempted to develop transparent, rational and equitable criteria for assessing research priorities. These were set out in terms of a five-step process to aid governments and other funding bodies in deciding how to allocate resources:

1. calculate the burden of the condition or risk factor, such as respiratory infections or tobacco use, on the given population;
2. identify the reasons why the disease burden persists, for example, because of failure to use existing tools efficiently, lack of tools, and/or lack of knowledge;
3. judge the adequacy of the current knowledge base;
4. assess the promise of the R&D effort; and
5. assess the adequacy of the current level of R&D effort.

The Ad Hoc Committee thus aimed to develop a framework for informing decisions about how to allocate resources, based not only on the relative scale of different health problems (such as tobacco use or malaria) but also considering the balance of different types of research needed on each problem: whether primarily to gain knowledge (strategic research), or, where that knowledge already exists, to proceed with putting products or other interventions to use and evaluating their effectiveness (intervention development and evaluation). In addition, the process was designed to help funding bodies and their scientific advisers to assess the relative weight that might be given to each discipline of research in each area, according to the nature of the problem. The Committee’s framework clustered the wide range of disciplines involved in health research into three groupings: the health policy sciences, the population sciences (taken to include epidemiology and the behavioural sciences) and the biomedical sciences.
The GTRI was set up, following the Ad Hoc Committee’s report, to apply similar logic specifically to tuberculosis. The terminology and definitions adopted in this position paper therefore correspond broadly with those adopted by the Committee; the Committee’s definitions are reproduced here, for ease of reference, in Annex 1.

The initiative is not, of course, the first attempt to draw up research priorities within the TB field. In the past dozen years or so, a range of different agendas, some interdisciplinary, some specific to biomedical TB research, have been identified, by researchers themselves, by representatives of funding agencies and by WHO (Annex 2). While all of these agendas have been valuable in generating ideas and helping to sustain a TB research community, the varying criteria on which they were based have usually been left implicit and the focus has often been too narrow to include all stakeholders. In some cases, there has even been a perceived conflict between agendas—for example between biomedical research and short-term operational research to improve the efficiency of existing tools. One aim of the GTRI is to assess TB research needs across all scientific disciplines, with the participation of all stakeholders. By applying more explicit criteria for analysing research resources, such as those suggested by the Ad Hoc Committee, it is hoped that the process of priority-setting can be made as transparent as possible.

4. The aims of this paper

This position paper is put forward by the WHO Global TB Programme (GTB) as a contribution to the consultative exercise. The paper is seen by the programme as a first step in the analysis of research needs and the degree to which current efforts reflect those needs. It draws on the approach for rational resource allocation set out by the Ad Hoc Committee. It is intended to stimulate discussion at the first meeting of the GTRI where the views of all partners in the initiative will be shared and debated.

5. The epidemic: current status and future trends

5.1 Epidemiological estimates

Every year, 7 million to 8 million people develop TB. Estimates of the annual number of deaths from the disease range between 1.9 million (5) and 2.9 million (6). While more precise estimates are clearly desirable and are currently being prepared, the conclusion remains that TB kills more adults than any other single infectious disease.

The regions worst affected by TB are South and East Asia and Sub-Saharan Africa; estimates by GTB suggest that there are more than 1 million deaths in South and East Asia and three-quarters of a million deaths in Africa each year from the disease (6). However, no region is free of TB. Within Europe, for example, the formerly socialist states are particularly severely affected. Poverty, and widening gaps between rich and poor in many populations, are important allies of the disease.

Over the past 20 years, the actual number of new cases of TB each year has risen (6). This is partly explained by growing populations in the regions of highest incidence and an increase, due to population aging, in the number of adults relative to children. The spread of HIV has further fuelled the TB epidemic, and an additional complication has
been the spread of drug-resistant strains of TB, although the impact of this factor on the global epidemic has yet to be fully quantified. Because of their particular importance, the effects of HIV and of drug resistance on the epidemic are further discussed in sections 5.2 and 5.3 below.

On present trends, the number of new cases of TB each year is set to rise to 10 million by 2020. As the number of young adults in the low-income and middle-income countries continues to grow in the coming decades, the number of cases of TB is likely to increase. This demographic trend, combined with the impact of HIV, could bring the number of deaths from TB to more than 3 million a year by 2020. By contrast, other major infectious killers, such as pneumonia and diarrhoeal disease, which mainly affect young children, may become less common, partly for demographic reasons and partly because of other factors.

5.2 HIV and TB

An estimated 30 million people are infected with HIV worldwide, of which about half are co-infected with M. tuberculosis. The impact of HIV on the global TB epidemic has become increasingly clear in recent years. Whereas a person infected with M. tuberculosis normally faces a lifetime risk of about 10 per cent of developing active TB, cohort studies in various countries, including Italy, Rwanda, Spain, the USA and Zaire have shown that the annual risk of developing active TB in a co-infected person ranges from 5 per cent to 15 per cent per year, depending on the degree of immunocompromise. There is also good evidence that HIV infection favours rapid progression from exposure to M. tuberculosis, through infection, to active TB, with disease developing over weeks rather than years. Numerous studies have shown that people with TB are more likely to be infected with HIV than other groups in the general population.

From a different perspective, TB is the most important opportunistic disease observed among HIV-infected people in Africa, because it is very common, transmissible to everyone, and life-threatening. In clinical surveys and autopsy studies in Ivory Coast, Tanzania, Zaire and Zimbabwe, as many as 54 per cent of patients with HIV infection or AIDS had TB. TB is now the leading cause of death in people with HIV/AIDS worldwide.

The burden of TB that is projected to be associated with HIV up to 2020 is shown for each region in Figure 1.

As well as increasing the numbers of people sick with TB, HIV complicates the diagnosis of this disease. The number of undetected cases may rise and hence increase opportunities for the transmission of infection. Co-infection also makes treatment more difficult. People with both HIV and TB suffer increased side effects from TB drugs, especially when thiacetazone is used. Rates of death and disease recurrence are higher in co-infected people.

