Final Report
Third External Review

of the
UNDP/World Bank/WHO Special Programme
for Research and Training in Tropical Diseases (TDR)

to the TDR Joint Coordinating Board

Third External Review Committee

H. Wigzell, Chairman
F.K. Nkrumah, Co-Chairman
G.T. Castillo
J. Sepúlveda Amor
W.P. Thalwitz

H.G. Boyer, Executive Secretary
# Table of contents

Addendum ................................................................. 1

Executive Summary ..................................................... 3

1. Introduction ......................................................... 13
   1.1 Terms of reference ................................................. 13
   1.2 Methodology ...................................................... 14
   1.3 Outline of report ................................................. 14

2. TDR’s mandate and disease portfolio ............................. 15
   2.1 Burden of disease ................................................ 15
   2.2 Unfinished research agenda ..................................... 16
   2.3 Disease portfolio ................................................ 18
   Recommendation ....................................................... 18

3. TDR’s impact on science - a bibliometric study .................. 19
   3.1 Methodology ...................................................... 19
   3.2 Key findings ..................................................... 19
   Conclusion .......................................................... 21

4. TDR’s contributions to disease control ........................... 23
   4.1 Methodology ...................................................... 23
   4.2 Key findings ..................................................... 24
   Conclusion .......................................................... 31

5. Progress in development of new tools ............................ 33
   5.1 Investments for the future ....................................... 33
   5.2 New drugs and vaccines ......................................... 34
      5.2.1 TDR’s responsibility ........................................ 34
      5.2.2 Broad approaches to product development ................. 35
      5.2.3 Progress .................................................. 36
      5.2.4 Multilateral initiatives .................................... 38
      5.2.5 Key issues .............................................. 39
   5.3 Implementation of intervention packages ...................... 40
   Recommendations .................................................... 43
6. Capacity development ........................................ 45
   6.1 Evolution of RCS policy and grant formats ............... 45
   6.2 Allocation of resources .................................... 46
   6.3 Training grants ............................................. 47
   6.4 Re-entry grants ............................................. 50
   6.5 Institutional support ....................................... 50
   6.6 Multilateral Initiative on Malaria in Africa (MIM) ........ 53
   6.7 Key issues .................................................. 53
Conclusions ......................................................... 54
Recommendations .................................................... 54

7. Collaboration .................................................. 57
   7.1 Collaborations with WHO units .............................. 57
   7.2 Collaborations with the scientific community ............................ 58
Recommendations .................................................... 58

8. Management of resources ...................................... 59
   8.1 Contributions to TDR ........................................ 59
   8.2 Allocation of resources ..................................... 60
   8.3 Governance .................................................. 62
   8.4 Monitoring and evaluation .................................. 62
   8.5 Communications strategy ................................... 64
Recommendations .................................................... 64

9. Organizational issues ........................................ 65
   9.1 TDR reorganization .......................................... 65
      9.1.1 Mixed reviews ........................................ 66
      9.1.2 Retain the positive and address the negatives ............. 67
   9.2 CTD - TDR interface ........................................ 68
      9.2.1 Setting the context .................................... 68
      9.2.2 Defining the problem .................................. 71
      9.2.3 Options for consideration .............................. 72
Recommendations .................................................... 74
References .......................................................... 75

Annex 1: Terms of reference ........................................ 77
Annex 2: Disease portfolio ........................................ 87
Annex 3: Methodology for case studies ............................ 97
Annex 4: Collaborations - selected examples ...................... 105
Annex 5: List of countries by development status .................... 119
Annex 6: References ................................................ 127
ADDENDUM

The recommendations of the External Review Committee were drafted in May 1998, prior to the reorganization of the World Health Organization under the leadership of Dr Gro Harlem Brundtland. The report does not specifically address the many issues raised by the reorganization of WHO’s activities into clusters, nor TDR’s role within the Communicable Diseases cluster or its relationships with other clusters.

The recommendations need to be interpreted in light of the high quality and relevance of TDR’s activities to R&D in endemic tropical diseases. However, debate on the internal reorganization of WHO should not detract from the overall conclusions and recommendations of the Committee. These remain valid, even though they may need to be interpreted in a much wider context. The following points should be taken into account when reviewing and discussing the recommendations made by the Committee:

1. TDR is a Special Programme co-sponsored by UNDP, the World Bank and WHO (executing agency); it is governed by a Memorandum of Understanding between the parties. This agreement needs to be maintained over the short term, in order to ensure increased co-sponsor and donor commitment, but should be open to re-negotiation in the future.

2. WHO is responsible for the internal management of all its programmes and for determining how best to ensure increased synergy between programmes within the Communicable Diseases cluster and with other clusters. Discussions on the continuum between research and control and the best governance structure to meet these challenges should take place within this larger context.

3. The Committee remains open to a pragmatic and incremental expansion of TDR’s disease portfolio as additional resources become available to the Programme. Clear criteria for expansion of the portfolio should be established. R&D activities with a clear focus and direction are still essential to ensure the overall effectiveness of the Programme.

4. TDR needs to develop a long-term vision for its future, taking into account some of the wider challenges in the field of research on communicable diseases and the broad research capacity development needs of countries where the burden of these diseases is greatest.
EXECUTIVE SUMMARY

TDR

TDR is a Special Programme co-sponsored by the United Nations Development Programme (UNDP), the World Bank and the World Health Organization (WHO), with WHO as the executing agency. TDR is financed almost entirely by voluntary contributions from governments, intergovernmental and non-governmental agencies, foundations and other external sources. It was established in 1975 with two interdependent objectives:

C to undertake research and development of new and improved tools for the control of major groups of tropical diseases (malaria, schistosomiasis, lymphatic filariasis, onchocerciasis, leishmaniasis, Chagas disease, African trypanosomiasis, leprosy); and

C to strengthen research capabilities in countries where these diseases are endemic.

The External Review Committee

The Committee is transdisciplinary and multicultural bringing together expertise in the biomedical, socio-economic, health systems and international management fields. This report represents the views of the External Review Committee only.

This report is not a scientific review, nor a financial audit or a microlevel analysis of all of TDR’s activities, but rather an overall strategic assessment of the Programme. As such it is selective in its reporting. It focuses on fundamental questions, including:

- the need for TDR’s continued existence and its longer term evolution;
- TDR’s mandate and disease portfolio;
- the impact of TDR on the generation of scientific knowledge;
- the impact on the development of tools for disease control;
- the strengthening of research capacity in developing countries.
Mandate and disease portfolio

Despite significant progress made in the last two decades, the diseases in TDR’s portfolio remain an important burden for the world’s poorest populations. These ‘orphan’ tropical diseases are far from conquered. Both biomedical and operational research are needed to provide better tools for control, improvements in the quality of life and to alleviate the health constraints on economic development.

Recommendation:

1. TDR’s activities and disease portfolio are still highly relevant to the health agenda of the coming decade. Given the importance of these diseases for the poorest populations, the unfinished research agenda, and the present financial situation of TDR, the External Review Committee feels that it would not be prudent at this time to suggest any additions to the portfolio. However, this decision could be revisited at a later date should additional resources become available to the Programme.

R&D achievements

TDR is a leading funding body for tropical disease research. Its influence in the field is strong. Through its contributions to the generation of scientific knowledge it has, in a highly significant manner, contributed to progress and innovation in the field.

Case studies demonstrate that TDR has been a key contributor to the successful development of a number of tools - ivermectin for the treatment of onchocerciasis, multidrug therapy for leprosy and the fumigant canister for the vector control of Chagas disease. With only limited resources, TDR must rely on other partners to help it achieve its objectives. National governments, academia, foundations, commercial companies, non-governmental organizations and national and international control programmes are equally important to the attainment of the ultimate objective - better disease control products for communities in need.

TDR has a comparative advantage in several aspects of product development. Its unique access to an international network of experts and institutions that can exchange ideas and collaborate for large-scale field trials; its reputation for scientific rigour and its role as an advocate of people exposed to tropical diseases allow it to lever support from other bodies and give legitimacy to projects it supports.
Agenda for the future

Tropical diseases are among the “Cinderellas” of health research and development. As the costs of drug discovery and development have risen sharply in recent decades, the pharmaceutical industry has largely abandoned research into this low-return area. Yet the need for new tools remains very present.

TDR employs the latest tools and advances in science to explore basic disease mechanisms in order to achieve its goal of producing radically new solutions to disease control. Seed funding by TDR has served to highlight the need for additional sequencing of specific organisms and a number of other agencies are now supporting these endeavours. Research at the interface between the new molecular biology - technology intensive and complex - and product R&D will be essential to future product development.

TDR has been successful at the development and application of drugs, previously used for other indications, to tropical diseases. Significant progress has also been made in the last five years in the development of new drugs and vaccines. Tool development should continue to be a main strategic focus of the future TDR.

Unrealistic expectations and time frames, underestimation of the real costs of development, the size and breadth of the portfolio versus the limited resources of TDR, as well as the yet unfilled need for other tools useful for disease surveillance and vector control are, however, of some concern to the Committee.

The implementation in the field of cost-effective intervention packages is a challenge which TDR is addressing in different ways. However, success in applied field research requires close collaboration with disease control programmes - national, regional and international - as well as significant cross-organizational linkages with external partners.

Recommendations:

2. Investments in strategic research need to be sustained over the long term before results can be translated into disease control tools. TDR will need to maintain a broad spectrum of strategic research, based on new molecular biology, to deal with future uncertainties and develop breakthroughs in product R&D.

3. Tool development should be a main focus for the future TDR. To carry out these activities, TDR needs to provide gap-filling investments, in partnership with other public agencies, to support early discovery and preclinical developments; provide the technical expertise and necessary infrastructure for clinical trials; and aggressively pursue collaborations with private industry, and play a strong advocacy role through targeted actions.
4. In this regard, the command of a critical mass of expertise in drug and vaccine development is essential as will be the expansion of the membership of advisory bodies with representatives from the pharmaceutical industry.

5. As research progresses in the field of vaccine development, TDR also needs to explore ways of establishing more formal linkages with WHO’s Global Programme for Vaccines and Immunization (GPV) to ensure access to the broad range of expertise and networks needed to carry these initial developments towards application.

Research capacity strengthening

The Committee endorses the emphasis on the development of research and control capacities in disease endemic countries. The training of individuals and the development of networks of collaborating centres focusing on tropical disease research are essential if the disease endemic countries themselves are to define and implement their own health strategies and adapt new technologies to their particular circumstances. It is not just a question of experienced institutions in rich countries putting tools in the hands of research and control agencies in poorer countries but to help establish that capacity in the countries themselves.

The Committee has found evidence of TDR’s positive impact on the training of individual scientists, the establishment of independent research units and the transfer of modern technology and methods to research groups in developing countries. There is also evidence of scientific productivity and contributions to national health research and disease control needs.

However, the Committee also notes that the new competitive approach to institution strengthening has tended to favour the more established research institutions and middle-level countries where the research infrastructure is more developed. Many of these institutions have received high levels of TDR support over extended periods of time. The Committee is however concerned about the long term sustainability of efforts with respect to the least developed countries (LDCs) and to the present approaches to institution strengthening in LDCs.

Recommendations:

The Committee feels that different strategies and more focused activities will increase the effectiveness of capacity development efforts, particularly in the least developed countries (LDCs). It therefore recommends the following:

6. TDR should facilitate and contribute to the creation of networks of centres of excellence in those countries and regions where the disease burden is heaviest with an increased focus on meeting
the needs of the least developed countries. These could become, as originally planned, the nuclei for future South-South collaboration.

7. In view of the diversity of situations existing in the LDCs, TDR should assist in the development of specific regional and/or national strategies (e.g. sub-Saharan Africa, South America) which would reflect not only TDR priorities but the needs of the region as a whole. TDR should work more closely with national training institutions, medical or research councils, and other collaborating centres or networks to determine research capacity development priorities. This will ensure the long-term sustainability of these efforts and their full integration with national health services.

8. TDR needs to maintain a more balanced approach between the training of individuals and the support provided to institutions, particularly in the LDCs. The training of graduate and postgraduate scientists is important, but it is also critical to ensure that their home institutions have the resources and infrastructure necessary to sustain them upon re-entry. A balance should also be kept between training in biomedical fields and applied field research (epidemiology, entomology, social sciences) in LDCs.

9. TDR should maintain a comprehensive database on all TDR trainees and grantees, as they are an important resource for the creation of future networks of collaborating centres. Public recognition of achievements by TDR trainees and TDR-supported institutions should be encouraged.

Future strategy can then, with all the recognition for disease specific tool development needs, strengthen the community based attention to target diseases and integration with national health services.

Collaborations

Beyond all indicators of past performance, valuable in themselves, the Committee’s broad endorsement of TDR is based fundamentally on TDR’s record of attracting influential and innovative scientists. TDR’s convening authority and the often pro bono response by scientists are unparalleled.

Collaboration with other players in the field of tropical disease research has been the cornerstone of all TDR activities. TDR has demonstrated that effective strategic alliances need not be permanent constructs or involve the creation of a “super structure” but can be virtual, focused and time limited. Concerns were raised in a number of interviews about the lack of recognition by TDR of the contributions of different partners (both in kind and financial resources) to various projects.
Another area of concern raised was the importance of establishing networks of collaborating centres for disease control and surveillance, particularly in developing countries with the heaviest burden of communicable diseases. These centres are and will continue to be important elements in the creation of global networks for disease control and surveillance. They could also constitute an important mechanism for capacity development in Member States of WHO.

**Recommendations:**

10. **In future, full recognition must be given to the contributions (both in-kind and financial) made by all partners in the many collaborative projects and strategic alliances undertaken by TDR.**

11. **In collaboration with the Division of Emerging and other Communicable Diseases Surveillance and Control (EMC), TDR should support WHO’s efforts to identify centres for disease control and surveillance in developing countries where the infrastructure is presently weak but the burden of communicable diseases heavy. TDR could then play a role in developing the research and control capacity of these centres to ensure that they can participate effectively in national, regional and global networks.**

**Management issues**

The Committee has found TDR labouring under increasing financial constraints. The concentration on strategic activities is laudable and necessary. However, the fundamental effectiveness of donor funds could also be enhanced by value-for-money audits and additional monitoring of activities. Diminishing financial resources could also influence the choice of priorities and put the focus on activities with immediate, short-term impacts while possibly missing out on major tool development avenues. The Committee can see no evidence that the current processes for resource allocation are deficient. However, there remains a need to ensure that funds are allocated primarily to those countries that bear the heaviest burden of endemic tropical diseases with a special emphasis on strengthening South-South linkages.

Areas identified as underfunded include product R&D, the interface between strategic research and product R&D, and institution strengthening activities, particularly in LDCs. TDR is also well placed to play an expanded role in a renewed global effort against malaria. Expansion of TDR’s resource base would represent a good investment in the broader development context.

TDR is really a matrix organization. To function properly, matrix organizations need entities responsible for lateral as well as vertical aspects of a programme. Re-enforcing the role of disease coordinator and the development of a strategic plan that would set the overall context for TDR’s
priorities by disease - and which would balance the present work plans organized by components -
could be ways of addressing this issue without significantly modifying the organization.

The peer review process is well established in TDR. Ex-post evaluations of different strategies, value-
for-money audits, and the development of performance frameworks would be useful additional tools
for programme monitoring and evaluation.

TDR has made considerable progress in the development of a good library of material for field use and
towards establishing modern and effective lines of communication with researchers worldwide. The
development of a formal communications strategy would allow the organization to focus its efforts
more effectively.

TDR is a well managed Programme and its co-sponsorship has served it well in the past to secure
resources and position the Programme in the global health agenda. The Standing Committee can play
an important role in guiding the activities of the Programme and providing analytical feedback on
proposed strategies or new opportunities. Given the importance of the contributions by various
organizations, the Committee feels that it will be important to ensure some elected representation of
these contributors on the Standing Committee, perhaps by inviting the JCB chairperson and vice-
chairperson to participate in these meetings.

Recommendations:

12. **TDR should develop more specific strategies to ensure that financial support is available and
directed towards those countries that bear the heaviest burden of endemic tropical diseases
with a special emphasis on strengthening South-South linkages. The focus should be on
institutions and collaborating centres where a strengthening of the research infrastructure
would yield significant national and regional benefits.**

13. **In addition to the peer review process, which is well established in TDR, the Programme should
examine the feasibility of conducting ex-post evaluations of different strategies, value-for-
money audits and the development of performance frameworks which could serve as a basis
for reporting to its governing bodies.**

14. **TDR should develop a formal communications strategy that would allow the Programme to
focus its efforts more effectively and identify significant gaps for advocacy purposes.**

15. **TDR should develop a long-term vision and a strategic plan that would set the overall context
for TDR’s priorities. The strategic context for the setting of priorities will include the specific
challenges in the field of endemic tropical diseases, the role of other stakeholders in the field,
the “niche” filled by TDR, as well as country, regional and global priorities.**
Organizational issues

Our review shows TDR to be a Programme characterized by excellent strategic research, an impressive portfolio of achievements in product development, and innovative approaches to the implementation of intervention packages for disease control.

However, TDR, as a Special Programme, is facing a number of challenges:

C it is “fragile” - the 1990's brought a gradual decline in the financial and human resources available to the Programme to carry out its work;

C rapid and significant changes in WHO’s internal operating environment will require the Programme to reposition itself; and

C there are significant external challenges and opportunities which will require new and broader approaches to research and control of endemic tropical diseases.

The External Review Committee feels that the Programme’s reorganization in 1994 has increased efficiency and effectiveness in strategic research and product R&D. It has, however, led to a complex and burdensome advisory structure in applied field research. The task force structure itself appears to have exacerbated tensions between research and control.