5.3 Resistance to drugs

Like other bacteria, M. tuberculosis is capable of developing resistance to antimicrobial drugs. Drug-resistant mutants arise naturally but poor treatment regimens select them out. Such strains affect not only those individuals who have already received ineffective treatment (acquired resistance) but can also arise in previously untreated individuals (primary resistance). Multidrug-resistant (MDR) strains have spread particularly efficiently in HIV-infected people, often in hospital outbreaks.
Once infected with MDR strains, individuals become more difficult to cure and their treatment also becomes much more costly: in the US, for example, treatment costs rise at least tenfold (6) in low-income countries (where annual per capita health spending may be $7), estimates suggest that the cost of the drugs alone is likely to rise to between $1000 and $3,500 per patient, the higher figure applying to cases where a person is infected with strains resistant to all five common drugs.

Until recently, it was believed that multidrug-resistant strains of TB (MDR-TB) were relatively rare outside the industrialised countries. However, recent WHO data (9) indicate that MDR-TB is ubiquitous and that its prevalence is particularly high in the former Soviet states, India, the Dominican Republic and Argentina. It is not yet known whether or not the prevalence of MDR-TB is rising; nor is the impact of MDR-TB on control efforts fully elucidated.

6. Controlling the epidemic

6.1 International best practice: the impact of DOTS

The range of strategies currently available to prevent and treat TB includes active case-finding, vaccination with Bacille Calmette-Guérin (BCG), environmental controls and preventive chemotherapy. However, current international best practice is encapsulated in the strategy recommended by WHO and known as directly observed treatment, short-course (DOTS). DOTS brings together decades of work by many different teams and partnerships between control programmes and researchers into a practical approach to TB control. It consists not merely of directly-observed treatment but of a five-point policy package (10):

- government commitment to a National Tuberculosis Programme;
- case detection through sputum smear microscopy examination of TB suspects attending general health services;
- directly-observed, standardised short-course chemotherapy to, at least, all smear-positive TB cases under proper case management conditions;
- regular, uninterrupted supplies of all essential anti-TB drugs; and
- monitoring system for programme supervision and individual patient outcome evaluation.

The essential features of the DOTS strategy were brought together in the 1980s by Dr Karel Styblo, first in Czechoslovakia, then at the International Union against TB and Lung Disease (11). In 1995 the components of DOTS were unified as the DOTS strategy by WHO and promoted intensively.

The DOTS strategy has been shown to be highly effective in a number of different settings. For instance, treatment success rates of more than 90 per cent have been documented in a Chinese study involving 112 000 people (12) and, since the study, more than 500 000 Chinese patients have been treated with similar success. The high cure rate maintained in Tanzania (13), despite the HIV epidemic, and the increase in successful treatment in Malawi after years of decline (14), suggest that DOTS works equally well in entirely different situations. The evidence is further strengthened by results from Bangladesh (14), where high cure rates were achieved, and from national TB programmes in Morocco and Peru, which have both achieved consistently high cure rates for a number of years, together with a reduction in case notifications.
A worldwide evaluation of the performance of national TB programmes by GTB also suggests that overall, countries that had already adopted DOTS in 1994 cured 76 per cent of new cases registered in that year (16). This means, in effect, that three out of every four TB patients with access to DOTS are definitely cured and will not spread the infection further. By contrast, in programmes not using DOTS, only two out of four patients on average are cured while the remaining two die, fail treatment or interrupt treatment before being cured. Thus, if all TB patients had access to DOTS today, the direct impact would be a substantial cut in the death rate from the disease, resulting in 2 million deaths per year averted.

DOTS has also been shown by health economists to be highly cost-effective; in three sub-Saharan African countries the average incremental costs per year of life saved were around $2 for short-course chemotherapy with hospital admission and around $1 for ambulatory therapy (16). This compares favourably even with other highly cost-effective interventions such as measles immunisation or oral rehydration therapy. (For low-income countries, most health economists consider any intervention that costs less than $25 per year of healthy life saved to be cost-effective (1)).

6.2 Who receives DOTS today?

At the end of 1997, 94 of the WHO's 212 member states had adopted DOTS. However, coverage of the population within these countries may not be extensive. According to the Global TB Programme's most recent assessments, only some 12 per cent of those people who develop smear-positive TB each year are notified by DOTS programmes (17). It is not clear what type of treatment the remainder of patients receive, if they receive treatment at all. Although an increasing number of countries are now adopting DOTS, the rate of growth is slow.

6.3 What DOTS could achieve with wider use

In 1991, the World Health Assembly set global targets for the control of TB by the year 2000. These were as follows:

- to detect 70 per cent of existing cases of sputum smear-positive TB.
- to cure 85 per cent of detected new cases of sputum smear-positive TB.

Models have been developed for GTB to assess the probable impact of meeting these targets by the year 2000 and at later dates, both globally and by region. The models take account of population growth, the pace of socioeconomic development, the quality of current TB control programmes and the scale of HIV epidemics in each region. To date, they do not explicitly take account of the spread of drug-resistant strains of M. tuberculosis.

The models suggest that, if the WHO targets could be met by the year 2000 as desired, using DOTS, the incidence of TB would fall in all regions, and that worldwide about 71 million cases, and 32 million deaths, could be averted over the next two decades. This is equivalent to more than one-third of the total global burden of TB (6). If these targets are not reached until 2010, some 28 million extra cases of TB and 14 million extra deaths are likely in the next two decades. Under a more pessimistic scenario, which assumes that no extra effort is put into TB control in the immediate future, the burden of cases and deaths will continue to grow to 10 million cases per year worldwide by 2020 (see Figure 2).
The models also show the projected numbers of new cases of TB per year under these same scenarios in each WHO region (see Figure 3).

7. Why does the burden of TB persist? An analysis of research needs

In order to begin the process of identifying research needs, GTB has made an initial assessment of the reasons for the persistence of the TB burden, following the process advocated by the Ad Hoc Committee and summarised above. This consists of analysing whether a given disease persists because of failure to use existing tools to the full (for example, if coverage is poor); because of a lack of tools; and/or because of a lack of knowledge. The discussion below is clearly a first step in this process, and more detailed analysis will be required as part of the GTRI.

7.1 Inadequate use of existing tools: a need for wider implementation of DOTS

DOTS has now been adopted by 94 of the WHO's member states. However, as discussed above, only 12 per cent of those who develop TB each year are notified by DOTS programmes. Thus, DOTS is not being used widely within countries that have adopted it. A few of the constraints to wider use are discussed below, in outline form, as a stimulus to a more detailed debate about the agenda for research to close the gap between the actual and potential impact of DOTS.

7.1.1 Socioeconomic constraints

Economic, social and political factors are major obstacles to the wider use of DOTS. Underfunding is an obvious problem. Some developing countries' governments spend as little as $7 per head on health care each year. In such situations, government health workers may be unable to obtain a regular supply of drugs and diagnostics, people are likely to seek healthcare elsewhere or not at all, and the number of cases that go undetected is likely to rise. A second challenge is health system reform, which may result in piecemeal introduction of user charges, reorganization of service delivery and other changes that may sometimes adversely affect TB control programmes. A third difficulty, particularly in low-income countries, is the poor motivation of health workers, most of whom are poorly paid. In some cases, health workers can survive only with informal payments from their patients or by conducting additional, private, practice. This may create disincentives to best practice. A fourth problem is that some governments do not see TB as a national problem but one to concern only the international agencies that combat the disease. If TB programmes are reliant on external funding, for example from donors, rather than government support, they may be difficult to sustain in the long term. Fifth, not all physicians are enthusiastic in implementing DOTS. Some prefer to emphasize individual clinical judgment, while others may feel threatened by the fact that the strategy can be delivered by less highly qualified workers. Sixth, TB is socially tolerated and seen as inevitable in some societies. In such cultural contexts, there is unlikely to be a zealous commitment to reducing the burden of the disease.

7.1.2. Technical constraints

At the individual level, there are practical difficulties with the treatment component of DOTS itself that may deter patients' adherence to therapy. There is as yet no single combined formulation on the world market that contains all the necessary ingredients of the standard effective chemotherapy in one tablet. Moreover, the course of
treatment, while shorter than in the past, still takes at least 24 weeks, which may discourage adherence in any patient, regardless of education, income or gender. For the poorer and more disadvantaged groups within a community among whom the incidence of TB is greatest, the inconvenience, cost and stigma associated with travelling or taking time off work for treatment over this long period may prove particularly serious barriers to adherence. The length of treatment also creates problems for staff, particularly where personnel are expensive or difficult to train, where patients are widely dispersed over a large rural area, or where populations are transient, as in many inner cities. In addition, diagnosis is hampered by a low index of suspicion on the part of many health workers, and a diagnostic test with low sensitivity, which demands an onerous series of patient-health worker intervention for the diagnosis to be made.

Additional challenges include the diversity of settings in which DOTS must be delivered and the need to adapt the strategy for varying local conditions. More efficient delivery systems need to be designed, for example through the use of existing community organisations or private practitioners.

7.2 Lack of tools: a need for new disease control technologies

Models developed within the Global TB Programme indicate that, even if WHO targets for case detection and cure rates are met by 2000, DOTS will be unable to prevent some two-thirds of the TB deaths expected between now and the year 2020 (6). DOTS alone cannot prevent the development of TB in those already infected with *Mycobacterium tuberculosis*. After full implementation of the strategy, incidence will fall over two to three decades, eventually reaching a rate of 2 million people per year continuing to develop the disease unless other strategies become available. Other tools such as vaccines to prevent the reactivation of disease are therefore needed.

7.3 Lack of knowledge: a need for better interventions

To fully implement DOTS, and to develop additional new tools, new information will be needed. This new knowledge base, the foundation for improved interventions, will require strategic research in a number of fields. For example, there may be a need for strategic health policy research, to establish whether certain organizational structures enable more effective deployment of DOTS than others. Equally, strategic biomedical research may be needed, for example to determine what constitutes immunity to *M. tuberculosis* in humans, as a step towards the development of new vaccines. Similarly, strategic epidemiological surveillance and clinical research may be necessary, for example to establish the prevalence of multidrug-resistant strains in a country and the extent to which these strains reduce the effectiveness of DOTS.

7.4 Summary of research needs

The needs analysis above suggests a broad range of research efforts should be pursued, with apparent priorities summarised as follows:

a) in the short term, research to widen the implementation of the DOTS strategy. Researchers must establish clearly why the DOTS strategy has not been implemented in various settings, and then apply the findings to improving delivery strategies and policies for its success. This research agenda, to be discussed by stakeholders in detail, is likely to focus on strategic policy research and behavioural research, and on operational research to evaluate and improve the delivery of the DOTS strategy.
b) in the medium and longer term, research to develop new tools to prevent and treat TB in the populations where the burden of the disease is greatest. This need will be met only with the help of a focused strategic biomedical research agenda to provide the base of underpinning knowledge. Critically, however, the new tools must be appropriate for the budgets and conditions of low-income countries where the burden of TB is greatest.

Clearly, these broad areas of need, and others that may yet be identified, will require more analysis and investigation by the GTRI. It is hoped that the participants in the initiative will discuss and agree on methods for assessing these (and other) research needs in greater detail.

8. TB research today

According to the process recommended by the Ad Hoc Committee, the development of a prioritised research agenda requires an assessment of existing research activities in TB and of the degree to which these activities do or do not match the research needs identified above for:

a) improving the use of existing tools,
b) developing new tools and
c) gaining new knowledge.