The External Review Committee is concerned about the continuing friction between the research programme (TDR) and the WHO Division of Control of Tropical Diseases (CTD), which manifests itself more significantly in the area of applied field research. These problems are longstanding and go beyond mere bureaucratic issues and can have an impact on the effectiveness of efforts to combat tropical diseases, particularly in a time of constrained resources. Staff interactions in retreats and strategy sessions and written collaborative agreements may help to alleviate the problem, but the Committee judges a need for a more radical institutional anchoring of the research and control functions. It offers two options for consideration.

The first - which could be called the “Siamese twin option” - focuses on the interface between research and control. The two programmes remain as separate entities with different directors, advisory structures, financial systems, but are “joined at the hip” for one component, applied field research. The second - which could be called the “umbrella option” - proposes a single management structure for the two programmes with joint governance and technical advisory structures.

The External Review Committee is aware that these two proposals, considered separately or in a phased approach, require broad discussion and negotiation among the co-sponsors and the donor
community. However, there is every reason to presume that a partially or wholly unified governance would enhance the output of separately financed and managed research and control activities.

**Recommendations:**

16. **The relationship between research and control needs fundamental restructuring.** The Committee believes that a significant part of the problem lies in the current approaches to priority setting and the parallel review mechanisms. Critical issues that need to be addressed include: the need for joint planning, priority setting and ownership of applied field research projects; the recognition of regional and country priorities in setting priorities for operational research; the need to rationalize the current advisory structure (task force/steering committee/STAC) and the importance of establishing transparent linkages between research and control and surveillance programmes.

17. **Two options are proposed for consideration.** The first - which can be called the “Siamese twin option” - focuses on the interface between research and control. The two programmes remain as separate entities with different directors, advisory structures, financial systems, but are “joined” for one component, applied field research. The second option - the “umbrella option” proposes a single management structure for the two separate programmes with joint governance and advisory structures.

**General conclusion**

We have during this review been convinced that TDR is not only a “special” Programme in the bureaucratic sense of the word, but also special in terms of its flexibility, its capacity to take initiatives and its leadership. Our conclusions and recommendations need to be interpreted in light of the high quality and relevance of TDR’s activities in the field of endemic tropical diseases.
1. INTRODUCTION

The UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR) is co-sponsored by the United Nations Development Programme (UNDP), the World Bank and the World Health Organization (WHO), with WHO as the executing agency. It was established in 1975 as an international response to major health problems of developing countries in the tropics. The Programme coordinates, with members of the world’s scientific community, the planning and supporting of research, training and institution strengthening activities towards two interdependent objectives:

- to develop through scientific research, new methods of prevention, diagnosis, treatment and control of major tropical diseases - malaria, schistosomiasis, lymphatic filariasis, onchocerciasis, leishmaniasis, Chagas disease, African trypanosomiasis, leprosy; and
- to strengthen the capability of developing disease endemic countries to undertake the research required to develop new disease control technologies.

The Programme has over twenty years of experience in the funding of basic and applied research on the diseases in its portfolio. It also has an established and well recognized network of scientific experts from both North and South institutions which ensures the scientific excellence and relevance of its work.

1.1 Terms of reference

TDR’s main technical and advisory bodies - the Joint Coordinating Board (JCB), the Scientific and Technical Advisory Committee (STAC) and the Standing Committee - review the Programme’s scientific and technical activities and guide and support its administrative and financial requirements. The Programme is financed by voluntary contributions from governments, international organizations, foundations and other non-governmental sources.

In June 1996, JCB approved the terms of reference for the Third External Review of the TDR Programme (Annex 1). The External Review Committee is transdisciplinary and multicultural bringing together expertise in the biomedical, socioeconomic, health systems and international management fields. This report is not a scientific review nor a financial audit but rather an overall assessment of the Programme with a focus on fundamental questions like:

- the need for TDR’s continued existence;
- the disease portfolio;
- contributions of TDR to the generation of scientific knowledge; the development of tools for disease control; and the strengthening of research capacity in disease endemic countries; and
- the positioning of the Programme for the future.
1.2 Methodology

Numerous techniques have been used to support the External Review including:
C bibliometry to determine TDR’s impact on science
C case studies to examine the role played by TDR in the development of products for disease control
C assessment of the burden of endemic tropical diseases on the poorest 20% of the global population
C in-depth reviews of two key components: product research and development, and research capability strengthening
C interviews with internal and external stakeholders
C participation by Review Committee members (as observers) in task force, steering committees and STAC meetings
C review of relevant policy documents and major studies on the World Health Organization.

The following reference documents form an integral part of the final report:

C *The burden of tropical diseases among the poorest and richest 20% of the global population -* Davidson R. Gwatkin and Michel Guillot, International Health Policy Program, Washington D.C. TDR, 1998 (TDR/ER/RD/98.1)
C *TDR’s impact on science - a bibliometric study*, Catherine Michaud, Harvard University, TDR, 1998 (TDR/ER/RD/98.2)
C *TDR’s contributions to the development of ivermectin for onchocerciasis*, Tomoko Fujisaki and Michael R. Reich, Takemi Program in International Health, Harvard School of Public Health, TDR, 1998 (TDR/ER/RD/98.3)
C *TDR’s contributions to the development of multidrug therapy for the control of leprosy*, Rania Milleron, Tomoko Fujisaki and Michael R. Reich, Takemi Program in International Health, Harvard School of Public Health, TDR, 1998 (TDR/ER/RD/98.4)
C *TDR’s contributions to the development of the fumigant canister for controlling Chagas disease*, Tomoko Fujisaki and Michael R. Reich, Takemi Program in International Health, Harvard School of Public Health, TDR, 1998 (TDR/ER/RD/98.5)

1.3 Outline of report

The report first focuses on TDR’s general mandate and disease portfolio. The next sections examine TDR’s activities and its development of scientific knowledge; its contributions to the development of disease control tools; and progress to date in the development of new drugs and vaccines. It demonstrates how numerous collaborators have sustained and contributed to the final outcomes. This is followed by a review of TDR’s research capability strengthening activities, including recommendations for the future. TDR’s organizational structure, the interface with control programmes and other management issues are examined in the last sections.
2. TDR’s MANDATE AND DISEASE PORTFOLIO

Several factors influenced the original choice of TDR’s disease portfolio including public health impact, absence of satisfactory methods of control in tropical disease endemic countries, and the existence of research leads towards improved methods of control. These constitute the fundamental “inheritance and soul” of the Programme. Annex 2 provides an overview of each of the diseases in the TDR portfolio including:

- Characteristics of the disease
- Global health burden/endemic regions or countries
- Primary interventions
- Progress and key issues for disease control.

2.1 Burden of disease

Global figures for the burden of disease, as identified by the Ad Hoc Committee on Health Research Relating to Future Intervention Options, although valid from a global perspective, may be quite misleading when trying to understand the burden of endemic tropical diseases on the world’s poorest populations. To the extent that the pattern of disease among upper income groups differs from that prevailing among the poor, the use of such an expanded population base produces a set of disease priorities that differs from the priorities most relevant for those in poverty. Concerns for equality, equity and the health of the poor require the setting of a different research agenda.

“Whatever their mode of transmission, most infectious diseases are chronic problems for all age groups. Chronic because of the persistence of the pathogens themselves and of the conditions they need for survival and transmission, and because in addition to the immediate impact that diseases such as leprosy, malaria or onchocerciasis have on individuals and communities, they have devastating consequences that can last a lifetime.”

Despite the important progress that has taken place over the past two decades, endemic tropical diseases remain an important problem for most of the world’s poorest populations. The percentage of deaths and Disability Adjusted Life Years (DALYs) caused by the TDR diseases are heavily concentrated in the poorest 20% of the global population, to a much greater degree than almost any other category of disease. For example:

- Malaria causes nearly 250 times as many deaths and the other TDR diseases cause a probably even larger number of deaths among the global poorest 20% of the population than among the richest 20%. These are far larger multiples than for any other disease category; the next highest, for the childhood cluster of diseases, is around 85. DALY multiples tell a similar story.
C about 58% of total global deaths and DALYs from malaria occur in the poorest 20% of the world’s population. This is the highest percentage of deaths for any disease category, and the second highest percentage of DALYs. The other TDR diseases are not far behind, with 46% of total global deaths and 51% of total global DALYs experienced by the world’s poorest 20%. This places the other TDR diseases in fifth place, with respect to both deaths and to DALYs.

A DALY (Disability Adjusted Life Year) expresses the years of life loss due to premature death and years lived with a disability of specified severity and duration. One DALY is thus one lost year of healthy life. The tables on the following page summarize key statistics with respect to the burden of disease for the poorest and richest 20% of the population.

2.2 Unfinished research agenda

Many problems contribute to infectious diseases, including poverty, population growth, migration and urbanization and these are often compounded by inadequate or deteriorating public health infrastructures in disease endemic countries. Other factors, such as the resistance of microorganisms to the drugs used to combat them and the resistance of vectors to pesticides used to control them, have a profound implication on society’s ability to deal effectively with infectious diseases. In many cases, the vector of transmission of these diseases cannot be eliminated and therefore there will be a continuous need for post-control strategies and epidemiological surveillance.

There is general agreement that investments in human resources play a critical role in the economic development of nations. Investments in health, like investments in education, can lead to improvements in the human capital of a country and higher levels of development. The impact of scientific research on improvements in the health situation of populations cannot be overestimated. Yet there are grounds for serious concerns with respect to global investments in R&D devoted to problems that overwhelmingly burden developing countries. In 1992, no more than 5% of the total spent on health research worldwide was devoted to such problems. There is disturbing evidence that even the meagre share of funds that are allocated to the health problems of low-income countries are declining due to shrinking government budgets for bilateral aid and reduced investments by the pharmaceutical firms on antimicrobial and parasitic research. With the exception of malaria which has attracted additional funds in recent years, the funds available for research in endemic tropical diseases remain limited.

<table>
<thead>
<tr>
<th>Examples - Unfinished research agenda</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leprosy</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Onchocerciasis</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Chagas disease</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>
Causes of deaths and DALYs in the world’s population (1990)

<table>
<thead>
<tr>
<th>Principal Causes</th>
<th>Wildest 20% of Global Population</th>
<th>Richest 20% of Global Population</th>
<th>Global Population (total)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of Deaths</td>
<td>% of DALYs</td>
<td>% of Deaths</td>
</tr>
<tr>
<td>I - Communicable, Maternal, Perinatal, Nutritional</td>
<td>58.6</td>
<td>63.6</td>
<td>7.7</td>
</tr>
<tr>
<td>II - Non Communicable Diseases</td>
<td>32.0</td>
<td>23.3</td>
<td>85.2</td>
</tr>
<tr>
<td>III - Injuries</td>
<td>9.4</td>
<td>13.1</td>
<td>7.1</td>
</tr>
<tr>
<td>Total</td>
<td>100.0</td>
<td>100.0</td>
<td>100.0</td>
</tr>
</tbody>
</table>

Comparison of the number of deaths experienced by different population groups (1990)

<table>
<thead>
<tr>
<th>Cause</th>
<th>No. of deaths among global Wildest 20% (in 000s)</th>
<th>No. of deaths among global Richest 20% (in 000s)</th>
<th>Poor-rich death ratio (col. 2/col. 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>96</td>
<td>2</td>
<td>248.00</td>
</tr>
<tr>
<td>Other TDR diseases</td>
<td>59</td>
<td>0</td>
<td>Inf.</td>
</tr>
</tbody>
</table>

Comparison of the number of DALYs experienced by different population groups (1990)

<table>
<thead>
<tr>
<th>Cause</th>
<th>No. of DALYs among global Wildest 20% (in 000s)</th>
<th>No. of DALYs among global Richest 20% (in 000s)</th>
<th>Poor-rich DALY ratio (col. 2/col. 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>18,387,000</td>
<td>61,000</td>
<td>301.43</td>
</tr>
<tr>
<td>Other TDR diseases</td>
<td>5,547,000</td>
<td>31,000</td>
<td>178.94</td>
</tr>
</tbody>
</table>

Source: The burden of tropical diseases among the poorest and richest 20% of the global population, Davidson R. Gwatkin and Michel Guillot, 1998
Although four TDR diseases have been targeted by WHO for eradication or elimination - Chagas disease, leprosy, lymphatic filariasis and onchocerciasis - there remain important unfinished research agendas which need to be continued until targets for elimination are achieved or until research brings even better tools to bear on the existing problems. That investment is important if one is to avoid the real risk that elimination will not be achieved and that prior investments in research and control may be wasted. It is essential to view elimination over a long timescale and to ensure an appropriate level of investment is maintained to sustain gains achieved to date.

2.3 Disease portfolio

There has been much discussion about potential additions or deletions to the TDR disease portfolio. The Committee has seriously considered the possibility of expanding TDR’s portfolio to include emerging or re-emerging diseases, such as dengue, and to add other geohelminth infections, which are recognized as important health problems in the tropics. The Committee is aware that a new, more flexible configuration of the disease portfolio could strengthen the ability of TDR to contribute to essential R&D needs in the field of endemic tropical diseases. However, in light of TDR’s declining financial resources, the importance of sustaining current R&D investments and the need for focused efforts, the Committee feels that it would not be prudent to suggest any additions to the portfolio at this time.

The situation could be revisited in the future should additional resources become available to TDR. Criteria for inclusion could include the burden of these diseases in developing countries, the absence of effective control tools, the potential for scientific advances and building on past biomedical knowledge, and the need for global attention (North-South and South-South collaborations). R&D activities with a clear focus and direction are still essential to ensure the overall effectiveness of TDR.

However, TDR could consider completely devolving the responsibility for research in leprosy to the well established WHO Action Programme for the Elimination of Leprosy. Since 1992, TDR’s leprosy research component has collaborated with WHO’s Global Tuberculosis Programme and is managed through two mycobacterial disease steering committees, one concerned with immunology (IMMYC), the other with chemotherapy (THEMYC). These essentially function outside the present TDR transdisease structure and are managed by personnel outside of TDR. During the 94-97 period only 4% of TDR funds were designated for support to leprosy. Although there are no significant cost savings to be achieved with this devolution, it would be a logical step in TDR’s evolution.

**Recommendation:**

1. **TDR’s activities and disease portfolio are still highly relevant to the health agenda of the coming decade.** Given the importance of these diseases for the poorest populations, the unfinished research agenda, and the present financial situation of TDR, the External Review Committee feels that it would not be prudent at this time to suggest any additions to the portfolio. However, this decision could be revisited at a later date should additional resources become available to the Programme.
3. TDR’S IMPACT ON SCIENCE - A BIBLIOMETRIC STUDY

A metaphor for the world fund of scientific knowledge could be the chemical engineer’s concept of a well-stirred reactor. The contents are more or less homogeneous and can be sampled from different points. Innovation occurs as ideas in the pool interact with each other and influence the generation of new ideas. Ideas are thus both the inputs and the products of interactions and also function as catalysts which influence the development of new technologies, products and processes. One of the major drivers for innovation in any discipline and across disciplines is the role of ideas.

Using the techniques of bibliometry, a study was designed to measure TDR’s influence on research - the development of knowledge and ideas - into the eight targeted diseases. Using these techniques:

- Scientists’ output is measured in terms of the number of published papers in their name that can be retrieved from various scientific databases,
- The output of a funding body is measured in terms of the number of published papers acknowledging it as a source of funds, where databases include this information, and
- Scientists’ impact on their field is measured in terms of the number of times each paper is cited by other scientists. Although this is not a measure of the quality of an individual’s work, it gives an indication of its usefulness to other researchers.

Bibliometry techniques have certain well-known drawbacks, in particular a bias towards English language publications in electronic databases, which may produce a misleading picture of the activity of scientists in some regions. However the method remains one of the most important ways of measuring how much a funding body achieves in terms of “bang for its buck”.

3.1 Methodology

In order to assess TDR’s overall influence on the field of tropical diseases, the entire literature for the eight target diseases published between 1992-96 and held on the major databases was searched. For each disease, a random sample of 100 of these papers was analyzed to find out how many of them received TDR support, and how often TDR-supported research was cited. Because there is a time lag between the receipt of a grant and the publication of the work on which it is based, the publications analyzed probably represent the outcome of grants made between 1989-92.

3.2 Key findings

TDR dominates the field. The Programme was acknowledged as a source of funds more often than any other funding body on papers published in six of the eight target diseases. The Programme’s dominance was most marked in research on African trypanosomiasis, onchocerciasis and filariasis. Only research on Chagas disease and schistosomiasis received greater support from other bodies: these were the Brazilian Government and the US National Institutes of Health (NIH), respectively. The most frequently acknowledged co-funder overall was NIH.
Malaria is the most heavily-researched of the TDR diseases. More than one-third of the tropical disease papers indexed in the major database, Medline, between 1992-96 were devoted to malaria. The least studied diseases were African trypanosomiasis, onchocerciasis and lymphatic filariasis, which each accounted for only about 3 percent of the total papers.

TDR science is valued. Most research funded by the Programme appeared to be useful to the scientific community as a whole, as judged by the number of TDR-funded papers that were cited and the frequency of citations per paper. Citation frequency is one mechanism used to demonstrate scientists’ impact in their field. For research on Chagas disease, malaria, onchocerciasis, leishmaniasis and filariasis, at least 85% of TDR-funded papers were cited at least once.

Frequently cited papers are not confined to the North. The maximum number of citations for any one TDR-funded paper was 43, for a paper on malaria by researchers in Tanzania. Of the 24 most highly-cited papers in all subject areas, four were authored by researchers in Africa, six by researchers in Latin America, and the remainder by researchers in the industrialized countries. Overall, however, scientists in the industrialized countries averaged a higher number of citations than scientists in the developing countries, perhaps reflecting a well-known regional bias in science.