As a preliminary exercise, the Global TB Programme has begun this process with a survey to find out how much the major public-sector players and the foundations spent on TB research in 1995, and how they spent it. The GTRI may wish to include a more detailed analysis.

8.1. Spending on TB research

In 1997, GTB conducted a preliminary survey of major public and non-profit research funders to seek information about their spending on all aspects of TB in 1995. The Programme first identified the largest funding agencies in research, and asked each to report back on their levels of spending in TB-related research. Spending by the private sector has been more difficult to assess and has not been addressed so far.

Seventeen publicly-funded agencies and foundations reported TB-related expenditure in 1995, to a total of $92 million, with the results are summarised in Table 1. In 1995, the largest public investor by far in TB research was the US National Institute for Allergy and Infectious Diseases (NIAID), one of the institutes of the National Institutes of Health (NIH). NIAID increased its investment from $3 million in FY 1990 more than elevenfold by 1995, mainly for competitive extramural awards and in part by redirecting funds for HIV/AIDS research. About half of the awards made for TB research in 1995 by NIAID were linked to HIV/AIDS grants. Of the five highest spenders the remaining four were, in descending order, other institutes within the National Institutes of Health; the US Centers for Disease Prevention and Control (largely through AIDS-related funds), the Medical Research Council of South Africa, the Medical Research Council of the UK, and the Robert Wood Johnson Foundation in the US.
GTB has no systematic data on investment in TB research by the private sector. However, Glaxo-Wellcome's Action TB initiative is one well-known programme, in which $16 million has been made available over 5 years in a collaboration between researchers in the company and within the UK, Canada and South Africa.

For a meaningful assessment of the importance accorded to TB by the world's health research funding bodies, it is obviously important to know what these bodies spend on health research overall, so that TB research funds can be assessed as a proportion of that overall spending. GTB has not been able to make its own assessment of the world's total research spending in 1995, but the Ad Hoc Committee's own recent review, using 1992 data, estimated that a total of $56 billion was spent on all health research worldwide in that year, of which 0.2 per cent was estimated to have been spent on TB research \(^1\). By comparison, 3 per cent of the burden of disease worldwide is due to TB. While few would suggest that all research funding should be rigidly allocated in direct proportion to the scale of disease burden and without consideration of other factors, such a stark mismatch between need and activity suggests that resources are not being allocated in a rational manner.

Future trends are difficult to predict. Following rapid growth in research resources during the early 1990s, the stability of the US government's funding for TB research is uncertain. Since this area of research is not earmarked by Congress, and given the public perception that TB has been contained in New York City and other urban "hotspots" in the US, it is possible that research funding for the disease will fall in the near future.

8.2 Spending on TB research by type of activity

In an effort to assess the balance of R&D activity in tuberculosis and the extent of its match or mismatch with the identified research needs, GTB also sought information about institutions' relative spending on different areas of research (for example health policy research or biomedical research) and activities (for example vaccine development, clinical trials, operational research)\(^2\).

Because different institutions use different terminologies, and some use none at all, the information on research categories must be handled with caution. Clearly, certain institutions have defined objectives that restrict their research to particular disciplines, for example to biomedicine, but others, including some government agencies, have a wider interdisciplinary remit.

The breakdown of spending is shown in Figure 4. It is important to note that, with the exception of the National Institute of Allergy and Infectious Diseases, GTB was unable

\(^{1}\) The preliminary research spending exercise did not use the terminology adopted by the Ad Hoc Committee (see Annex 1) but instead asked institutions to report on spending on the following categories: "basic research, vaccines, discovery of new drugs, new diagnostic agents, clinical trials, epidemiological studies, operational research, health policy research, and non-classified research". For the purposes of this position paper, these categories correspond approximately to the Ad Hoc Committee's terminology as follows:

<table>
<thead>
<tr>
<th>The health sciences</th>
<th>Types of health research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biomedical</td>
<td>basic research, vaccines, discovery of new drugs, new diagnostic agents</td>
</tr>
<tr>
<td>Population (Behavioural) Sciences</td>
<td>epidemiological studies</td>
</tr>
<tr>
<td>Health Policy Sciences</td>
<td>health policy and systems research</td>
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</table>
to obtain categorised spending information from the institutes of the National Institutes of Health, yet their spending amounted to nearly one-third of the total assessed.

GTB has analysed this spending to provide an initial guide to the extent that current research activity matches the needs described in Section 7 above—that is, how much of it is aimed at a) wider use of existing tools; b) development of new tools; or c) new knowledge as the basis for better interventions.

By this analysis, those agencies that classified their spending into different research categories spent most on strategic research to gain new knowledge in biomedicine and on the development of new biomedical tools (vaccines and drugs but not, surprisingly, diagnostics, which were comparatively under-resourced). They spent least on research to improve the use of existing tools (operational research and health policy sciences).

It is important to bear in mind that some research disciplines may be more expensive than others, in terms of dollars invested per finding, or per product. In the meantime, the results above provide a preliminary overview of the balance of current activity. The GTRI may wish to discuss more sophisticated methods of analysis to inform its decisions.

8.3 Current research efforts

In a further effort to assess how well current research matches identified research needs, the Programme also conducted a preliminary overview of the major institutions' activities in the TB field. The resulting picture is far from complete; rather, in some areas, it points out how little is known, and simply emphasises the need for more information on research activity. GTB will ask speakers at the GTRI's first meeting to present further information on their own institutions' work. The participants will need to decide whether or not more information is necessary for the eventual objective of designing a global research agenda.