All regions pull their weight. There was a strikingly close match between the resources allocated to each region and the output of that region, in terms of grants allocated and papers published per region. For example, one fifth of all TDR grants to researchers between 1989-92 went to Africa, and about one-fifth of the randomly selected papers published between 1992-96 came from Africa. Scientists in Latin America published slightly more papers than would be expected from the number of grants given, while scientists in South-East Asia and the Western Pacific regions were slightly less productive than expected from the grants given.
Another independent study also confirmed the importance of TDR’s contribution to research. The Unit for Policy Research in Science and Medicine (PRISM) of the Wellcome Trust completed an audit of international activity in malaria research in 1996. An analysis of malaria publications and citations for the period 1984-94 was used to identify relative outputs and scientific impact by different countries and funding bodies. TDR was the fourth largest funder of malaria research globally and had a high rate of acknowledgements per million dollars invested. The study identified TDR’s contributions to malaria research:

“International cooperation in scientific research has been identified more as a feature of tropical medicine research than of other areas of biomedical research (Narin and Whitlow, 1990). This feature is supported in the current analysis by the high co-authorship in malaria, compared with cardiovascular science (Anderson et al., 1994).... The organizations receiving the highest number of acknowledgements were the TDR Programme, followed by the DoD and NIAID. Acknowledgements were also high for the MRC, the Wellcome Trust and USAID. The acknowledgement data identified several sources of support in the private sector.... The analysis indicates that between three and twenty-three acknowledgements to the largest contributors were made in the scientific literature for every million dollars they each invested. The TDR and the Wellcome Trust had the highest number of acknowledgements per unit of investment. They were closely followed by the MRC.... However interesting though these findings are, they should not be taken to represent greater or lower levels of productivity by different funding bodies. The costs and the nature of the research supported by different agencies may vary greatly”.

Conclusion

TDR emerges as an important funding body for tropical disease research and its influence in the field as a whole can be considered significant. Through the generation of scientific knowledge it has, in a highly significant manner, contributed to progress and innovation in the field of tropical disease research.
4. TDR’s CONTRIBUTIONS TO DISEASE CONTROL

Although increasingly important for most research sponsoring organizations, measuring the impacts of research is difficult and there are some well recognized problems in the process.

First, very often the impacts occur years, if not decades, after the original research is performed.

Second, as the research moves along the continuum from basic research, to proof of concept and implementation (and this process is not linear but dynamic in nature), other actors enter the field and contribute to product development, distribution and implementation. This makes attribution of the results to one single event or contributor impossible.

Third, the relationship between a proposal’s original acceptance through peer review, bibliometric ratings and the ultimate downstream impact is not readily trackable. An advanced pool of knowledge must be developed before synthesis and innovation occur.

Fourth, indirect impacts can be difficult to describe, much less quantify. These indirect impacts include contributions to the ever expanding pool of general knowledge which encourages innovation, the development of standards and test protocols, or again the training of scientific and technical personnel which contributes to a country’s research infrastructure.

4.1 Methodology

Although it has limitations, the ex-post tracking of research product evolution - through case studies - is one widely used mechanism to identify in a qualitative way the impact of research in a particular field - in TDR’s case the development of disease control tools and best practices.

In order to better understand the nature of TDR’s contributions to the development of tools for tropical disease control, three case studies were undertaken: ivermectin for the treatment of onchocerciasis; multidrug therapy for leprosy; and the fumigant canister for vector control in Chagas disease.

Information for these case studies was collected through a review of published and unpublished documents as well as interviews with key persons who were involved in the development process. The methodology is described in Annex 3. Each case study will identify TDR’s specific contributions, as well as those of its partners - national governments, non-profit foundations, commercial companies - to the discovery, testing and development of these tools and how their introduction into disease control programmes led to demonstrated reductions in the disease burden of endemic countries.
By analyzing the interactions between TDR and its partners in each case, it will also be possible to draw conclusions on the Programme’s particular strengths, its potential weaknesses and lessons for the future. A summary of the key results of each individual case is presented on the following pages. The complete case studies are available as separate documents appended to this report.

4.2 Key findings

Each case study shows how TDR worked with national governments, non-profit foundations, commercial companies and others to discover, test and develop these three tools. By analyzing the interactions between TDR and its partners, it is possible to draw conclusions on the Programme’s particular strengths and comparative advantages.

4.2.1 TDR was a key contributor to the successful development of all three tools - particularly in identifying a problem early, supporting initial screening, organizing and monitoring field trials, and improving each tool to make it more user-friendly in a community setting, leading to improvements in best practices for programme delivery.

Ivermectin for onchocerciasis: TDR played an important role in the development and use of ivermectin, the safest and most effective existing treatment for onchocerciasis. Once Merck & Co. Inc., the company that developed the drug, had tested the compound in volunteers in 1980 and showed it to be safe; TDR contributed to the clinical trials of the drug, providing Merck with access to an international network of experts and institutions for multi-country trials. TDR, together with the Onchocerciasis Control Programme in West Africa, argued the case to make the drug accessible to all who needed it. Merck made the decision to offer the drug free. TDR also made significant contributions to the improvement of mass treatment programmes through operational research.

Multidrug therapy for leprosy (MDT): TDR made most of its contributions to the development of the MDT strategy in three areas. It performed epidemiological surveys which provided vital evidence that an increasing number of people worldwide were infected with drug-resistant strains of the leprosy bacillus, *Mycobacterium leprae*. This evidence was a key factor in the decision to adopt MDT, which strongly impedes the emergence of drug-resistant strains. TDR then set up and monitored clinical trials for testing appropriate regimens of MDT; demonstrating that persisting *M. leprae* were not significant threats to control. TDR also strengthened national control programmes by training scientists in techniques essential for monitoring MDT programmes.

Fumigant canister for Chagas disease: TDR acted as a catalyst in supporting the work of Argentine scientists and companies in developing the fumigant canister, a tool for controlling the triatomine bug vectors of Chagas disease. In particular, TDR contributed modest but continuous funding over 11 years that gave the project legitimacy with the Argentine Government and with researchers elsewhere. Organizational support through TDR’s committees of scientists helped the development process and gave the researchers responsible for the canister contact with an international network of experts. TDR also promoted the fumigant canister outside Argentina as one component of multi-country field trials of new tools for vector control in Chagas disease.
Curing river blindness - a collaboration of equals

Onchocerciasis, or river blindness, is caused by the larval stages of the worm *Onchocerca volvulus* and spread by *Simulium* blackflies. People infected with the worms may suffer blindness, skin damage and severe itching. The disease hampers productivity and can lay precious fertile land to waste. This study shows how the first successful treatment for the disease emerged through the combined efforts of TDR and its partners.

The problem: When TDR was founded in the mid-1970s, up to 40 million people in endemic areas were affected by onchocerciasis. The existing treatments had serious side effects and the Programme decided that the search for new drugs was a priority.

The solution: During the 1970s, researchers at the company Merck & Co, Inc. discovered that ivermectin, a compound derived from chemicals known as macrocyclic lactones, killed the larval forms of filarial worms in animals. In 1980 the compound was tested in people as a potential treatment for onchocerciasis. Trials showed that the drug dramatically reduced the number of larvae in the body for at least six months, without causing any significant side effects. The drug was registered as a treatment for onchocerciasis in 1987. Because the populations who needed it, mainly in sub-Saharan Africa, could not afford to buy it, Merck offered it free to onchocerciasis control programmes.

The outcome: Since 1988, ivermectin has been distributed to about 13 million people. The disease burden has fallen sharply, and the prevalence of infection also appears to be declining. During the 1990s, mass treatment has been extended from 11 pioneer countries in West Africa to virtually all those at risk in sub-Saharan Africa, with the aim of eliminating onchocerciasis as a health problem early next century.

The roles of the major actors: The key players in this success story played distinct, but related, roles and none could have acted alone.

Merck: discovered the drug through routine screening; initiated human trials; made the decision to offer the drug free; and set up the Mectizan Expert Committee, which represents the company, WHO, governments and others and approves control programmes to receive free supplies of the drug.

TDR: established a world-wide effort to screen for new drugs; provided Merck with access to an international network of experts and institutions for multi-country trials of ivermectin; argued the case, with others, for Merck to make the drug widely accessible; demonstrated that ivermectin was effective and safe for mass treatment programmes in the community by designing, monitoring and paying for large field trials; and improved treatment programmes through applied field research. This prepared the technical basis for the African Programme for Onchocerciasis Control (APOC).

The Onchocerciasis Control Programme in West Africa: helped to finance trials of the ivermectin; argued the case, with TDR and others, for Merck to offer the drug free; helped to monitor trials and surveillance of the treatment; together with TDR, the World Bank, several non-governmental organizations and others, formulated and implemented the plan to eliminate onchocerciasis in western Africa.

Findings and lessons learned: A central finding of the study was that TDR’s aim—the development of a widely available tool to control onchocerciasis—could not have been achieved by the Programme alone. TDR’s partnership with others, particularly in the private sector, was crucial. For example, TDR waited for Merck to provide the first evidence of ivermectin’s safety and efficacy in humans and, later, relied on the company to absorb the cost of providing the drug free. In turn, Merck benefited from TDR’s unique ability to help organize and fund large-scale trials in endemic countries, through its network of experts and institutions. Merck also benefited from the Programme’s field research to improve treatment in the long term. TDR and Merck both needed the help of the Onchocerciasis Control Programme (and at a later stage APOC) and non-governmental organizations. The World Bank played a particularly important role. The collaboration was a success because all parties were prepared to establish new forms of partnership.
Multidrug treatment: the beginning of the end for leprosy

Leprosy is a long-lasting infection of the skin, the peripheral nerves and the airways. It is caused by the bacterium *Mycobacterium leprae* and spreads on airborne droplets. Between the mid-1980s and the mid-1990s, the estimated number of people with leprosy world-wide—including unregistered cases—fell by 80% to around 1.26 million. The main reason for this success is multidrug therapy (MDT). This report examines the roles of TDR and other key players in developing MDT.

**The problem:** When TDR began work in 1975, researchers estimated that there might be 12 million people with leprosy worldwide. At that time, most doctors used one drug alone, dapsone, but a course of therapy lasted for years and many supposedly cured individuals relapsed. Meanwhile, drug-resistant strains of the leprosy bacterium were rapidly spreading and there was no vaccine or other means of preventing the disease.

**The solution:** MDT, the use of combined drugs, had been shown to work well in certain other diseases such as tuberculosis. Not only do combined drugs hasten a cure; they also keep drug resistance dramatically in check. In 1981, WHO recommended that leprosy patients should receive MDT. Nevertheless, WHO’s decision was controversial among some scientists. Field trials of MDT for leprosy had not finished, so no one could yet be certain that the treatment would work better than drugs used singly. But WHO believed that the weight of evidence supported MDT, and that without it, drug-resistant bacteria might threaten existing control efforts.

**The outcome:** Between 1986-95, the proportion of people with leprosy who received MDT rose tenfold to 91% and the number of registered cases fell from 5.3 million to under one million. The length of treatment has been shortened from years to months and the relapse rate has fallen sharply. At between $3 and $40 for a cure, MDT is a highly cost-effective health tool.

**The roles of the major actors:** Several key players were responsible for this success:

**WHO’s Leprosy Unit (and its successor the Action Programme on the Elimination of Leprosy):** recommended MDT in 1981 on the advice of its Study Group on the Chemotherapy of Leprosy; negotiated with the pharmaceutical industry and others to make the drugs available; and supported control programmes in affected countries, for example by funding experts to help organize these programmes, and by training thousands of managers.

**TDR:** convinced many countries of the need for MDT through surveys showing that drug-resistant bacteria were widespread and increasing; set up the first clinical trials of MDT whose early results helped WHO to justify its decision to recommend the therapy; showed through further research that mild, early cases of leprosy can be treated in as little as one day; trained workers in endemic countries in laboratory techniques needed for monitoring the success of a control programme.

**The Nippon Foundation:** This not-for-profit, Japanese private foundation has paid for MDT since 1994, pledging $50 million between 1994-99 to buy the drugs following negotiations between WHO and the affected countries; and has enabled the Action Programme for the Elimination of Leprosy to supply the drugs to control programmes in user-friendly blister packs.

Other bodies, especially other non-governmental organizations dedicated to leprosy, also played important roles.

**Findings and lessons for TDR:** TDR’s contribution to the development of MDT was critical: it provided the scientific evidence that convinced affected countries and funding bodies that the therapy was worth investing in. TDR first showed that drug resistance was a real and growing problem. Second, the Programme’s research showed that a combination of drugs could cure the disease more quickly and effectively, and therefore more cheaply, than single drugs alone. But knowledge such as this was not necessarily enough. MDT would probably not have been adopted and used so widely without the actions of other bodies, critically WHO’s Action Programme for the Elimination of Leprosy and the Nippon Foundation.
Chagas disease: A local solution with an international champion

Chagas disease can damage the heart, the digestive system and the peripheral nerves through chronic inflammation. It is caused by a parasite, *Trypanosoma cruzi*, which is spread by the bites of bloodsucking triatomine bugs that live mainly in houses. In 1991, WHO estimated that up to 18 million people were infected with the parasite, all of them in the Americas. About 45,000 people die of Chagas disease each year, and many more are disabled by it. This report examines how TDR catalyzed the development of a tool to control the vector.

The problem: When TDR began work in 1975, insecticide spraying of houses was the only really practical way to stop Chagas disease from spreading. But these spraying programmes lasted many months, and relied on sustained commitment to succeed. In some areas, political apathy and a lack of money were taking their toll on the programmes, and many communities felt helpless to control the disease.

The solution: In the 1970s, Argentine scientists discovered that insecticidal gases had a synergistic effect if they were used consecutively: they killed more of the bugs than when used separately. The researchers designed a fumigant cartridge to exploit this synergistic effect for household treatment. During the 1980s, the canister was refined and the first commercial version was sold in Argentina in 1988, the same year that the Argentine health ministry approved it. Since 1994 the canister has been refined further.

The outcome: Fumigant canisters have helped Argentina’s dramatic recent progress against Chagas disease. The Argentine National Chagas Disease Program, which used the canisters as part of its control strategy, halved the number of houses infested with triatomine bugs between 1982-94. The number of cases of infection has also fallen, by 80% in children and by a quarter in older adults. Fumigant canisters help to keep houses bug-free after conventional spraying, so they help to sustain control programmes at a vulnerable stage where previously control often broke down. They cost less than $5 and can be used by local people, so they cut programme costs.

The roles of the major actors: The fumigant canister’s success is due largely to Argentine scientists and their commercial partners. However, TDR played an important catalytic role.

CIPEIN, the Centro de Investigaciones de Plagas e Insecticidas: employed and supported the scientists throughout, together with other Argentine research institutes.

The Argentine Government, including the ministry of health and disease control agencies: funded the CIPEIN scientists’ research; approved the canister and adopted it for the national control programme, buying about 500,000 canisters in the first half of the 1990s.

Various Argentine companies including Medex-Omicron, Aguvac and Sintyal: helped to develop the canister through several versions; marketed it in Argentina, initially to the public sector and latterly privately as well; and are seeking product licences for the canister in other Latin American countries.

TDR: provided modest but sustained funding to the CIPEIN scientists throughout, from research into the bugs’ physiology to field tests of the canister; supported key field tests in Argentina showing that local, home-based control efforts using the canister and other tools were as effective as professionally-run programmes, for a quarter of the cost; through its long-term support, encouraged other sponsors to become involved, probably influencing the Argentine government’s decision to adopt the canister; and helped to fund and organize tests of the canisters and other new tools in five other countries, Bolivia, Chile, Honduras, Nicaragua and Paraguay.

Findings and lessons for TDR: TDR was a key player in the development of the fumigant canister. Two lessons emerge: first, TDR can be a catalyst to a project even when its funds are modest. It contributed only an estimated 10% of the funding, but it drew other sponsors into the project, convinced the Argentine Government to adopt the tool and alerted other countries’ control programmes to its potential. However, a catalyst is only effective when the reactive elements are already present. Argentina’s commitment to controlling Chagas disease was vital, as was the existence of competent scientists and commercial partners in Argentina. A second lesson is that TDR cannot expect to control the outcomes of a project when its financial contribution is small. Here the key role was played by local governments.
4.2.2 The Programme’s success depended on its ability to forge fruitful links with other agencies - not only in public health but also in the private sector. TDR’s partners played effective roles in enabling the tools to reach the communities who needed them the most. The presence of strong and effective control programmes, at both the international and the national level, was crucial to reaching out to these communities. TDR also played a significant role in the creation of a broad-based scientific community interested in the field of infectious tropical diseases research.

Ivermectin for onchocerciasis: The report found that TDR’s partners, especially the company Merck & Co. Inc. and the Onchocerciasis Control Programme in West Africa (OCP) and, at a much later stage, the African Programme for Onchocerciasis Control (APOC) were equally important in enabling ivermectin to reach the communities who needed it. Without its partners, TDR could not have successfully reached this goal. TDR’s comparative advantage as a partner in this success story is judged to be threefold. TDR’s unique role representing the needs of people with tropical diseases enabled it to persuade its partners that a mass treatment for onchocerciasis was necessary, despite some initial scepticism among its critics. TDR’s access to a network of experts and institutions provided a structure for trials and built links between private and public sectors. TDR’s culture, as a scientific research organization, allowed it to change its strategy from pursuing one type of drug to pursuing another on the basis of new evidence. At a later stage, TDR prepared the technical basis for APOC.

**Contributions of major actors: ivermectin for onchocerciasis**

<table>
<thead>
<tr>
<th></th>
<th>TDR</th>
<th>Merck</th>
<th>OCP</th>
<th>Academic institutions</th>
<th>Governments of endemic countries</th>
<th>Mectizan Expert Committee</th>
<th>NGOs</th>
<th>World Bank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Registration</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Production</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pricing</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Distribution</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Programme</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>

Contributions: ++ significant + moderate - negligible

**Multidrug therapy for leprosy:** Besides a number of non-governmental organizations active in leprosy control and the national leprosy control programme managers in endemic countries, two other important players were: WHO’s Action Programme for the Elimination of Leprosy (LEP), formerly known as the Leprosy Unit and the Nippon Foundation, a non-profit Japanese foundation. The report also found that networks of scientists formed effective bridges between researchers and the disease control community.
Contributions of major actors: MDT for leprosy

<table>
<thead>
<tr>
<th></th>
<th>TDR</th>
<th>LEP</th>
<th>Nippon Foundation</th>
<th>Other leprosy NGOs</th>
<th>Leprosy endemic countries</th>
<th>Pharmaceutical companies</th>
</tr>
</thead>
<tbody>
<tr>
<td>The decision</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Dapsone resistance survey</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Clinical trials</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Laboratory studies</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Production</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Pricing</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Distribution</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Programme implementation</td>
<td>-</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>-</td>
</tr>
</tbody>
</table>

Contributions: ++ significant  + moderate  - negligible

Fumigant canister for Chagas disease: The report found that TDR could not have achieved success without the help of several important external factors. Latin American governments and health authorities were politically committed to fighting Chagas disease and therefore willing to fund the projects. There was already scientific and technical capacity in Chagas disease in the endemic countries of Latin America, a situation that was comparatively rare in tropical disease research. There was also a competent industrial base in Argentina, which fostered the development of the tool beyond the initial research stages.

Contributions of major actors: fumigant canisters for Chagas disease

<table>
<thead>
<tr>
<th></th>
<th>TDR</th>
<th>CIPEIN</th>
<th>Other Argentine Research Institutions</th>
<th>Argentine Chagas disease control agencies</th>
<th>Local industry in Argentina</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discovery</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Product testing and improvement</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Registration</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Production</td>
<td>-</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Pricing</td>
<td>+</td>
<td>++</td>
<td>-</td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>Distribution</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Programme implementation</td>
<td>+</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

Contributions: ++ significant  + moderate  - negligible
4.2.3 These tools have had an important impact on disease control and elimination - surveillance data demonstrates clearly the importance of these tools in controlling the spread of the disease and in helping to reduce the prevalence of infection.

**Onchocerciasis:** Since 1988, ivermectin has been distributed to about 13 million people. The disease burden has fallen sharply, and the prevalence of infection also appears to be declining. During the 1990's, mass treatment is being rapidly extended to cover, by 2002, virtually all those at risk in Africa with the aim of eliminating onchocerciasis as a health problem early next century.

**Leprosy:** Between 1986-95, the proportion of people with leprosy who received MDT rose tenfold to 91% and the number of registered cases fell from 5.3 million to under one million. The length of treatment has been shortened from years to months and the relapse rate has fallen sharply. At between US$3 and US 40 for a cure, MDT is a highly cost-effective health tool.

**Chagas disease:** In 1991, the Ministers of Health of Argentina, Bolivia, Brazil, Chile, Paraguay and Uruguay, launched the “Southern Cone initiative for elimination of transmission of Chagas disease.” The progress towards elimination of transmission of Chagas disease by vectors and through blood transfusion in Uruguay, Chile, Argentina and Brazil has been documented (WHO, Weekly Epidemiological Record, Geneva, 6:38-40, 1994; 3:13-16, 1995; 2:12-15, 1996). Current data on disinfecting of houses, screening in blood banks and serology in children and young adults indicate that interruption of the transmission of Chagas disease by vectors and through blood transfusion will be achieved in Uruguay and Chile in 2000, Brazil and Argentina in 2003.

4.2.4 The case studies also demonstrate the importance of sustained long-term investments in research - these investments are needed to develop the necessary tools and strategies that can contribute to the control and often elimination of debilitating diseases and lead to improvements in the health situation of populations. In all three cases research investments have spanned more than a decade.

4.2.5 TDR has only limited resources and therefore must rely on other partners to help it achieve its key objective: good disease control tools for all who need them. Without an external source of finance - such as Merck & Co. Inc. in the case of ivermectin or the Nippon Foundation in the case of multidrug therapy - few products are likely to succeed. However, TDR also needs to discover how to keep its influence on the final product so that it remains accessible to the poorest people in need.
Conclusion

TDR has certain characteristics that give it a comparative advantage in developing disease control tools and products:

- its unique access to an international network of experts and institutions that can exchange ideas and collaborate for large-scale field research;
- its culture as a scientific organization and its reputation for scientific rigour give legitimacy to the projects that it supports;
- its role as an advocate of people exposed to tropical diseases allows it to lever support from other bodies, such as non-governmental organizations, academic institutions and other research organizations; and
- its role in steadily increasing DEC’s scientists’ capacity to participate in and eventually lead R&D efforts in tropical diseases.

<table>
<thead>
<tr>
<th>TDR’s comparative advantage</th>
</tr>
</thead>
<tbody>
<tr>
<td>( International networks</td>
</tr>
<tr>
<td>( Scientific culture</td>
</tr>
<tr>
<td>( Advocacy role</td>
</tr>
<tr>
<td>( Capacity development</td>
</tr>
</tbody>
</table>
5. PROGRESS IN DEVELOPMENT OF NEW TOOLS

5.1 Investments for the future

The Strategic Research Component in TDR employs the latest tools and advances in science to explore basic disease mechanisms, such as host-parasite relations and parasite biology, in order to achieve its strategic goal of producing radically new solutions that could, in the long term, strengthen disease control.

The Strategic Research component includes parasite genome, molecular entomology and pathogenesis. For each parasite (except malaria for which there is an ongoing international project initiated by the Wellcome Trust) TDR has launched a genome project with responsibility for identifying the strain of parasite to be used, developing gene libraries, and mapping and sequencing the genome. Seed funding by TDR has served to highlight the need for more sequencing of specific organisms. A number of other agencies are now providing significant funding towards genome sequencing. Interagency collaboration is essential to this endeavour. There is evidence of rapid progress in DNA sequencing and discussions about the post-genome agenda were held in 1998. These discussions will help to identify how to use genome information for product development.

Molecular entomology is highly focused on malaria - its objective is to understand the molecular basis of the parasite-vector relationship of mosquitoes and to genetically modify mosquitoes in order to disrupt the parasite’s development in the vector. There are still many problems to overcome but progress to date indicates the approach is feasible - however, it will require sustained investments over a 10-15 year period.

Pathogenesis research is entirely investigator driven and highly competitive - less than 30% of the research proposals are accepted. Priority setting both among research topics and disease area is extremely difficult as resources available to fund this are are diminishing.
Future research developments will be heavily influenced by the new molecular biology - technology which is intensive and complex. It is important for TDR to participate and support international networks and collaborations in these fields. One of its major objectives should be to ensure that research centres in DECs can fully participate in these new developments. Investments in strategic research are investments for the future and will need to be sustained over the long term before results are translated into disease control tools.

TDR will need to maintain a diversified portfolio of broad spectrum R&D to deal with future uncertainties, develop breakthroughs and even to potentially rapidly exploit non-TDR funded breakthroughs. There will also be a need to ensure adequate research at the interface between strategic research and product R&D.

5.2 New drugs and vaccines

Tropical diseases are among the “Cinderellas” of health research and development. The people who need new tools to prevent, treat or control these diseases are overwhelmingly poor, live in developing countries, and are unable to contribute directly to health care. Therefore, anyone who develops a new tool is unlikely to make a profit on their investment. As the costs of drug discovery and development have risen sharply in recent decades, the pharmaceutical industry has largely abandoned research into this high-risk, low-return area. Yet the need for new tools remains very present.

TDR has a mandate to ensure that new tools for improving the health of poor populations are developed and made available at affordable prices through the public sector. To do so efficiently, the Programme needs access to those with resources, skills and experience in product development - in other words, the pharmaceutical industry.

However, not all the tools that poor populations need can find a backer in the private sector. In such cases, TDR has succeeded by working with partners in academia and in the public sector, including governments, international organizations, and others. In a few cases, however, TDR alone has financed and directly overseen the development of products itself, from discovery to field use, contracting out various stages of the process to public or private sector laboratories.

5.2.1 TDR’s responsibility

The primary responsibility of the Product R&D unit is to take lead compounds from discovery to development and ultimately through registration, where possible in collaboration with one or more pharmaceutical firms. A second responsibility is the extension of the range of indications for existing products, assessment of the combinations of existing products and technology transfer to industry. TDR is using the newest available technologies - high throughput screening, combinatorial chemistry - in drug discovery.
One of its priority tasks is to identify chemotherapeutic targets of parasites, to search existing libraries of compounds from pharmaceutical companies and academia for leads. In this regard, TDR has agreements with a number of pharmaceutical companies which facilitate access to compounds. Research and Consulting Company (RCC), Basel, which serves as a compound repository, handles and distributes these compounds to TDR-supported screening centres.

TDR supports five compound screening centres:

- C WRAIR for antimalarial compounds in vitro and International Institute for Parasitology (IIP), St Albans for in vivo;
- C London School of Hygiene and Tropical Medicine, Janssen Research Foundation, Beerse, Belgium, and Swiss Tropical Institute, Basel for screening and evaluation of compounds in an integrated fashion against the parasites which cause African trypanosomiasis, Chagas disease and leishmaniasis; and
- C the University of Michigan, USA, and IIP, St Albans for antifilaria activity.

Overall some 15 000-16 000 compounds were screened in all models during 1997 at the TDR-supported research centres. A chemical database has been established on compounds which have been screened in which results, suppliers, chemical structure, if available, are recorded. Advances in combinatorial chemistry and high throughput screening methods have given a stimulus in the search for chemical leads.

TDR is involved in preclinical and clinical development. Pharmacology and animal toxicology are contracted out to companies or contract houses with the necessary expertise. TDR also has a network of scientists and institutions in DECs which can be invited to workshops to prepare protocols and carry out clinical trials to Good Clinical Practice (GCP) at a moderate cost. Clinical monitoring is carried out by experts hired by WHO as consultants.

5.2.2 Broad approaches to product development

TDR has been engaged in three broad approaches to product development during the 1990s:

Collaboration with industry (often with additional partners in the public sector): The resulting products, some of which are already registered, include: artemether, an artemisinin derivative that is effective against severe malaria, developed with the company Rhône-Poulenc Rorer Doma; eflornithine, the only effective and safe treatment for African trypanosomiasis, developed in collaboration with Marion Merrell Dow (now Hoechst Marion Roussel, Inc); lipid-associated amphotericin B (AmBisome), which is effective against visceral leishmaniasis, developed with NeXstar Pharmaceuticals; and paromomycin for visceral leishmaniasis, developed with Farmitalia Carlo Erba (now Pharmacia & Upjohn).
Collaboration with public-sector partners: This has proved an effective way of working at early stages in the research and development of a new tool and where no private-sector backer is available. Some examples so far include: two candidate vaccines for malaria - one undergoing trials with government-funded scientists in Colombia, Spain, Switzerland, Tanzania and the United Kingdom, the other with scientists at the National Institutes of Health in Maryland, USA; and a candidate schistosomiasis vaccine, being tested with the support of the United States Agency for International Development (USAID), the European Commission, and the Governments of the USA and Egypt. With the decline in the activities of the private sector in product development for tropical diseases in recent years, the main public sector players in drug development are TDR and the Walter Reed Army Institute for Research (WRAIR), and in vaccine development, the European Commission (EC), USAID, the US Department of Defense, the US National Institutes of Health (NIH), TDR and the Governments of Australia, Colombia, Kenya and Tanzania, for example.

TDR sponsored research: The Programme has conducted its own product development, and invested in every stage of the process. For example, TDR is supporting studies on phosphatidyl choline inhibitors, compounds that interfere with the life cycle of the malaria parasite *Plasmodium falciparum*, by scientists at the University of Montpellier, France. In addition, leishmania vaccines of two types are being investigated by scientists in middle-income and low-income countries including Brazil, Venezuela, Iran and Ecuador supported by TDR. And over the past 17 years TDR has supported work on UMF 078, a compound that kills the various species of adult filarial worms that cause onchocerciasis and lymphatic filariasis. However, recent toxicity test results may jeopardise further development on this compound.

5.2.3 Progress

In spite of constraints - diminishing resources, low company priority, time-consuming legal arrangements - collaboration between TDR and its several partners has resulted in significant progress and achievements during the past five years in the development of drugs and vaccines for the control of tropical diseases. Examples include the following:

- artemisinin derivatives for severe malaria
- AmBisome for visceral leishmaniasis
- ivermectin with DEC or albendazole for lymphatic filariasis
- praziquantel plus albendazole in multidrug therapy for schistosomiasis
- paromomycin for cutaneous leishmaniasis
- candidate vaccines for malaria, schistosomiasis and leishmaniasis
**Selected examples - Drug development**

**Artemisinin derivatives:** *Artemether* has been registered for intramuscular use in the treatment of severe malaria in more than 30 malaria endemic countries, through a collaborative effort between TDR and Rhône-Poulenc Rorer Doma. A preferential pricing was obtained for the public sector in recognition of the financial contribution made by TDR to the preclinical and clinical studies. *Arteether* i.m. has gone through development, with partial funding provided by The Netherlands Ministry of Development Cooperation, in collaboration with Artecef, B.V., Netherlands, and the Walter Reed Army Institute for Research (WRAIR), USA. Regulatory filings were made in the Netherlands in 1997 and they are currently the subject of debate with the Netherlands regulatory authorities.  

**Artesunate suppositories:** Parenteral drugs cannot be given where facilities for injections and/or infusions are not available. Certain patients, often because of vomiting or coma cannot take medicine by mouth, and in malaria endemic areas with high mortality from the disease, treating such patients as early as possible with effective therapy, such as artemunate suppositories, may offer considerable promise. However, additional data on safety and efficacy, duration of administration, and regulatory approval are needed before field based studies can be conducted to assess the effect of prompt treatment on morbidity and mortality of severe and complicated malaria. This is being done in collaboration with Mepha.  

**Lipid Associated amphotericin B (AmBisome):** Through the collaboration between TDR and NeXstar Pharmaceuticals Inc. (formerly Vestar Inc.), and a number of institutions in DECs, liposomal amphotericin B was shown to be safe and effective for the treatment of visceral leishmaniasis. The drug was registered in Sweden in 1994 and subsequently in Denmark, France, Switzerland and UK. It is currently the best available treatment for visceral leishmaniasis.  

**Praziquantel and albendazole in a multdrug therapy:** Feasibility studies on combining praziquantel and albendazole were carried out in multicountry Phase II trials in China, Kenya, the Philippines and Sudan in 1994. It was shown that the two drugs were no less effective against their normal indication, when taken together. The trials were confined to children between the ages 6-14 and specifically excluded pregnant or lactating females. As a result of these studies, WHO has changed its advice and officially recommends that the two drugs be given together to schoolchildren. Bayer, AG, Leverkusen, Germany, provided free of charge the follow-up praziquantel for the treatment of formerly placebo-treated children and for community treatment of the population in the study villages. TDR’s other partners concerning multidisease chemotherapy of school aged children with schistosomiasis and geohelmint infections were: the Edna McConnell Clark Foundation, the James S. McDonnell Foundation, the Partnership for Child Development (PCD), the Rockefeller Foundation and UNDP.  

**Paromomycin (Aminosidine):** Collaboration between Farmitalia Carlo Erba s.r.l. and TDR started in 1991, for the development of the topical formulation of paromomycin for cutaneous leishmaniasis. Subsequently, when the company became Pharmacia Farmitalia, collaboration was extended to injectable paromomycin for visceral leishmaniasis in 1993. Memoranda of Understanding (MOU) were signed by the parties in December 1991 and June 1993 respectively. The former MOU expired in December 1995 and the latter continued until June 1997. Paromomycin is an anti-infective agent of the aminoglycoside family available as an injectable formulation. Clinical studies with it, conducted with the support of the company alone and jointly by the company and TDR, have provided efficacy and safety data which could support registration of the drug for visceral leishmaniasis in the near future. The dossier is in preparation and will be submitted during the course of 1998-99. Following the merger of Pharmacia & Upjohn Inc. in 1995, the company decided not to pursue any further development of this drug for visceral leishmaniasis but expressed willingness to assist TDR, within the limits of its current policy, to continue further development.  

**Ivermectin combinations with DEC or albendazole for lymphatic filariasis:** The antifilarial effects of each of these molecules have long been known. However, recent clinical studies supported by TDR have shown that given together in a single dose combination of two, they are able to reduce larval loads to very low levels for long periods of time. Such observations open the way to using such combinations to control lymphatic filariasis. SmithKline Beecham’s donation of albendazole will facilitate such programmes.
Vaccines

Candidate vaccines for malaria: *P. falciparum* asexual blood stage vaccine and transmission blocking vaccine: SPf66, a synthetic cocktail peptide vaccine against *P. falciparum* malaria developed in Colombia, has undergone extensive field trials in South America, Africa and South-East Asia. Results showed that the vaccine is safe and capable of giving partial protection against malaria attacks under conditions of high (Tanzania) and low (South America) transmission. However, results from a recent study in The Gambia, failed to demonstrate protection against seasonal malaria when tested in infants aged 6-11 months at the first injection. Results from a study in children aged 2-15 years in Thailand, using vaccine produced in California also gave no protection. A second Phase III trial in Tanzania, in the high-risk group of children under the age of one year old is underway and results are expected in late 1998. TDR has collaborated with Colombia, the National Institute of Medical Research, Tanzania, the Swiss Tropical Institute and Spain.

A new formulation of SPf66 with a novel adjuvant QS-21 has undergone preclinical studies and results showed improved immunogenicity and efficiency in *Aotus* monkeys and a Phase I trial testing this new formulation will begin very soon. In addition, studies in humans with the antigen AMA-1, together with the adjuvant SEPPIC began on 1 June 1998 and TDR is providing monitors for Smith Kline Biologicals’ (SKB) work on candidate vaccine, RTS, S.