8.3.1 Research to improve the use of existing tools

8.3.1.1 Operational research

GTB has been unable to find evidence that there is widespread research activity to widen and improve the use of DOTS, nor does it maintain a comprehensive database of global operational research activities. The Programme itself, together with partners in the US and the UK, is involved in relevant studies in several Sub-Saharan African countries and in India, for example in testing community contributions to TB care. CDC and DFID are involved in research to define the problems which HIV causes for TB control and to devise solutions. The International Union Against TB and Lung Disease also sponsors operational research in Tanzania and other Union supported countries, and increasingly some bilateral agencies, especially DFID and DANIDA are funding additional relevant studies. GTB is aware that much is being done by local researchers in individual countries to address locally specific problems, some of which is supported by local or international NGOs, but neither the extent of this research, nor its quality or its replicability, is generally known. The efficiency of preventive therapy against TB in high HIV prevalence settings has been recently studied by a number of groups in the Caribbean and Sub-Saharan Africa.

8.3.1.2 Health policy research and health systems research

As with operational research, GTB is aware of relatively little health policy research or health systems research devoted to tuberculosis. Importantly, however, health policy
research related to TB may form part of much broader issues or studies, and may therefore be difficult to identify. Traditionally, the health policy sciences deal with issues such as health system organization that are not specific to one particular disease but which "cut across" the interests of many different disease specialities. Nevertheless, the findings may have important implications for TB control.

8.3.2 Development of new tools

Efforts to develop new tools are comparatively well supported. Some of these activities are summarised below. The GTRI will, it is hoped, discuss methods for assessing the likely benefit of potential products to low-income countries.²

8.3.2.1 Drugs

Rifaxetine, a neglected anti-tuberculosis drug whose long half-life could in principle benefit TB patients as part of a treatment strategy with fewer doses, is currently being developed. Trials are now in progress in the US. GTB has approached Hoechst, the current owner of the product, to ask it to proceed with trials in developing countries.

Efforts are under way to develop a single combination product that includes all four drugs for the initial phase of treatment in a single tablet or capsule, although such products are not yet generally ready for market.

Some public funds have been provided to drug companies to re-examine compounds that are potentially effective against *M. tuberculosis*, including those abandoned in the past and those developed and marketed for other indications. Some compounds with promise have been identified, but have not emerged in the public domain. Many companies appear reluctant to market drugs that were originally licensed for other indications as anti-TB agents, due to the usual perceived disincentives to investing in products for poor populations, which have been extensively discussed elsewhere (see, for example, reference 8).

8.3.2.2 Vaccines

Vaccines against TB fall into two broad categories: those intended to protect against infection with *M. tuberculosis*, and those intended to prevent disease progression. Although a number of candidate vaccines exist, researchers are held back from testing them by the lack of a good animal model for tuberculosis and insufficient understanding of what constitutes immunity to the microbe. Without this information, there are insufficient laboratory data to justify the cost of long field trials in humans. WHO and other partners have developed a strategy to speed up the process of vaccine development. The UK Medical Research Council has also decided to focus its mycobacterial research on a TB vaccine.

² Clearly, it is difficult for biomedical researchers to foresee whether or not products are likely to benefit low-income countries or not when development is at an early stage. However, studies can be targeted to some extent in appropriate directions. For example, WHO's mycobacterial immunology committee has already agreed that vaccines intended to protect against infection with *M. tuberculosis* are less practical than vaccines intended to prevent disease progression, in part because of the difficulties of testing the former in high-prevalence countries. Similarly, outside the TB field, researchers have analysed the economic potential of different hypothetical designs of malaria vaccine(3).
8.2.2.3 Diagnostic agents

Existing diagnostic tests are slow and inadequate. However, despite two decades of research, no modern replacements that are appropriate for field use have emerged. Some of the major biotechnology and pharmaceutical companies have recently become involved in the development of sophisticated rapid detection tests but these are aimed mainly at the industrialized countries. Until very recently there have been relatively few efforts to develop robust, simple and low-cost tests that can be used in low-income countries, but these are now increasing.

8.3.3 Research to provide the knowledge base for further or better interventions

8.3.3.1 Biomedical strategic research

This field is comparatively well supported. Certain recent developments are likely to lead to new interventions in future. For example, the genome of *M. tuberculosis* has now been sequenced, a step that should provide important information for vaccine development and for targeted drug discovery. Equally important, automated technologies for screening compounds are now being deployed by the pharmaceutical industry, raising the prospect that anti-tuberculous compounds may be identified more rapidly than before.

8.3.3.2 Epidemiological research and surveillance

Epidemiological research specifically in TB is today relatively scarce. Natural history studies on TB using modern epidemiological and statistical methods have not, to our knowledge, been conducted, although the interaction between HIV and TB has been extensively studied epidemiologically, as has drug resistant TB. The recent increase in international TB surveillance efforts suggests that there is also a research agenda to be explored in this domain.

8.4 Conclusions: identifying the gaps between need and effort

GTB's current opinion is that there appears to be a mismatch between need and effort in TB research. In particular there appears to be neglect of:

- strategic health policy research and development/evaluation research to increase the coverage of DOTS;
- development of new tools specifically geared to the needs of low-income countries.

9. Conclusions and next steps

In this paper, GTB has described the current status of the TB epidemic, analysed the reasons for its persistence and identified some areas where research appears necessary to reduce the burden of the disease. These areas include:

a) research to improve the use of existing tools (health policy, health systems, and operational research);

b) research to develop new tools, including diagnostics, especially those that will benefit poor populations; and

c) research to provide the knowledge base for further or better interventions, including vaccines and new approaches to disease prevention.
Using this position paper as a basis for discussion, GTB will ask the participants of the first meeting of the GTRI to:

1. Voice the need for an adequately resourced global TB research agenda.
2. Agree on the current status of (a) the TB epidemic world-wide, (b) global control efforts, and (c) the research response to date.
3. Define the key research areas and agree on unmet research needs in these areas.
4. Define a process to address these current research needs by:
   • determining what further information needs to be collected as an input to the formulation of the agenda;
   • developing a framework for analysis of the key research areas, including the formulation of specific issues to address in collecting this information and identification of who will conduct these analyses;
   • defining the next steps for addressing the gap between research needs and current research efforts; and
   • determining how this assessment should be used to define the global research agenda.
Figure 1. The burden of TB expected to be associated with HIV between 1997 and 2020. TB cases (white bars) and deaths (black bars) associated with HIV, by WHO region, 1997-2020 (assuming targets are reached by 2010). The burden of TB/HIV is predominantly in Africa south of the Sahara.