Schistosomiasis vaccine: TDR is concentrating its schistosomiasis research on vaccine development for the only clinical strategy that could end re-infection. TDR’s partners in this undertaking are the European Commission (EC), the Government of Egypt, the United States Agency for International Development (USAID) and the US National Institute of Allergy and Infectious Diseases (NIAID). Recent demonstration of strong immune responses against certain schistosome antigens has paved the way for moving some vaccine candidates forward into a development phase. A 5-year development plan for scaled-up production and Phase 1/II trials of paramyosin and MAP4/TPI from *Schistosoma mansoni* in Egypt were recently adopted by the Schistosome Vaccine Development Programme (SVDP), a bilateral programme of USAID with Egypt. TDR is supporting complementary work on *S. japonicum*.

Leishmaniasis vaccine: A vaccine is probably the most cost effective and sustainable tool to control leishmaniases with their different epidemiology, vectors and reservoirs. TDR is leading the global efforts in vaccine development against different forms of leishmaniasis. While second generation vaccine candidates (recombinant proteins, genetically constructed parasites with limited virulence and live bacterial/viral vectors carrying leishmanial genes) are being supported (both by TDR and other agencies), the first generation vaccines (killed *Leishmania* mixed with BCG), produced in developing countries are being field tested in DECs with very modest budgets. The early results with single vaccine dose are encouraging and the results of multiple doses are expected in 1-2 years against cutaneous and visceral disease.
5.2.4 Multilateral initiatives

A serious attempt to develop a private-public *multilateral partnership* for drug development, particularly in the context of malaria, was first initiated in 1997. At that time, industry decided that there were too many uncertainties and potential conflicts to go ahead. However, following a series of discussions over the past year a new proposal - New Medicines for Malaria Venture (MMV) - is being reviewed by interested parties in both the public and private sectors. The proposed MMV would be made up of four elements: a fund; a dispersed “actual” drug discovery operation; a “virtual” drug development operation, and a small management group to coordinate and administer the activities. Negotiations are ongoing and progress towards this goal could be announced by early 1999. Alternative approaches may be examining ways of working with individual firms on a case-by-case basis, instead of building up an R&D consortium.

5.2.5 Key issues

In 1994, TDR prioritized its activities in the field of product development, phasing out R&D for vector control and diagnostics. This allowed TDR to put its resources behind the development of a more limited range of products.

TDR has in the past been most successful at the application of drugs registered for other indications to tropical diseases and in these cases, TDR’s investments were relatively small. Over its lifetime it has generated multiple partnerships - with both the private and public sector - for product development and has gained considerable experience. And, despite constraints, there is clear evidence of progress in the development of both drugs and vaccines.

The External Review Committee recognized the significant progress made by TDR in the development of drugs and vaccines. However, the Committee is concerned about the financial strain in light of the yet unfilled need for further tool development, which could include not only drugs and vaccines but other tools useful for monitoring and surveillance of interventions; for example, tools for drug resistance assessments, innovative vector control tools, rapid assessment methods, and diagnostics.

**TDR is not a pharmaceutical company:** Although it is essential that TDR behave in a very business like manner in supporting product development (and the present structure of the unit properly reflects this need), TDR is not a pharmaceutical company and will need assistance from industry to bring products through the full continuum of development until registration. Unrealistic expectations and timeframes; underestimation of the real costs of development; and the size and breadth of the portfolio versus the limited resources available to TDR are of concern to the Committee.
TDR can serve as a “hub” around which interested stakeholders can interact successfully: TDR’s role includes the provision of gap-filling money to support early discovery and preclinical developments; the provision of technical expertise and infrastructure for clinical trials; the development of mechanisms to promote the exchange of knowledge and information; proactive advocacy to raise awareness among decision makers and populations; the development of earlier forecasts of demand for new products based *inter alia* on epidemiological criteria; and other targeted actions.

TDR needs to continually and proactively seek private-public sector collaborations: To do this more effectively, TDR needs to be in command of a critical mass of expertise both for drug and vaccine development. This does not need to be fully met within the Programme but can be achieved by engaging outside expertise and by expanding membership of advisory bodies to include more representatives from the pharmaceutical industry.

TDR’s relationship with the Global Programme for Vaccines and Immunization (GPV) has been good, if informal, and often based on personal initiative as opposed to a functional integration. The two Programmes have developed separate mechanisms for financing, networking and scientific collaborations. As TDR progresses in the development of vaccines, the External Review Committee feels that there could be mutual benefits from greater interaction and joint activities between TDR and GPV, if only to take advantage of the extensive know-how and industry networks already established within GPV.

### 5.3 Implementation of intervention packages

Over the past two decades TDR has generated, with its various partners, a wide range of tools for controlling tropical diseases. Some of these are “health products” in the conventional sense of the word - drugs, vaccines, diagnostics or vector control tools. Others are less tangible, but equally valuable, products of research, such as rapid assessment techniques or socioeconomic research that allow a better understanding of the nature of the disease and its impact on the community, the impact of financing changes or of user charges, the development of more cost-effective strategies for delivery of health services, etc. These various products have in different ways and at various levels influenced both national and regional disease control policies.

A report prepared for the first Global Forum for Health Research (26-27 June 1997) identified a number of R&D areas which are likely to be good investments for maximum impact on the continuing threat of infectious diseases. Priority areas included: improvements in the delivery of existing interventions; improvements in the utilization of existing interventions; development of new tools - the most promising of which were vaccines; and more understanding of the mechanisms which influence the spread of resistance.
The implementation in the field of cost effective intervention packages designed to remove some of the burden of infectious tropical diseases in the poorest populations is a challenge which the Applied Field Research component in TDR is addressing through different task forces: tropical diseases and health sector reform; community-directed treatment; operational research on bednets; home management of malaria in Africa; and operational research on Chagas disease and African trypanosomiasis and gender sensitive interventions. Selected examples of the products generated by applied field research are provided in the following box.

The use of insecticide impregnated bednets is one example of an intervention package that could have a significant future impact in the field. Efficacy trials (Burkina Faso, Gambia, Ghana, Kenya) confirmed the impact of insecticide-treated bednets on child mortality, with observed reductions on all-cause child mortality in differing epidemiological situations of between 16% and 33% in children under five years of age. The findings have emphasized the underestimated contribution of malaria to child mortality in Africa and the potentially large benefits of malaria-preventive interventions. An international meeting held in the WHO Regional Office for Africa in Brazzaville, Congo, in March 1996, reviewed the results of the trials and called for a “phased and continuously monitored introduction of treated nets” in Africa. Guidelines on how to implement and sustain impregnated bednet programmes have been developed by the WHO Division of Control of Tropical Diseases. These are now cautiously being introduced in over 20 countries in Africa as part of an overall malaria control strategy.

There are other examples of successful collaboration by TDR in WHO initiatives, for example TDR’s participation in the UNICEF/WHO initiative for Integrated Management of Childhood Illness, under the direction of WHO’s Division of Child Health and Development (CHD), where it formed a task force focusing on the malaria component of management of childhood illness. Following contributions to development of the “fever” component of the integrated approach, and in conjunction with the malaria unit of the WHO Division of Control of Tropical diseases (CTD/MAL), field research focused on clinical diagnosis of malaria in areas where most fevers are not due to malaria and where microscopy is not available for parasite confirmation.

The Committee recognizes the importance of linking operational research to surveillance and control needs. Research is an indispensable tool to ensure better access to disease control tools for populations in need, to find cost-effective ways of delivering health care and ensure that available tools are introduced into very different health care systems. The relationship between TDR and the Division of Control of Tropical Diseases will be examined in Section 9.
Selected AFR outcomes

Effectiveness of intervention tools

C Effectiveness of two-dose antimalarials in pregnancy. Can replace weekly prophylaxis throughout pregnancy (except in HIV cases)

C Effectiveness of iron supplementation to reduce death from severe anaemia exacerbated by malaria in high transmission areas. Introduced in control policy.

C Demonstration of long-term effectiveness of different combinations of insecticidal paints and canisters. Adopted by Chagas disease control programmes in Southern Cone.

Rapid assessment methods

C Rapid Epidemiological Mapping of Onchocerciasis (REMO). Development and testing of REMO and its application for nationwide mapping of onchocerciasis in APOC countries. Creation of a sub-regional Geographical Information System (GIS) for onchocerciasis which is the basis of planning of control in APOC.

C Rapid assessment methods to identify high risk communities for schistosomiasis. Development and large-scale testing of school questionnaires for assessment of _S. haematobium_. Application in several African countries to guide control.

C Rapid assessment methods to identify high risk communities for Bancroftian filariasis. Development and testing of methods and diagnostic tools for rapid community diagnosis. Soon to be applied on a large scale in rapid mapping of Bancroftian filariasis.

Socioeconomic impact of tropical diseases

C Documentation of the social and economic burden of lymphatic filariasis and the effect of chronic disease on productivity. Results helped justify global elimination programme.

C Documentation of the socio-economic impact of onchocercal skin disease and discovery of the importance of severe itching for affected communities. Provided justification for control in areas with the non-blinding parasite strain (>50% of infected population)

The impact of financing changes and user charges

C Discovery that the introduction of user charges leads to a drop in the use of health services and that people delay seeking care. The exception being where quality of care improved. These and other studies resulted in the introduction of exemption mechanisms for the poorest populations in many countries.

Cost-effective strategies for delivery of health care

C Pre-packaging of antimalarials. Demonstration of effectiveness in South-East Asia. Adopted in several countries. First studies in Africa showed improved compliance and reduced cost. Comprehensive intervention package being developed and tested on large scale in Africa.

C Community-directed treatment of onchocercasis with ivermectin (ComDT). Development and large-scale testing. ComDT has been adopted by APOC and OCP as the principal strategy for ivermectin delivery

C Overcoming factors that prevent women from seeking appropriate health care: Healthy Women Counselling Guide and Health Workers for Change. Wide distribution in Africa and impact evaluation started.

C Schistosomiasis treatment through the school system of children who do not attend school. Adopted by control programme in Egypt.
Recommendations:

2. Investments in strategic research need to be sustained over the long term before results can be translated into disease control tools. TDR will need to maintain a broad spectrum of strategic research, based on the new molecular biology, to deal with future uncertainties and develop breakthroughs in product R&D.

3. Tool development should be a main focus for the future TDR. To carry out these activities, TDR needs to provide gap filling investments, in partnership with other public agencies, to support early discovery and preclinical developments; provide the technical expertise and necessary infrastructure for clinical trials; and aggressively pursue collaborations with private industry, and play a strong advocacy role through targeted actions.

4. In this regard, the command of a critical mass of expertise in drug and vaccine development is essential as will be the expansion of the membership of advisory bodies with representatives from the pharmaceutical industry.

5. As research progresses in the field of vaccine development, TDR also needs to explore ways of establishing more formal linkages with WHO’s Global Programme for Vaccines and Immunization (GPV) to ensure access to the broad range of expertise and networks needed to carry these initial developments towards application.
6. CAPACITY DEVELOPMENT

Since TDR began its operations in 1976, a second objective has been intimately related to the search for new disease control tools - the development of manpower and the strengthening of research institutions in disease endemic countries of the tropics.

“To these ends, institution strengthening activities focus upon the creation of a network of collaborating centres in tropical countries... The Special Programme is concerned to ensure that the full spectrum of technologists and scientists is trained to carry out the required research... Thus, while (it) is especially concerned with training leaders in research, it is not neglecting the training of supporting workers in the laboratory, the clinic and the field.”

The External Review Committee endorses the emphasis on the development of research and control capacities in disease endemic countries. Capacity development is essential to ensure that the countries themselves can define and implement their own health strategies, contribute to the development of control tools and adapt technologies to their particular circumstances. This leads in turn to long-term sustainability and an enabling environment that facilitates human development.

Capacity development by which individuals, organizations, institutions and societies develop abilities (individually and collectively) to perform functions, solve problems and set and achieve objectives... It is a continuing learning and changing process. It emphasizes better use and empowerment of individuals and organizations. And it requires that systemic approaches be considered in devising capacity development strategies and programmes.

Source: UNDP, Capacity development, Technical Advisory Paper 2, 1997

6.1 Evolution of RCS policy and grant formats

TDR’s policy on Research Capability Strengthening (RCS) passed through broad phases. In the first decade all RCS activities were focused on and restricted to institutional development in TDR supported institutions. By 1986-87, there was a major policy change which would link RCS ever more closely to the objectives of the R&D programme. This new policy emphasized:

- the use of research projects as a basis for all activities
- improvement of South-North and South-South linkages
- rapid build-up of capacity for field trials in endemic countries
- the introduction of highly competitive mechanisms; and
- maximization of opportunities for research in developing countries.

Mechanisms for integration with R&D objectives included joint membership between the Research Strengthening Group and the R&D steering committees, a “small grants” programme to support field
research and “group learning activities” to build research capacity in subjects particularly relevant to applied field research task forces.

This resulted in a number of new initiatives, such as the carrying out of workshops for protocol development, data analysis and report writing conducted in relation to multi-country studies. For example training workshops were held over a period of four years. These were partly funded by TDR; 150 scientists with multidisciplinary backgrounds from 21 disease-endemic countries (16 of which are “least developed”) participated in these workshops. These were conducted by the Task Force on Onchocerciasis operational research and its successor, the Task Force on Community-directed treatment. Training sessions for the acquisition of specific skills, e.g. qualitative data analysis, geographical information systems (GIS) and ultrasonography were also funded on an ad hoc basis by the Research Strengthening Group.

Grants to provide institutional support also evolved significantly over the two decades. The original RCS grant was a non-competitive, long-term grant designed to help an institution acquire or upgrade research facilities. These grants were awarded for a 5-year period and supported by capital grants and short term grants for a 2-year period. Many institutions received extended support approaching a 10-year period. This type of grant was terminated in 1989. In the 1990s, the RCS grants evolved into increasingly competitive formats. The competitive nature of the major institutional strengthening grants required as a prerequisite fairly well established research institutions and viable scientific communities.

There were many recommendations (by both STAC and JCB) during the 1990s to:
C ensure that a balance be kept between institution strengthening and training activities;
C encourage TDR to provide support to existing training establishments in developing countries;
C focus on the research capability strengthening needs of the least developed countries.

In 1995, the JCB requested that TDR develop a strategic plan for its future research capability strengthening activities, with special attention to the least developed countries. An updated strategy was presented to the Board in June 1996. The foundation for this strategy remains “training through research” or “learning by doing”. The JCB session of June 1997 “urged TDR to make further efforts to fund as much research as possible in the developing disease endemic countries”.

Over the past two decades, TDR has provided training to over 1300 persons and strengthened over 161 institutes in 80 countries.

6.2 Allocation of resources

During the 1994-97 period, less than 30% of RCS funds were allocated to the least developed countries (LDCs) both for institutional and training activities; 70% of the funds were allocated to other developing endemic countries. In fact, further analysis of the TDR-RCS funding indicates that the
proportion of funds going to LDCs versus other developing countries for institution strengthening has substantially decreased over this period. LDCs received about 32% of funds for institution strengthening during the 1976-85 period and less than 17% of funds in 1991-95. LDCs received over two decades about 22% of all funds for research capability strengthening. TDR has, however, over the last biennium (1996-1997) made efforts to increase RCS funding to the LDCs.

### Research capability strengthening grants by development status

<table>
<thead>
<tr>
<th>Type of Grant</th>
<th>1976-80 (US$ 000)</th>
<th>1981-85 (US$ 000)</th>
<th>1986-90 (US$ 000)</th>
<th>1991-95 (US$ 000)</th>
<th>Total (US$ 000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Developing</td>
<td>3 672</td>
<td>10 339</td>
<td>9 513</td>
<td>13 509</td>
<td>37 033 (77.3%)</td>
</tr>
<tr>
<td>Least developed</td>
<td>823</td>
<td>3 149</td>
<td>3 400</td>
<td>3 484</td>
<td>10 856 (22.7%)</td>
</tr>
<tr>
<td>Sub Total</td>
<td>4 495</td>
<td>13 488</td>
<td>12 913</td>
<td>16 993</td>
<td>47 889 (100%)</td>
</tr>
<tr>
<td>Institution Strengthening</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Developing</td>
<td>6 165</td>
<td>9 034</td>
<td>13 773</td>
<td>9 019</td>
<td>37 991 (77.6%)</td>
</tr>
<tr>
<td>Least developed</td>
<td>2 901</td>
<td>4 406</td>
<td>1 849</td>
<td>1 805</td>
<td>10 961 (22.4%)</td>
</tr>
<tr>
<td>Sub Total</td>
<td>9 066</td>
<td>13 440</td>
<td>15 622</td>
<td>10 824</td>
<td>48 952 (100%)</td>
</tr>
<tr>
<td>Total</td>
<td>13 561</td>
<td>26 880</td>
<td>28 535</td>
<td>27 817</td>
<td>96 841</td>
</tr>
</tbody>
</table>

Source: TDR Information Management System

### 6.3 Training grants

During the 1990s TDR instituted a number of mechanisms for training individual scientists. These included grants for graduate studies, post-doctoral studies, re-entry grants and career development grants.

Training grants are awarded, on a competitive basis, to persons who are nationals of the developing disease endemic countries (DECs), working in the developing countries, and whose research interests are related to one or more of the TDR target diseases. These are awarded for studies towards a graduate degree or for acquiring special skills. Applicants must have a letter of endorsement from their home institutions guaranteeing them a position for three years upon completion of study.
Distribution of grants by degree type in developing countries

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MSc</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>PhD</td>
<td>30</td>
<td>26</td>
<td>11</td>
<td>11</td>
<td>16</td>
<td>94</td>
</tr>
<tr>
<td>POST-DOC</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>1</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>SHORT-TERM</td>
<td>1</td>
<td>1</td>
<td>4</td>
<td>0</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Total</td>
<td>41</td>
<td>35</td>
<td>18</td>
<td>16</td>
<td>29</td>
<td>138</td>
</tr>
</tbody>
</table>

N.B. No grants awarded in 1994

Distribution of grants by degree type in least developed countries

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MSc</td>
<td>3</td>
<td>0</td>
<td>2</td>
<td>9</td>
<td>1</td>
<td>15</td>
</tr>
<tr>
<td>PhD</td>
<td>11</td>
<td>9</td>
<td>7</td>
<td>13</td>
<td>14</td>
<td>54</td>
</tr>
<tr>
<td>POST-DOC</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>SHORT-TERM</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>15</td>
<td>10</td>
<td>10</td>
<td>23</td>
<td>16</td>
<td>74</td>
</tr>
</tbody>
</table>

N.B. No grants awarded in 1994

Distribution of grants by developmental status of home country by sex of grantee

<table>
<thead>
<tr>
<th>DEVELOPMENTAL STATUS</th>
<th>SEX</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>Developing country</td>
<td>52</td>
<td>85</td>
</tr>
<tr>
<td>Least developed country</td>
<td>17</td>
<td>57</td>
</tr>
<tr>
<td>Total</td>
<td>69</td>
<td>142</td>
</tr>
</tbody>
</table>

Distribution of degree types by WHO regions

<table>
<thead>
<tr>
<th>DEGREE</th>
<th>WHO REGIONS</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AFRO</td>
<td>AMRO</td>
</tr>
<tr>
<td>MSc</td>
<td>17</td>
<td>5</td>
</tr>
<tr>
<td>Not recorded</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>PhD</td>
<td>66</td>
<td>26</td>
</tr>
<tr>
<td>POST-DOC</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>SHORT-TERM</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>TOTAL</td>
<td>94</td>
<td>35</td>
</tr>
</tbody>
</table>
Over the period 1991-96, a total of 74 research training grants were awarded to candidates from the LDCs and a total of 143 to candidates from other developing countries. About a third of the research training grants were awarded to candidates from LDCs. The tables on the previous page provide statistical information on the training grants.

A number of changes occurred in the 1990s13:

- in 1991, only 17.5% of training was carried out in DECs; by 1996, 60% of the training took place locally;
- training was more balanced between biomedical disciplines and applied field research (entomology, epidemiology, social sciences) in a ratio of 71:29 in 1991 and 49:51 in 1996;
- there was a substantial increase in the proportion of female grantees, from 29% in 1991 to 44% in 1996; and
- there was a substantial increase in the number of grantees studying for a PhD (68% at present versus 27% in the past 15 years).

In order to assess the impact of TDR’s contributions to training, a review was undertaken of research training grants for doctoral studies14. Data was compiled on all TDR-funded grantees who had completed their PhD studies between 1991 and 1997. These PhD graduates came for the most part from universities (55%) or research institutes (29%) with only 16% from ministries of health or control programmes. Only 4% of them breached their contract after completing their studies - an excellent retention rate - the majority returning to their home institutions.

There was evidence of increased publication activity after training and of a stronger ability to compete for re-entry or other research grants, thus allowing these scientists the opportunity to establish an independent research career for themselves.

Graduates in applied fields (epidemiology, entomology) were as successful as laboratory scientists (immunology, molecular biology) in post-training publication record, success in securing re-entry and research grants. The file review also indicated that at least 14% of TDR’s PhD graduates have successfully established an independent research career, as evidenced by securing TDR R&D funding as a principal investigator. The PhD graduates securing subsequent R&D funding are those with the longest exposure to TDR, and those that have successfully passed the greater number of selection mechanisms - TDR funded MSc training, PhD training, re-entry grant, R&D funding.

Records show no reference to either country, regional or institutional capacity development needs. Although many middle-income countries in Asia and Latin America have established their own programmes to support graduate and post-graduate training; many countries in Africa still lack the resources necessary to support training and must rely on international or bilateral funding mechanisms. The training of PhDs without regard for some form of strengthening of their home institutions may be costly and ineffective over the long run.
6.4 Re-entry grants

The objective of re-entry grants is to develop the competence and independence of developing disease endemic country researchers, who have recently completed a period of graduate training, by financially supporting a research project upon their return to their home institution following graduation. This also helps to strengthen their institution’s capacity to carry out research. Re-entry grants are considered essential, for without this support there is a substantial risk of losing some of these doctoral scientists because of a general lack of resources. Between 1992-97, TDR provided re-entry grants to scientists from 28 different countries, with a total value of US$ 2.03 million.

A total of 30 re-entry grants awarded between 1992-95 and completed between 1994-97 were reviewed to obtain indications of outcomes resulting from the funding. Data show that re-entry grants have:

- allowed promising new graduates to establish independent research teams and laboratories in both biomedical and health economics;
- served as an effective mechanism for transferring modern technology and methods;
- contributed to the development of post-graduate training courses; and
- provided additional opportunities for research training.

**Distribution of funds for re-entry grants by development status (US$ 000)**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Developing</td>
<td>30</td>
<td>336</td>
<td>499</td>
<td>265</td>
<td>261</td>
<td>203</td>
<td>1,594 (78.7%)</td>
</tr>
<tr>
<td>Least developed</td>
<td>90</td>
<td>85</td>
<td>124</td>
<td>81</td>
<td>10</td>
<td>40</td>
<td>431 (21.3%)</td>
</tr>
<tr>
<td>Total</td>
<td>120</td>
<td>421</td>
<td>623</td>
<td>346</td>
<td>271</td>
<td>243</td>
<td>2,025 (100%)</td>
</tr>
</tbody>
</table>

6.5 Institutional support

Programme-based grants and partnership grants were awarded on a competitive basis and required, as a prerequisite, fairly well established institutions and viable scientific communities. This strategy focused essentially on middle-income countries. Programme-based grants included new areas of research: biotechnology, social sciences and health economics and operational research on malaria.
control. Partnership grants focused on strategic research including genome sequencing of parasites to improve drug and vaccine development. The majority of the institutions qualifying for these competitive grants have received extended TDR funding over a 10-15 year period, both in terms of R&D grants and RCS funding for training of scientists and institution strengthening.

Eleven institutions received a “3+2 institution strengthening grant” during the period 1990-96. These were awarded on a non-competitive basis with the major criterion for selection being the probability that the institution could contribute to disease control. The focus was on LDCs or poorer regions of countries like China. A general plan for capacity development focused on a research project was the basis for selection. These grants offered opportunities to establish core groups of scientists involved in tropical disease research and to establish external linkages.

A file review of 25 institution strengthening grants awarded and completed between 1990-97 was carried out by consultants to assess the impacts of these grants. Nine programme based grants; nine “3+2 institutional strengthening grants (IST)” and seven partnership grants were reviewed.

<table>
<thead>
<tr>
<th>Grant Format</th>
<th>Number of grants</th>
<th>Publications</th>
<th>MSc</th>
<th>PhD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Programme-based</td>
<td>9</td>
<td>91</td>
<td>6</td>
<td>15</td>
</tr>
<tr>
<td>“3+2” IST</td>
<td>9</td>
<td>54</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Partnership Grants</td>
<td>7</td>
<td>143</td>
<td>11</td>
<td>48</td>
</tr>
</tbody>
</table>

The following table shows the overall summary of the analyzes in terms of publications and training of MSc and PhD students graduated or undergoing training within each individual grant format.
The box below provides selected examples of institutional support. These different types of grants have been replaced with a generic category called “research capability strengthening grant” (RCS). The RCS grant has an open format and is awarded on the basis of scientific soundness of the proposal, attainability of the objective(s) and inclusion of an explicit capacity building component, i.e. human resource development, technology transfer, and establishment or improvement of information and communication systems.

**Selected examples - institutional support**

**Programme-based grant**

Of the four grants awarded in 1991 in the area of social and economic research programmes, one was specifically designed to strengthen a new training centre for health economics which had emerged at Chulalongkorn University, Faculty of Economics, Thailand. TDR supported training of 25 MSc students from South-East Asia and Africa through the programme-based grant, and additional students were supported under the research training grant mechanism and the regional linkage grant. The majority of the students attended the programme with TDR funding, WHO regional or country budget support, but the support is slowly changing to other sources. The development of a terminal graduate MSc programme in health economics is a major achievement. In addition the centre has developed capacity to play an increasingly international supporting role in the region.

**Partnership grant**

A partnership grant was awarded to the collaboration between four institutions in Mexico. The Principal Investigator (PI) is at the Centro de Investigación de Paludismo, Tapachula, Mexico and a research group in Heidelberg. The objective of the project is, in the long term, to generate transgenic anopheline mosquitoes. This group worked initially with one peptide by the name Shiva, which they had identified. The project has now expanded, and a new, totally unknown natural peptide which is 100-fold more active than Shiva 3 in interfering with the sporogonic cycle is being isolated and chemically analyzed. Substantial scientific progress has been achieved. The project has also allowed the development of MSc and PhD research capacity.

**“3+2 institution strengthening grant”**

In 1992, a “3+2” grant was awarded to the Medical Faculty, University of Papua New Guinea, Port Moresby. TDR’s support to this centre goes back to 1989 where it initially funded the PI to a partnership grant with Oxford University, UK. The grant was modified to the format of a 3+2 grant in order to allow the development of research capacity in the institution. Research progress has been modest, but the project has assisted in the establishment of a malaria research laboratory within an isolated LDC with a high malaria disease burden. The grant has succeeded in developing a research competence as shown by the award of new TDR funding to carry out in vivo studies on various antimalarials and a Phase IIb clinical trial of pyronaridine.
6.6 Multilateral Initiative on Malaria in Africa (MIM)

In the past year, a group of major biomedical funding organizations and malaria researchers from around the world have agreed on the outlines of a Multilateral Initiative on Malaria in Africa. The initiative which consists of a loose-knit collection of projects run by individual agencies will be focused on Africa, where 90% of the world’s malaria cases occur. All the separate initiatives will be coordinated by a contact group; the Wellcome Trust will perform this coordinating function for the first year.

As part of this initiative and with funds received from different organizations for that specific purpose, TDR established a task force which will support multicountry partnership proposals in the following priority areas:
\[\text{C antimalarial drug policy and chemotherapy; }\]
\[\text{C epidemiology; }\]
\[\text{C pathogenesis; }\]
\[\text{C studies on vectors; and }\]
\[\text{C health systems and operational research, including social sciences.}\]

The objective of these grants is to develop or strengthen core African research groups engaged in developing tools for malaria control and in improving health policy. Although it is too early to judge the impact of these projects which have just been initiated, the External Review Committee feels that this is a good example of a focused and dedicated effort to build capacity in Africa where the burden of malaria is particularly heavy.

6.7 Key issues

A number of issues were raised in interviews and debated by the Committee, including:

\[\text{C balance between training and institution strengthening: many of the institutions now competing successfully for programme and partnership grants, training and re-entry grants as well as research grants, received significant TDR funding during the foundation phase. Capacity development involves the identification of strong individual research leaders, but there are other determinants of success over the long term, these include: adequate resources, international collaborations, and political commitment to training and research within the country itself.}\]

\[\text{C balance between advanced developing countries (ADCs) and least developed countries (LDCs): the least developed countries are still getting the smaller share of resources for capacity development. Their research and training infrastructure is generally weaker and they have less resources available to them generally. On the other hand, many of the middle-income countries have established their own programmes to fund graduate and post-graduate training. Mechanisms for long-term institution strengthening no longer exist within TDR and there is a need to examine}\]
alternative ways of addressing capacity development needs in LDCs where the burden of endemic diseases is heaviest.

**C links between R&D and RCS**: although the linking of RCS funding to TDR’s research priority is legitimate and works well for middle-income countries and institutions with well established international collaborations (North-South, South-South), the mechanism may not be as effective for many of the LDCs or research centres. In the case of the partnership grants for example, it is difficult to distinguish the research component from the capacity development component.

**C linkages with in-country research organizations**: there is little reference in TDR documents to country or regional priorities, linkages with medical or national research councils and ministries of health, or to the need to identify and strengthen centres in countries which bear the heaviest burden of disease and have the weakest infrastructure, particularly the LDCs.

### 6.8 Conclusions

The External Review Committee recognizes the important contributions made by TDR to strengthening the research capacity of DECs. However, it also notes that the new competitive approach to institution strengthening has tended to favour the more established research institutions and middle-income countries where the research infrastructure is relatively well developed. The short-term nature of some of the efforts in the LDCs (3-5 year period) also leads to concerns with the long-term sustainability of these efforts. Although the increase in the number of PhD trainees from LDCs is encouraging, it is also important to ensure that the institutional environment upon their return is capable of absorbing them. The Committee feels that there is now an increasing urgency to develop more effective strategies to meet the capacity development needs of the LDCs and to focus on countries bearing the largest burden of endemic tropical diseases.

**Recommendations:**

The Committee feels that different strategies and more focused activities will increase the effectiveness of capacity development efforts, particularly in LDCs. It therefore recommends the following:

6. **TDR should facilitate and contribute to the creation of networks of centres of excellence in those countries and regions where the disease burden is heaviest with an increased focus on meeting the needs of the least developed countries. These could become, as originally planned, the nuclei for future South-South collaboration.**

7. **In view of the diversity of situations existing in the least developed countries, TDR should assist in the development of specific regional and/or national strategies (eg. Sub-Saharan Africa, South America) which would reflect not only TDR priorities but the needs of the region as a**
whole. TDR should work more closely with national training institutions, medical or research councils, and other collaborating centres or networks to determine research capacity development priorities, taking into account not only TDR priorities but the needs of the countries and regions. This will ensure the long term sustainability of these efforts and their full integration with national health services.

8. TDR needs to maintain a more balanced approach between the training of individuals and the support provided to institutions, particularly in the least developed countries. The training of graduate and post-graduate scientists is important, but it is also critical to ensure that their home institutions have the resources and infrastructure necessary to sustain them upon re-entry. A balance should also be kept between training in biomedical fields and applied field research (epidemiology, entomology, social sciences) in LDCs.

9. TDR should maintain a comprehensive database on all TDR trainees and grantees, as they are an important resource for the creation of future networks of collaborating centres. Public recognition of achievements by TDR trainees and TDR supported institutions should be encouraged.

Future strategy can then, with all the recognition for disease specific tool development needs, strengthen the community-based attention to target diseases and integration with national health services.
7. COLLABORATION

The partnership and collaboration theme runs throughout the report. Research alone is not enough and TDR could not have reached its objectives without collaboration from equally strong partners bringing to bear complimentary expertise and/or financial resources. The case studies and the review of progress to date in the development of new tools clearly demonstrate how essential the contributions of other players are to the attainment of TDR’s final objective. This section will provide additional information on TDR’s collaborations with other WHO units and with the scientific and academic community. The interface between TDR and WHO’s Division of Control of Tropical Diseases (CTD) will be discussed separately in Section 9 of the report.

7.1 Collaborations with WHO units

Since 1992, TDR’s leprosy research component has collaborated with WHO’s Global Tuberculosis Programme and is managed through two mycobacterial disease steering committees, one concerned with immunology (IMMYC), the other with chemotherapy (THEMYC). This umbrella provides opportunities for valuable scientific exchanges. The managers of these steering committees work in other WHO units, LEP and GPV.

The case studies provided examples of collaborations with multiple partners in the development, testing and implementation of disease control tools, and highlighted the role of other WHO programmes - the Onchocerciasis Control Programme in West Africa (OCP) and the Action Programme for the Elimination of Leprosy (LEP) - in reaching a common objective, better tools, products and processes for disease control. Annex 4 provides a list of “selected examples” of TDR collaborations with different organizations with a focus on product development. It is not exhaustive.

In other areas, the collaboration is informal in nature and often based on personal initiative. There is little evidence of functional integration or the existence of specific mechanisms to foster active communication and exchange. One example is the Division of Emerging and other Communicable Diseases Surveillance and Control (EMC). Both TDR and EMC have developed separate mechanisms for financing, networking and scientific collaborations.

WHO was selected as the executing agency for TDR because of its strong biomedical knowledge base, its global scientific network and the direct access to ministries of health in developing

“Of global significance is the need for collaborative research into the methodologies for strengthening local, national and international surveillance, and better epidemiological understanding of existing, new or re-emerging diseases and conditions of ill health, together with related continuous evolution of ongoing prevention and control strategies and technologies, and monitoring of microbial and other resistance to available drugs, vaccines and preventive or therapeutic means, worldwide.”

countries. Yet, as a co-sponsored Special Programme, TDR has little direct interactions with WHO regional offices. Another area of concern raised in different interviews is the importance of establishing networks of collaborating centres for disease surveillance, particularly in countries with the greatest burden of endemic diseases. These centres are and will continue to be important elements in the creation of a global network for disease surveillance and control. They could also constitute an important mechanism for capacity building in member states. Yet there are very few such centres in Africa, for example, devoted to the surveillance and understanding of the evolution of infectious tropical diseases.

7.2 Collaborations with the scientific community

TDR has a recognized and well established network of highly competent scientific advisers in both developed and developing countries which provide advice and guidance on the technical aspects of the Programme. Although the steering committee structure has evolved over the years, the peer review of TDR activities and work plans and the competitive allocation of resources to individual research projects ensures not only scientific excellence but relevance.

Up to 31 December 1997 the Programme had granted direct support to institutions and scientists worldwide for over 7300 projects (totalling over US$ 390 million) in 124 Member States of WHO. Over 5300 scientists have been involved in projects supported by TDR or in the management of TDR activities. Many of these projects foster international collaborations in the field of tropical disease research - both North-South and South-South.

Beyond all indicators of past performance, valuable in themselves, the Committee’s broad endorsement of TDR is based most fundamentally on TDR’s record of attracting the most influential and innovative scientists. TDR’s convening authority and the often pro bono response by scientists are unparalleled.