Source: Dye, C. WHO internal report GTB/CARG1997
Figure 2a. Projected incidence of TB worldwide under 4 different scenarios. Lines represent incidence if WHO targets for case detection (70%) and cure rates (85%) are met in the years 2000, 2010, 2020 and at current effort.

Figure 2b. Projected deaths worldwide from TB under the same scenarios.

Source: Dye, C. WHO Internal Report GTB/CARG 1997
Figure 3. Projected incidence of TB in each region under four different scenarios. Lines represent incidence if WHO targets for case detection (70%) and cure rate (85%) are met in the years 2000, 2010, 2020 and at current efforts.

Table 1. Summary of total research spending on TB, major institutions, 1995


<table>
<thead>
<tr>
<th>Rank</th>
<th>Organization</th>
<th>Total TB research spending (US $)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>National Institute of Allergy and Infectious Disease</td>
<td>34,142,000</td>
</tr>
<tr>
<td>2.</td>
<td>National Institutes of Health (all institutes other than NIAID)</td>
<td>27,839,000</td>
</tr>
<tr>
<td>3.</td>
<td>US Centers for Disease Prevention and Control</td>
<td>17,065,018</td>
</tr>
<tr>
<td>4.</td>
<td>Medical Research Council, South Africa</td>
<td>3,623,850</td>
</tr>
<tr>
<td>5.</td>
<td>Medical Research Council, United Kingdom</td>
<td>2,375,806</td>
</tr>
<tr>
<td>6.</td>
<td>Robert Wood Johnson Foundation</td>
<td>1,650,000</td>
</tr>
<tr>
<td>7.</td>
<td>JATA-RIT</td>
<td>1,313,626</td>
</tr>
<tr>
<td>8.</td>
<td>WHO/GTB</td>
<td>1,128,627</td>
</tr>
<tr>
<td>9.</td>
<td>United Kingdom Overseas Development Administration (now Department for International Development)</td>
<td>1,054,839</td>
</tr>
<tr>
<td>10.</td>
<td>Eight institutions each spending less than $700 000 (combined)*</td>
<td>1,852,140</td>
</tr>
<tr>
<td></td>
<td><strong>TOTAL</strong></td>
<td><strong>92,044,906</strong></td>
</tr>
</tbody>
</table>

* IDRC, Canada; IUATLD, Karolinska Institute; KNCV, Ministry of Health, Russian Federation; Royal Tropical Institute (Netherlands); Russian Academy of Medical Sciences - Central TB Research Unit; Wellcome Trust, UK
Figure 4. Major institutions' research spending on TB in 1995, by reported categories

Source: GTB survey 1997
WHO Global TB Programme: Global TB Research Initiative Position Paper

ANNEX 1

RESEARCH TERMINOLOGY DEFINITIONS from pages 2-3 of Investing in Health Research and Development, WHO 1996 (1)

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Box 1.1 Definitions and explanations of terms used in this Report

**Types of health research**

Health research: a process for obtaining systematic knowledge and technology that can be used to improve the health of individuals or groups.

Health research provides basic information on the state of health and disease of the population; it aims to develop tools to prevent and cure illness and mitigate its effects; and it attempts to devise better approaches to health care for the individual and the community (Advisory Committee on Health Research 1993). Information about health needs may consist of measurements of conditions, measurements of the relative importance of various risk factors for ill-health, and analysis of the sources of inequity in health services which have a direct impact on health.

Health research embraces different types of activity, ranging from fundamental research—whose primary purpose is to advance knowledge—to development and evaluation research—whose primary purpose is to solve specific problems relating to health care and its delivery (see Box Figure 1.1.1).

Each stage of research is to some extent dependent upon others, and a linear model of the different stages of research is unhelpful in understanding the process. The diagonal line in Box Figure 1.1.1 seeks to stress the interrelatedness of each stage and the fact that there is likely to be substantial movement back and forth between stages. Nevertheless, it is generally true that the proportion of the defined research objective that seeks to change practice rather than to advance knowledge will increase with the spread of the dark section towards the left side of the bar.

**Fundamental research**: research whose purpose is principally to increase knowledge about questions of scientific significance.

**Strategic research**: research whose purpose is primarily to increase knowledge and understanding of a health problem, with a view eventually to solving or reducing the impact of the problem through further development and evaluation.

The relative importance of the knowledge-gaining component and the problem-solving component will vary depending on the type of project and the nature of the problem. Importantly, the definition of strategic research adopted by this Report is not purely biomedical but encompasses also the work of behavioural scientists, epidemiologists, demographers and health policy scientists. Specific examples of strategic research within each discipline might include sequencing the genome of an important pathogen, analysing what proportion of the burden of a given disease can be attributed to a specific risk factor in a specific population, and analysing what effects the decentralization of health services have on the coverage of a given service within a given population.
Development outcomes: products, interventions and policy instruments

Products. These encompass five basic groups of health-related material products: drugs, vaccines, equipment including tools for public health, prostheses, and diagnostics.

Interventions. These may be combinations of products, algorithms, information or policies that reduce the risk, duration or severity of an adverse health condition. They may be usefully subdivided as either:

a. Public health interventions—those that are sought of or directed towards entire populations or subgroups, including immunization, mass chemoprophylaxis such as the addition of iodine or medications to salt or the fluoridation of water, and nutritional interventions, such as encouraging women to take folic acid supplements before and after conception:

or

b. Personal health service interventions—those that are provided at facilities and usually to individuals; these include inpatient and outpatient medical treatments, screening and rehabilitation.