Recommendations:

10. In future, full recognition must be given to the contributions (both in-kind and financial) made by all partners in the many collaborative projects and strategic alliances undertaken by TDR.

11. In collaboration with the Division of Emerging and other Communicable Diseases Surveillance and Control (EMC), TDR should support WHO’s efforts to identify centres for disease control and surveillance in developing countries where the infrastructure is presently weak but the burden of communicable diseases heavy. TDR could then play a role in developing the research and control capacity of these centres to ensure that they can participate effectively in national, regional and global networks.
8. MANAGEMENT OF RESOURCES

As mentioned previously, it is easy to be confused by the term “extra-budgetary funds” when applied to both special co-sponsored programmes and regular programmes. From WHO’s perspective - as executing agency - TDR, as a Special Programme, is almost exclusively financed through extra-budgetary contributions designated for its activities. It receives very limited direct support from the regular WHO budget. TDR, on the other hand, receives extra-budgetary contributions to the Programme and designated contributions targeted by donors to support certain areas.

TDR is financed almost entirely by voluntary contributions from governments, intergovernmental and non-governmental organizations, foundations and other external sources. Less than 25% of the resources are contributed by the co-sponsors; the rest comes from other voluntary contributions.

8.1 Contributions to TDR

Since the early 1990s, contributions have steadily declined (Figure 1). Contributions to TDR in 1996-97 were US$ 54.4 million, a decrease of US$ 2.0 million (3.5%) compared to contributions of US$ 56.4 million in 1994-95. Some contributors have reduced their contributions and this has not been compensated by increases from other contributors. Contributions were received from 35 donors during the biennium, including the three co-sponsoring agencies - the UNDP, the World Bank and WHO. Five developing countries made financial contributions to TDR in 1996-97: the Governments of China, India, Malaysia, Mexico and Thailand. The Oswaldo Cruz Foundation of Brazil has also contributed to TDR. No new contributors joined the list in 1996-97.

This represents a continued erosion in the current value of the TDR budget, since not only has there been an actual decrease in the level of TDR obligations, but the budget level does not take into account the steady erosion of the value of the budget because of inflation. Similar constraints have also been experienced with respect to staffing levels.
Designated contributions received in 1996-97 for TDR totalled US$ 6.9 million, about 12.8% of total TDR contributions during the biennium. Sixteen contributors made designated contributions. The major designated contributions were for the Multilateral Initiative on Malaria in Africa (MIM) under the Research Capability Strengthening component, totalling US$ 1.7 million and for various task forces under the Applied Field Research component, totalling US$ 2.5 million. These designated contributions support TDR established priorities.

Beginning in 1994, TDR, with the agreement of the Joint Coordinating Board, assumed responsibility for receiving contributions designated for the Ad Hoc Health Research and Development Review. The designated contributions for the Global Forum for Health Research (Ad Hoc Review and follow-up activities, Global Forum, etc.) are handled separately and are not included in the TDR budget. Contributions to these activities from 1994-97 totalled US$ 6.0 million.

8.2 Allocation of resources

During the 1994-1997 period, close to US$ 74 million was allocated to the four different components: Strategic Research, Product R&D, Applied Field Research and Research Capability Strengthening. Fifty per cent of funds were allocated to malaria, which is a significant burden in disease endemic countries, with decreasing amounts to other diseases as shown below.

TDR expenditures 1994-1997 (US$ 74 million)
The TDR Secretariat makes an estimate of total funds available for the biennium on the basis of past experience and indications from contributors. In consultation with the Standing Committee, the Secretariat uses these estimates to establish budget options from which the Programme Director develops a detailed Programme Budget, taking into account the workplans of the various steering committees, task forces and the Research Strengthening Group. The draft Programme budget is submitted to STAC for review and comment on the scientific and technical activities, and it is also reviewed by the Standing Committee, which submits the final draft budget to the JCB for approval.

In reviewing the financial situation of the Programme, the External Review Committee found:

- A Programme constrained by diminishing resources;
- A Programme with little room to address new initiatives or to finance them through internal substitution or reallocation of funds;
- Some underfinanced areas: strategic research; product R&D and institution strengthening;
- Lack of resources for adequate project evaluation and value-for-money audits.

Overall, the Programme appears to have exercised prudent financial management: it has concentrated on essential strategic activities and has made some difficult choices. The Committee could find no significant reason to change the present resource allocation in terms of disease focus or Programme component.

The External Review Committee found TDR labouring under increasing financial constraints. The concentration on essential strategic activities is laudable and necessary. However, the fundamental effectiveness in using donor funds could also be improved through the use of managerial tools such as project monitoring and value-for-money audits. Diminishing financial resources could also influence the choice of priorities and put the focus on activities with immediate impacts while possibly losing out on major tool development activities.

Given that 50% of TDR funding is devoted to malaria, the Committee examined whether this funding pattern should be maintained. It is also a legitimate question in light of new international initiatives in malaria and a reordering of WHO priorities with the “Roll Back Malaria” initiative. The Committee feels that TDR can make important contributions to a broader attack on this disease. The Committee also realizes that this initiative will require significant and important contributions by the international community, and South-South as well as North-South alliances to develop more effective disease control and surveillance tools, such as vaccines, and improve the delivery of existing tools and interventions.

However, a review of funding patterns by the development status of countries raised some issues. The Programme is not an ordinary research granting council but has, as one of its objectives, to ensure that the countries which bear the heaviest disease burden can develop their research and control infrastructure to the point where they are able to carry out the full spectrum of activities required in
accordance with the decisions and needs of the countries themselves. The need to focus on the LDCs has been confirmed by both STAC and JCB in the past several years.

Resource allocation for the 1994-97 period indicate that less than 13% of total TDR funding goes to least developed countries. They receive 9% of R&D funds and 26% of RCS funds. Developed countries still receive 59% of R&D funds; while advanced developing countries receive 70% of research capability strengthening funds.

A review of funding patterns since TDR began operations indicate that this pattern has not changed significantly over time and that actually more funds went to the least developed countries in 1981-85 period than in 1991-95. However in the last biennium (1996-97), there have been increased efforts by TDR to fund more activities in the least developed countries.

There is no evidence that the current processes for resource allocation by Programme area or disease are deficient; however there will be a need to develop specific strategies for ensuring that support is available and directed towards those countries that bear the heaviest disease burden, with a special emphasis on strengthening South - South linkages. The focus would be on institutions and networks of collaborating centres where a strengthening of the research infrastructure would yield significant national and regional benefits.

8.3 Governance

TDR is a well-managed Programme and its co-sponsorship, and the role played by the Standing Committee, have served it well in the past to secure resources and position the Programme in the global health agenda. The Standing Committee can play an important role in guiding the activities of the Programme, providing analytical feedback on proposed strategies or new opportunities. Given the importance of the contributions by various other organizations, the Committee feels that it would be important to ensure some elected representation of these contributors on the Standing Committee, perhaps by inviting the JCB chairperson and the vice-chairperson to participate in the meetings.

8.4 Monitoring and evaluation

Peer review of research represents evaluation by experts in the field and is the method of choice for most research sponsoring organizations. The objective of peer review is to promote science accountability and allow for efficient and effective resource allocation. It is also a mechanism allowing policy makers to direct scientific efforts, while providing a valid and reliable measure of scientific performance. Three of the most important intangible factors for a successful peer review system are: motivation, competence and independence.

Peer review -- a qualitative assessment of project proposals by external experts - is well established in the TDR Programme. It provides scientific rigour in the initial assessment of project proposals (ex-ante assessment) and it also allows for the monitoring of a project during the course of its life, suggesting modifications, alternatives or even, in certain cases, the cancelling of a project.
Peer review of projects is carried out by steering committees, task forces and the Research Strengthening Group, composed of scientists and other experts in the field of tropical disease research and control acting as independent advisors to the Programme. Ex-post evaluation of different strategies as well as value-for-money audits could be useful additional tools for programme monitoring and evaluation.
In recent years, a number of public sector organizations have developed performance frameworks which provide the context for the preparation of a yearly report to key stakeholders on the activities of the programme and progression towards some very well-defined objectives. These frameworks focus on inputs, outputs, client reach and results, including the identification of specific performance indicators. These reports are of an administrative nature and need to be distinguished from "marketing" or advocacy documents. TDR might wish to consider the preparation of such a model for reporting to its advisory bodies. It does however require well defined goals and clear strategies against which progress can be measured.

8.5 Communications strategy

There is a need for a greater flow of information to different audiences both as a tool for advocacy on behalf of the disease endemic countries and to inform policy makers, educators, scientists, disease control specialists, non-governmental organizations and current and potential contributors of progress to date and critical issues. Efforts have been made by TDR to build a good library of material for field use and to establish modern and effective lines of communications with researchers worldwide. There is definite evidence of progress. However, the development of a formal communications strategy would allow the organization to focus its efforts more effectively.

Recommendations:

12. **TDR should develop more specific strategies to ensure that financial support is available and directed towards those countries that bear the heaviest burden of endemic tropical diseases with a special emphasis on strengthening South-South linkages. The focus should be on institutions and collaborating centres where a strengthening of the research infrastructure would yield significant national and regional benefits.**

13. **In addition to the peer review process, which is well established in TDR, the Programme should examine the feasibility of conducting ex-post evaluations of different strategies, value-for-money audits and the development of performance frameworks which could serve as a basis for reporting to its governing bodies.**

14. **TDR should develop a formal communications strategy that would allow the Programme to focus its efforts more effectively and identify significant gaps for advocacy purposes.**

15. **TDR should develop a long-term vision and a strategic plan that would set the overall context for TDR’s priorities. The strategic context for the setting of priorities will include the specific challenges in the field of endemic tropical diseases, the role of other stakeholders in the field, the “niche” filled by TDR, as well as country, regional and global priorities.**
9. ORGANIZATIONAL ISSUES

TDR has contributed, through the generation of scientific knowledge and the development of tools for the control of the diseases within its portfolio, to the reduction of the burden of these diseases in developing countries. Investments in the Programme over the past 20 years have clearly paid dividends. Despite the progress made in the past two decades, investments in research are still needed to sustain these advances and to develop new and better tools. TDR’s mandate and disease portfolio is still highly relevant to the challenges of the next decade in terms of infectious diseases. However, as a Special Programme it is facing new challenges:

- it is “fragile” – the 1990’s brought a gradual decline in the financial and human resources available to carry out its work;
- rapid and significant changes in WHO’s internal operating environment will require the Programme to reposition itself;
- the external environment is evolving at an increasingly rapid pace, bringing together both opportunities and challenges for those involved in the field of tropical diseases research and control; and
- there is room for improvements in some areas of the Programme - preventive maintenance and fine tuning is needed on a regular basis for any programme.

This section will examine two critical areas: TDR’s reorganization and the continuum between research and control.

9.1 TDR reorganization

Until 1994, TDR was largely organized by disease and operated through a series of steering committees. These committees covered all aspects of research within a disease, from basic research to operational research; although malaria and leprosy were exceptions, each having several steering committees (malaria: immunology, chemotherapy, applied field research / leprosy: immunology, chemotherapy). In addition there were two discipline-specific groups: social sciences and epidemiology. This organization reflected, by and large, what was happening in the scientific community. Projects were investigator initiated and resources allocated on the basis of both relevance and merit.

Many reasons - declining financial resources, the need for more selectivity and focus as well as new scientific advances - led to the reorganization of TDR’s research and development programme into, what has been called, a transdisease approach, which cuts across all diseases. More focus was given to product development and applied field research under this new structure.

The steering committee structure was also changed to reflect the new organizational structure. The activities of the Strategic Research component are reviewed through three steering committees: Parasite
Genome, Molecular Entomology (Malaria) and Pathogenesis. In an effort to rationalize the technical advisory structure, a Steering Committee for Product Development and one for Vaccine Development were established to provide advice to the Product R&D unit. The Applied Field Research (AFR) component has a more complex advisory structure which includes both individual task forces and a steering committee. The area of applied field research was to cover post-registration research up to operational disease control problems. Various options were also explored for integrating Research Capability Strengthening (RCS) activities with R&D activities.

As mentioned before, leprosy is not really a part of this new structure. Since 1992, TDR’s leprosy research component collaborates with WHO’s Global Tuberculosis Programme and is managed through two mycobacterial disease steering committees, one concerned with immunology (IMMYC) and the other with chemotherapy (THEMYC).

9.1.1 Mixed reviews

In reviewing the structure and the progress achieved to date in each of the components, the Committee identified both positive and negative aspects to the reorganization, the “transdisease” approach, and the increased focus on product R&D and applied field research. Efficiency and effectiveness may have improved in some areas, but the outcome is less positive in others.

Strategic Research: the new approach has allowed TDR to take full advantage of new developments in biotechnology and molecular biology. It has helped to create new international networks in parasite genome and molecular entomology (malaria) with top scientists participating. These investments are for the long term and will need to be sustained if any ultimate impact is to be expected. There is evidence that scientific knowledge has been expanded and the prospects look promising.

Product R&D: the reorganization has resulted in a more streamlined and efficient advisory and management structure and has contributed positively to the pace of development of drugs and vaccines. The commonality of current drug development techniques and the technical requirements for preclinical and clinical trials can best be sustained by an “umbrella” approach. The disease element is still important - there is no such thing as a transdisease “magic bullet” - but can be met through the present umbrella structure.

Applied Field Research: is a heterogeneous group of projects covering a wide range of topics ranging from testing the efficacy of diagnostic tools, testing new drug regimens, applied entomological and epidemiological research; assessments of intervention, implementation and promotion techniques and socioeconomic research (e.g. gender). While the output has been important, the reorganization has not been as effective as in the other two components and has led to a number of problems, including: a cumbersome and complex advisory structure with the creation of de facto three levels of review: task forces, steering committee, STAC.
C scientific expertise in appropriate fields is more likely be found at the task force level than at the steering committee level.

C although time-limited in nature, there is a clear evolution from one task force to the next, both in terms of topics addressed and the need to follow-up, confirm or add to results obtained in the first phase or the need to move new tools closer towards control.

C there is no clear evidence how priorities were established or of clear linkages to disease control priorities.

C the task force structure itself does not appear to have been a very effective mechanism for establishing cross-organizational linkages with CTD.

As a result of the reorganization, there is closer collaboration between the Research Capability Strengthening activities and that of the research programmes. This has had some positive aspects for example: support has been given for training in genome research and molecular entomology; for research proposals by developing countries in pathogenesis, and grants given for the transfer of high throughput DNA sequencing technology. Investigator driven proposals in the applied field research area are also now being overseen by the Research Strengthening Group. However, it is important to keep a balance between close linkages with TDR priorities in the sponsoring of research projects and meeting the capacity development needs of DECs over the longer term.

9.1.2 Retain the positive and address the negatives

As a general rule, rigid compartmentalization between basic, product R&D and applied field research does not allow for a more systemic and broad based approach to disease research and control issues; thus efforts can often appear disjointed and unrelated to overall priorities. The Committee also feels that priority setting, monitoring and reporting on progress and impacts will still need to be done on a disease specific basis. For many reasons - including resource limitations and the structure itself - the concept of a disease coordinator has not worked very effectively in TDR.

**TDR is really a matrix organization:** and to function properly, matrix organizations need to have entities that are responsible for the lateral as well as the vertical aspects of a programme. Both these dimensions must also be reflected in the planning and setting of priorities, the identification of new challenges within each area, and the reporting on progress and achievements. The strategic context for the setting of priorities will be the specific challenges in each of the disease areas; the role of other stakeholders in the field; the “niche” filled by TDR; as well as country, regional and global priorities.

**Innovation and progress do not occur in a linear fashion:** the structure implies a linear progression from strategic to applied field research, when in fact the process of innovation and adaptation of new technologies is far more dynamic and involves constant feedback into the system as new knowledge becomes available and unanticipated problems arise which require re-examination and adaptation at the earlier stages.
Re-introduction of the role of disease coordinator as well as the development of a strategic plan that would set the overall context for TDR’s priorities by disease - and which would balance the present workplans organized by components - could be ways of addressing this issue without significantly modifying the organizational structure.

9.2 CTD - TDR interface

The External Review Committee found **evidence of increased separation between the research programme and the control programme for tropical diseases**. Different organizational cultures, different networks of experts and linkages with the field, the existing structure (co-sponsored versus regular); increasing competition for funds and budgetary constraints are all factors that have contributed to the present situation.

This problem is significant and has been long standing; however, it appears to have been exacerbated by TDR’s reorganization and the implementation of the task force structure in the applied field research component. Although staff on an individual basis are willing and open to more collaboration and increased communication, there is evidence that both parties are dissatisfied not only with the current process but also with the results.

The Committee is convinced that better research - in terms of outputs, quality and coverage - and control can be achieved if there were more recognition of the control needs from both a field and disease specific perspective. The case studies outlined quite clearly the equal contributions a strong research function and a strong control function make to the attainment of the ultimate objective - the reduction of disease burden in endemic countries.

Before defining the problem and discussing options for resolving the issues, it is important to set the more general context in which the two programmes have evolved.

9.2.1 Setting the context

The Division of Control of Tropical Diseases (CTD) is a regular WHO programme with responsibility for global, regional and country activities for controlling the tropical diseases under its mandate. TDR is a co-sponsored Programme, with WHO as executing agency, and has two interdependent objectives: the development of new tools and strategies for disease control and the strengthening of the capability of disease endemic countries to undertake the research required. The following box summarizes some of the key elements of each programme.

There is some confusion with respect to the use of the term ‘extra-budgetary funds’ and ‘co-sponsored’ or ‘special’ programmes. From WHO’s perspective, as executing agency, TDR is funded almost exclusively by extrabudgetary funds designated for its activities.
A study on extra-budgetary funds defined the two in the following way:  

C **WHO co-sponsored or Special Programmes:** these are large semi-independent programmes, funded and managed by a consortium of UN sponsors, including WHO, and interested donors under a specific memorandum of understanding. WHO is the executing agency. They receive limited direct support from the WHO regular budget, but receive administrative support from the Organisation (which is regular budget funded) and for which they pay varying levels of support costs (in kind or as a percentage of funds received).