Instruments of government policy. These encourage or discourage specific health interventions, e.g. pricing and/or taxing policies on tobacco, pricing policies for health services, essential drugs lists, policies for paying health workers according to the type and range of services they offer.

The health sciences

Biomedical sciences: includes all strategic biological, medical and clinical research, and biomedical product development and evaluation.

Population sciences: includes epidemiology, demography and the behavioural sciences. This category is not intended to denote solely that part of health research concerned with fertility, family planning and population control.

Health policy sciences: includes health policy research, health systems research and health services research.

It is understood that different traditions and institutional cultures may use some of the above terms in other senses than those adopted in this Report.

Essential national health research (ENHR)

This concept, first set out by the Commission on Health Research for Development (1990), aims to achieve equity in health and development. It holds that each developing country should establish and strengthen an appropriate health research base to "understand its own problems; improve health policy and management; enhance the effectiveness of limited resources; foster innovation and experimentation; and provide the foundation for a stronger developing country voice in setting international priorities".

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Box Figure 1.1.1 Definitions and purpose of R&D

<table>
<thead>
<tr>
<th>Definitions</th>
<th>Purpose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fundamental research...</strong></td>
<td>To advance knowledge</td>
</tr>
<tr>
<td>generates knowledge about problems of scientific significance.</td>
<td>To change practice</td>
</tr>
<tr>
<td><strong>Strategic research...</strong></td>
<td></td>
</tr>
<tr>
<td>generates knowledge about specific health needs and problems. These may be either conditions, risk factors or sources of inefficiency or inequity in health systems.</td>
<td></td>
</tr>
<tr>
<td><strong>Intervention development and evaluation...</strong></td>
<td></td>
</tr>
<tr>
<td>creates and assesses products (vaccines, drugs, diagnostics, prostheses or equipment), interventions (public or personal health services), and instruments of policy that improve on existing options.</td>
<td></td>
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</tbody>
</table>
ANNEX 2

PREVIOUS TB RESEARCH STRATEGY EFFORTS 1986-1996


**Aim:** to identify priority areas for research which would accelerate decline in TB in the US and the world.

**Cosponsors:** Pittsfield Anti-TB Association, Centers for Disease Prevention and Control, National Institutes of Health

**Recommended research:**
1. **To improve methods to prevent infection of the uninfected:** mainly studies on the physiology of the organism and the response of the human host. Identification of the virulence factors of *M. tuberculosis* and the epitopes that give rise to immunity. Improved methods for earlier identification of cases.
2. **Improve detection of the infected at risk of disease:** clone standard strains for studies. Laboratory studies on virulence; antigens, identification of products of *M. tuberculosis* in the infected. Immunologic memory, genetic factors of the host immune response, cellular and humoral defense mechanisms.
3. **Improving prevention of disease among infected:** new drug development and novel technological delivery systems; intermittent PT; causes of INH hepatitis; immunostimulation.
4. **Improving methods for diagnosis:** laboratory-based studies of detection in tissues and specimens, bacilli genes, monoclonal antibodies; host response.
5. **Improving treatment:** clinical research to locate and measure bacillary load; effects against persistors; animal models; basic research on mechanisms of drugs; laboratory-based enhancement of host response; new drugs; *compliance enhancers*.

Note: The agenda is almost entirely biomedical; there is little or nothing suggested in the fields of health systems research, treatment delivery issues, health economics, patient constraints and financing issues.


**Recommended research:**
Laboratory-based immunological research and the epidemiology required to test immunological hypotheses in the field.

Note: mainly biomedical research, as expected from the title.

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3 Italics denote non-biological research

Recommended research:
1. Operational research to apply and adapt proven technologies. Capacity building for operational research: provides few details but mentions training, learning by doing, scientific exchanges, information support, and broad based coalition of all interested parties.
2. Continue basic research due to threats from multidrug resistant (MDR) TB and HIV.
3. Test new drugs to shorten regimens; develop (and presumably test) techniques to improve compliance (blister packs, calendar packs etc); more sensitive detection using polymerase chain reaction; preventive therapy in HIV and epidemiologic studies on the containment of drug-resistant strains.
4. Urges partnerships of World Bank, UNDP, UNICEF and regional banks plus International Union against TB and Lung Disease, non-governamental organisations and bilateral development agencies.


Aim: to assist development of new tools in diagnosis, treatment and prevention

Recommended research:
High priority (in descending order): preventive therapy in HIV infected people; study of new drugs in MDR-TB; assessment of new, rapid diagnostics, for example, polymerase chain reaction; establishment of a programme for systematic evaluation of new drugs; identification of infected persons at increased risk for TB; basic research on mechanisms of drug action, resistance, and virulence; diagnostic specimen bank; methods to assess drug bioavailability.

Note: As expected given the aim, the agenda is biomedical.


Aim: To develop a strategic plan for TB research

Recommended research:
High priority (in descending order): drug resistance surveillance; studies to improve the application of existing diagnostic technologies; efficacy of preventive therapy; descriptive studies of diagnosis of TB in HIV infected people; TB in HIV infected children; optimal continuation phase; evaluation of methods to decrease case burden, for example, ambulatory treatment, home based care; feasibility and cost-effectiveness of preventive therapy; comparison of existing methods to diagnose smear negative and extrapulmonary cases; development and assessment of regimens to replace streptomycin and thioacetazone, improvement of patient and provider compliance; studies to improve existing diagnostic methods for smear negative and extrapulmonary cases; studies on optimal therapy for smear negative and extrapulmonary cases.
And similar number of medium and low priority issues.

Participants recognised the need to incorporate operational research, intervention-oriented research and studies relating to patient and provider compliance. There was discussion on how this agenda could be put into effect with suggestions that WHO act as a clearing house and disseminator of information on what is being done.

Note: many of recommendations listed are the same as in the previous meeting, but order of priority is different. Without analysis and transparent criteria for selecting priorities, this is likely to be a persistent problem.


Aim: formulation of a new TB/HIV research strategy.

This meeting deliberately widened the disciplines involved.

Recommended research:
Listed priorities in 4 areas:
1. Health economics and health care financing: research on expenditure and financing patterns for both TB and HIV care; cost-effectiveness analyses of different interventions including home based care and preventive therapy.
2. Care seeking and adherence: identify factors which affect this; improve patient/programme communication; communication/education programmes to support preventive care in TB/HIV.
3. Health systems: Care access and care delivery - co-ordinate/integrate TB services within community and district services; identify barriers to care and improve management in spite of increased case numbers due to HIV.
4. Epidemiology and clinical issues: improve accuracy of diagnosis in smear negative patients, determine role of preventive therapy; prevention of increased mortality among TB/HIV patients.

Note: This meeting widened the debate, but did not specify how the identified research priorities could be addressed. WHO's Global Tuberculosis Programme followed up on specific research issues, but did not co-ordinate international TB/HIV research efforts.


Aim: to lay out the agenda for research as a tool for development.

This report highlights huge health and development inequalities between rich and poor. Health research has been neglected as a tool for overcoming obstacles for development of the poor. Research is needed to apply existing solutions and to generate new knowledge. Research should not wait until current health service priorities are met. It can empower those who must accomplish more with fewer resources. There is a gross mismatch between burden of illness and research investment. Developing countries need stronger institutions and investment. Especially in need of investment are: epidemiology,
policy and social sciences, management research, research to inform resource allocation. TB is neglected, along with acute respiratory infections, sexually transmitted diseases (apart from AIDS), injuries, mental disorders, health information systems, costs financing, wasteful use of drugs.

Recommendations:
A set of strategies to harness the power of research. Health to be given higher priority in development plans; strengthen capacity of researchers and institutions; pluralistic worldwide health research system in transnational networks. Specifically:
1. Essential national health research (ENHR), to address resource allocation, improve efficiency in health sectors, examine health impact of development in other sectors, and define socioeconomic determinants of health. 2% of national health expenditures to go to ENHR, and a long term strategy to build and sustain research capacity.
2. International partnerships.
3. Expanded international financial support - at least 5% of health project aid for ENHR and research capacity building (RCB). Longer term support by bilateral agencies.
4. International mechanism to monitor progress.

Research specifically for TB:
Improved, simpler diagnostic tests; cheaper, shorter-acting drugs; better vaccine; studies on compliance behaviour; research on design, management and economics of control programmes.


Recommendations:
Better measures of incidence, therefore new survey techniques needed (not better surveillance). New vaccine, especially for the already infected. Most appropriate role for preventive therapy. New diagnostic tools appropriate for developing countries. Shorter acting drugs, depot systems and four drug fixed dose combinations. Operational and health economics research. Trade-offs, for example between costs of better supervision and effect on improved compliance, given an existing infrastructure. Organised approach to cost-effectiveness studies. Studies of the interaction between TB and HIV, especially the impact of HIV on annual risk of infection.

Note: The emphasis is largely biomedical. In spite of the radical nature of the analysis the research agenda suggested is conservative.


Carried out in synergy with an analysis of the global burden of disease (Murray and Lopez 1996, reference 3) this analysis continued and extended the work of the 1993 World Development Report (World Bank, 1993). Whereas the World Development Report attempted to define a more rational allocation of resources within the health sector, this report aimed to describe a methodology to make the allocation of resources
more logical within health research and development, and then applied these methods to a number of conditions.

The proposed methodology was as follows: first, the size of the disease burden is determined; second, the reasons are analysed for persistence of the burden; third, the presence or absence of effective interventions is decided, and if not present, possible interventions are defined; fourth, the cost-effectiveness of the existing or possible interventions is determined; and fifth, an assessment is made of what is already being done.

The Report emphasised the growing nature of the epidemic of non-communicable diseases in developing countries, especially those fuelled by the smoking explosion. However, it also stressed that infectious diseases are not a conquered force, and especially malaria, tuberculosis, AIDS and acute respiratory infections require a renewed research agenda. Drug resistance was highlighted as a source of major concern. The efficiency and equity of health services was also addressed.

Recommended research specific to TB:

1. **Strategic research**: sequence the genome of *M. tuberculosis*\(^4\). Understand better the reasons for spread of drug resistance.
2. **Intervention development**: improve existing technologies. Develop new strategies for the better dissemination of DOTS, including development of fixed-dose combinations, longer acting drugs to reduce the number of health worker/patient interactions; *community based systems for DOTS delivery*. Develop an effective, possibly one-shot, chemoprophylactic.

Recommendations concerning cross-cutting issues:

1. Establishment of a Special Programme for Research and Training on Health Systems and Policy.
2. Reallocate some HIV research resources to TB.
3. Establish a Health Product Development Facility with public/private collaboration.
4. Study impact of health on economic policies and vice versa.
5. Determine effect of different organisations and financial structures in health systems.
6. Measure health need and demand for services at household level.
7. Develop and evaluate cost-effective instruments of public policy.
8. Establish a Global Health Research Forum
9. Governments to develop national agendas for health research involving scientists, health providers, policy makers and community leaders. Strengthen national research capacity, improve training, explicit initiatives to translate research findings into policy; incentives for researchers; competitive research posts; peer-reviewed allocation of funds.
10. Explore new incentives for industry to develop necessary products (diagnostics, drugs, vaccines etc).

\(^4\) Since the publication of the report this has been completed.
References


(9) Anti-tuberculosis drug resistance in the World. WHO/TB/97.229


(18) Styblo, K. Overview and epidemiological assessment of the current global tuberculosis situation with emphasis on developing countries. Rev. Inf. Dis 1989 11 Supplement 2, S339-S346