C **WHO Regular Programmes:** these are programmes with full WHO ownership and no other formal authority than the World Health Assembly, where extra-budgetary funds (EBFs) are used to supplement regular budget funding (RBFs). There is considerable variation in the size, purpose and method of operation of these programmes and in the ratio of EBFs to RBFs. Depending upon their size, they may have external technical advisory boards and donor support groups, not dissimilar to those of the co-sponsored programmes, but with an advisory rather than a management role.

In donor countries, the regular budgetary funds are usually the responsibility of the Ministry of Health; whereas extra-budgetary funds represent Official Development Assistance (ODA) money and are the responsibility of the foreign ministry or the national aid agency of the country. Co-sponsored or special programmes (TDR, OCP, HRP) receive the largest share of extra-budgetary funds in WHO.

This study identified a number of issues related to WHO’s organizational structure and the impact of extra-budgetary funds. A few of these are highlighted here:

C co-sponsored and regular programmes (which both receive large volumes of EBFs) are consistent with WHO’s mandate;
C these programmes are targeting important health issues and disease burdens;
C EBFs however have contributed to the emphasis on vertically managed programmes, thereby weakening cross-programme linkages and coordination;
C separate programmes compete rather than cooperate on activities and fundraising; and
C multiple governing mechanisms aggravate the existing fragmentation in the organization, create artificial compartments and are extremely time consuming.

TDR and CTD have an almost identical disease portfolio. Their activities and areas of responsibilities are different but they share the same objective - the control and elimination of targeted diseases in endemic countries. However, as a result of the two different structures that co-exist within WHO, TDR and CTD have separate mechanisms for financing, fundraising, networking and scientific collaboration, and may have, at times, engaged in research and policy formulation processes which largely did not interact.
## Characteristics of the TDR and CTD Programme

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>CTD</th>
<th>TDR</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of programme</strong></td>
<td>Regular WHO programme</td>
<td>Co-sponsored programme: UNDP, World Bank and WHO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>WHO - executing agency</td>
</tr>
<tr>
<td><strong>Organizational structure</strong></td>
<td>Disease based programmes</td>
<td>Transdisease organization</td>
</tr>
<tr>
<td><strong>Areas of activity</strong></td>
<td>C coordination and normative functions</td>
<td>C strategic research</td>
</tr>
<tr>
<td></td>
<td>C country support</td>
<td>C product R&amp;D</td>
</tr>
<tr>
<td></td>
<td>C operational research</td>
<td>C applied field research</td>
</tr>
<tr>
<td></td>
<td>C training</td>
<td>C training and institution strengthening</td>
</tr>
<tr>
<td><strong>Disease portfolio</strong></td>
<td>C Malaria</td>
<td>C Malaria</td>
</tr>
<tr>
<td></td>
<td>C Dracunculiasis</td>
<td>C Filariases (onchocerciasis, lymphatic filariasis)</td>
</tr>
<tr>
<td></td>
<td>C Filariases (onchocerciasis, lymphatic filariasis)</td>
<td>C Leishmaniasis</td>
</tr>
<tr>
<td></td>
<td>C Leishmaniasis</td>
<td>C African trypanosomiasian</td>
</tr>
<tr>
<td></td>
<td>C Dengue</td>
<td>C Schistosomiasis</td>
</tr>
<tr>
<td></td>
<td>C African trypanosomiasian</td>
<td>C Chagas disease</td>
</tr>
<tr>
<td></td>
<td>C Schistosomiasis and intestinal parasites</td>
<td>C Leprosy</td>
</tr>
<tr>
<td></td>
<td>C Chagas disease</td>
<td></td>
</tr>
<tr>
<td>Other areas:</td>
<td>C WHO Pesticide Evaluation Scheme (WHOPES)</td>
<td></td>
</tr>
<tr>
<td><strong>Advisory structure</strong></td>
<td>Meeting of Collaborators (MOC)</td>
<td>Joint Coordinating Board (JCB)</td>
</tr>
<tr>
<td></td>
<td>Technical Advisory Group (TAG)</td>
<td>Standing Committee</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Scientific and Technical Advisory Committee (STAC)</td>
</tr>
<tr>
<td><strong>Financing mechanisms</strong></td>
<td>Regular WHO budget: 30-50%</td>
<td>Contributions from Co-sponsors: 20-25%</td>
</tr>
<tr>
<td></td>
<td>Voluntary contributions: 50-70%</td>
<td>Voluntary Contributions: 75-80%</td>
</tr>
</tbody>
</table>
Any option of change proposed for consideration will need to be considered in the light of the broader changes in WHO as, under new leadership, WHO organizes its programmes and activities around key functions that tell clearly what business it is in. The Director-General elect has stated this quite clearly in her speech to the Fifty-first World Health Assembly in May 1998:

“To succeed in this endeavour we must be able to say: WHO is one. Not two - meaning one financed by the regular budget and one financed by extrabudgetary funds. Not seven - meaning Geneva and the six regional offices. Not more than fifty - meaning the individual programmes.

WHO must be one: Setting its priorities as one, raising additional resources as one, speaking out as one. And then - but only then - can we act effectively in our decentralized diversity through skilled presence at the country level, through regional guidance by the regional offices and through global direction by the headquarters and the governing bodies.”

9.2.2 Defining the problem

The development of effective control strategies, policies and guidelines requires constant monitoring and evaluation. Operational research plays an important role in understanding the dynamics of diseases in the field and in the development of effective implementation strategies. The very nature of applied field research means that it must be closely linked to regional and country priorities and take into account the diversity of settings in which control programmes operate.

At the very heart of the interface between research and control is applied field research. Close collaboration between the two programmes is essential both to ensure the relevance of TDR’s applied field research projects and to facilitate the introduction of new tools for disease surveillance and control in endemic countries. A review of various documents indicates that this is acknowledged by both parties but has not worked out in practice. The Committee believes that a significant part of the problem lies in the current approach to priority setting and the existing review mechanisms.

A number of critical issues were identified by the Committee and were taken into account when developing options:

C the need for joint planning and priority setting to ensure that operational research is closely linked to control priorities - the Committee firmly believes that in order to be most optimal and effective, control issues must be a prime driver for operational research;
C disease related issues as well as specific regional/country needs are critical elements for consideration in the setting of priorities for operational research;
C the need for joint ownership and management of the applied field research projects;
C the need to rationalize the advisory structure in AFR (task force/steering committee/STAC) and yet ensure input from external reviewers; and
C the need for more transparent linkages between research and control programmes.

9.2.3 Options for consideration

The External Review Committee feels that the status quo is no longer possible and that serious alternatives have to be developed to address these issues.

Two options are proposed for consideration by the Joint Coordinating Board. The first option is more limited in scope and focuses essentially on addressing the interface problems between CTD and TDR, removing existing inefficiencies and providing for more transparent and shared decision making and monitoring in the applied field research area. The second option addresses the larger issue of the evolution of co-sponsored programmes and regular programmes within WHO.

Option A: Siamese Twin option

This option - which we have called the “Siamese Twin” option - focuses on the core of the interface between research and control - the applied field research element. It keeps the two programmes separate, with separate advisory structures and different managerial, financial and technical systems. However, the two programmes are “joined at the hip” for one component - applied field research.

It’s main objective is to provide:

C a transparent and joint process for planning and identifying priorities;
C joint ownership of the projects or task forces; and
C a rationalization of the current advisory structure.

This recommendation involves two distinct elements. The first suggests new mechanisms to review the ongoing TDR task forces and to reduce the current burden of review. The second sets out mechanisms to improve the setting of priorities for the next planning phase which is to begin in the second half of 1998.

Review of ongoing task forces: the proposal is to phase out the Steering Committee for Applied Field Research that reports to STAC in TDR. The workplans for the ongoing task forces have been reviewed and approved by both STAC and the AFR steering committee. Task forces already involve experts in relevant fields that provide external input into the work of the task forces.

Following the same principles as those adopted by STAC and TDR for the management of product development teams within the Product R&D unit, the work of the task forces should be reviewed internally on a yearly basis by both the directors of CTD and TDR, with the assistance of two or three
external experts as judged appropriate (could be the chairman of STAC and TAG). The reports would then be sent directly to STAC for consideration either by the committee as a whole or a sub-group of STAC members selected for their expertise in field research and control. These reports would also be made available to the CTD’s Technical Advisory Group.

Feedback from CTD on the introduction of research findings, the evaluation of their practical utility and the identification of areas of potential improvement would also be encouraged through the preparation of a report by CTD.

**Setting new priorities:** both CTD and TDR staff would be involved to play a proactive role in the identification of new research topics relevant and important for tropical disease control. Various mechanisms could be used to obtain new ideas for research and identify control priorities in the field. A group of internally designated staff, from both CTD and TDR, would prepare a report summarizing the key issues, priorities identified, estimated costs, and potential collaborators that could provide in-kind and financial resources.

An external review committee -- including selected representatives from both TAG and STAC - would be set up to review these proposals, to prioritize the issues and to make recommendations for a future workplan. This group should also give some consideration to the mechanisms that would be most appropriate for carrying out these projects: for example, the task force structure for multi-centre trials; small grants for projects critical at a regional level but with limited need for a global structure; investigator-driven proposals; identification, on a competitive basis, of a consultant or academic institution to carry out a specific activity, etc. The objective would be to find innovative and effective ways of addressing critical control issues. The recommendations of this review committee would then be forwarded to both STAC and TAG.

**Option B: Umbrella option**

Option B goes one step further and proposes a single umbrella structure that would manage the two separate programmes: research and training (TDR) and control activities (CTD). This option recognizes the strengths of both programmes; their specific contributions to the ultimate objective of reducing the disease burden in endemic countries; and tries to address in a proactive way some of the wider issues raised with respect to the general governance of WHO and the role of special programmes within a rapidly changing internal context. Without going into details, the key elements of such an option would involve:

- Joint governance and technical advisory structures - to be developed in close consultation with co-sponsors and other contributors to the programmes;
- Maintenance of two separate programmes but under one management authority - providing the setting for the development of strategic and action plans which would include a systemic overview
of the critical issues in both research and control and the contributions of both programmes to the ultimate objective - control of endemic tropical diseases;
C joint reporting on performance;
C joint financial systems; and
C joint communications and advocacy roles.

The External Review Committee is very much aware that these two proposals, which can be considered independently or in a phased approach, will require broad discussion and negotiation among the co-sponsors and the donor community. It will require creativity, openness and political will to arrive at a pragmatic and workable solution. It will also require the breaking down of barriers between scientists and control managers; between a “special” and a “regular” programme; between co-sponsors and other bilateral donors. Inevitably, we expect that there will be resistance from those with vested interests to maintain the status quo.

However, the ultimate objective, is to determine how TDR’s core competencies - its scientific rigour, its well-established international networks of collaborators, its contribution to strengthening the research capacity of DECs - can best be used to foster the ultimate goal which it shares with WHO, the monitoring, controlling and possible elimination of infectious tropical diseases. The idea is to build on past successes yet develop new strategies to respond to new opportunities. The hope is that the donor community will continue its support to the TDR activities while negotiating a different future for the Programme.

**Recommendations:**

16. **The relationship between research and control needs fundamental restructuring.** The Committee believes that a significant part of the problem lies in the current approaches to priority setting and the parallel review mechanisms. Critical issues that need to be addressed include: the need for joint planning, priority setting and ownership of applied field research projects; the recognition of regional and country priorities in setting priorities for operational research; the need to rationalize the current advisory structure (task force / steering committee / STAC) and the importance of establishing transparent linkages between research and control and surveillance programmes.

17. **Two options are proposed for consideration.** The first - which can be called the “Siamese twin option” - focuses on the interface between research and control. The two programmes remain as separate entities with different directors, advisory structures, financial systems, but are “joined” for one component, applied field research. The second option - which could be called the umbrella option” proposes a single management structure for the two separate programmes with joint governance and advisory structures.
References


3. *The burden of tropical diseases among the poorest and richest 20% of the global population*, International Health Policy Program, Davidson R. Gwatin and Michel Guillot, 1998 (TDR/ER/RD/98.1)


5. *TDR’s impact on science: a bibliometric study*, Catherine Michaud, Harvard University, 1998 (TDR/ER/RD$98.2$


7. *TDR’s contribution to the development of ivermectin for onchocerciasis*, Tomoko Fujisaki and Michael Reich, Takemi Program in International Health, Harvard School of Public Health, 1998 (TDR/ER/RD/98.3)

8. *TDR’s contributions to the development of multidrug therapy for the control of leprosy*, Rania Milleron, Tomoko Fujisaki and Michael Reich, Takemi Program in International Health, Harvard School of Public Health, 1998 (TDR/ER/RD/98.4)

9. *TDR’s contributions to the development of the fumigant canister for controlling Chagas disease*, Tomoko Fujisaki and Michael Reich, Takemi Program in International Health, Harvard School of Public Health, 1998 (TDR/ER/RD/98.5)

10. *A research policy agenda for science and technology to support global health development - A synopsis*, 1998 (WHO/RPS/ACHR/97.3)

11. *Memorandum of understanding on the administrative and technical structures of the special programme for research and training in tropical diseases* (TDR/CP/78.5/Rev.88)


ANNEX 1

TERMS OF REFERENCE
INTRODUCTION AND BACKGROUND

The Special Programme for Research and Training in Tropical Diseases (TDR) was established as an international response to major health problems of developing countries in the tropics. The Programme was planned and initiated by the World Health Organization (WHO) with the assistance and co-sponsorship of the United Nations Development Programme (UNDP) and the World Bank and operates under the guidance of, and with resources provided by, its Cooperating Parties represented by the Joint Coordinating Board (JCB). An interdisciplinary group of scientists serve in their personal capacities as the Scientific and Technical Advisory Committee (STAC) to advise the JCB on the Programme's scientific and technical activities and evaluate progress. The Programme coordinates with members of the world's scientific community, the planning and management of goal-oriented lines of research and training and institution strengthening towards two interdependent objectives:
C to develop, through scientific research, new methods of prevention, diagnosis, treatment and control of the major tropical diseases - malaria, schistosomiasis, filariasis (both onchocerciasis and lymphatic filariasis), trypanosomiasis (African sleeping sickness and Chagas disease), leishmaniasis and leprosy; and

C to strengthen the capability of developing countries to undertake the research required to develop new disease control technologies.

The Programme was established in 1975 and began operations in 1976. Up to 31 December 1995 the Programme had granted direct support to institutions and scientists throughout the world for 6387 projects (totalling almost US$ 360 million) in 121 Member States of WHO, with over 55% of these funds going to institutions and scientists of developing countries. Over 5300 scientists have been involved in projects supported by TDR or in the management of TDR's scientific activities.

The Programme has made valuable contributions to the knowledge of the target diseases, to the development of new tools to prevent, diagnose and cure the diseases and strengthen the capacities of institutions in endemic countries to conduct research on these diseases relevant to national needs. The development of new tools is a long-term endeavour - 20 years is a short time in product development. Up to 31 December 1995, 75 products had been developed with TDR support, of which 33 are in disease control use. For certain diseases, some of these tools have already had an impact on disease control and disease control strategies. Impregnated bednets for malaria, multidrug chemotherapy for leprosy, ivermectin for river blindness and community-based vector control methods for Chagas disease have all demonstrated their potential to save lives and reduce suffering.

The Programme is financed by voluntary contributions from governments, international organizations, foundations and other nongovernmental sources.

At the request of the Joint Coordinating Board, two external reviews of the Programme have been carried out by External Review Committees. The first Committee met in 1981-1982 to review the first five years of operations (1977-1981 inclusive) and made its report to the Fifth Session of the Joint Coordinating Board in 1982. The review focused on guiding the planning, organization, operation and management of the Programme over the next five years (1982-1986). The report of the first External Review Committee is contained in Annex IV to the Report of the Fifth Session of the Joint Coordinating Board [document TDR/JCB(5)/82.3]. The second external review was carried out five years later in 1986-1987 and examined TDR's achievements, the fundamental basis for its existence and its future role and development. The second External Review Committee submitted its report to the Eleventh Session of the Joint Coordinating Board in 1988. The report is contained in document TDR/JCB(11)/88.6 Rev.1.

JCB(11) agreed that "the continued existence of TDR was compellingly justified" and that "the Programme was clearly needed for at least another 10 years". The Board requested that "a review of the continuing need for the Programme should be set in motion in 1994 to be completed and considered by the Board in 1996 to coincide with the twentieth anniversary of the start of TDR's operations".

Accordingly, preliminary terms of reference for the third external review were presented to JCB(16) in 1993. However, JCB(16) considered that "as the new strategy and organizational structure of the Programme would come into force on 1 January 1994, the timing of a third external review of TDR would be more appropriate in 1997-1998, which would allow an examination of the strategy after three years of operation and of TDR's priorities into the next millennium".
JCB(17) in 1994 agreed that the functions and activities of the Research Strengthening Group, and the leprosy research component and other components should be examined in the course of the third external review. These issues were added to the objectives of the review (see section 3 below).

Draft terms of reference for the third external review were presented to JCB(18) in 1995. JCB(18) decided that the review should be carried out in 1997-1998. The Board added more topics to be included in the objectives of the review (see section 3 below) and commented on the composition of the External Review Committee (see section 5 below). JCB(18) requested that the final terms of reference for the review should be presented to JCB(19) in 1996 together with information from the preparatory phase of the review (see section 2 below).

JCB(19) in 1996 made further amendments to the terms of reference.

2. PREPARATORY PHASE

In order to facilitate the third external review, the Scientific and Technical Advisory Committee, at its seventeenth meeting in March 1995, decided to carry out a prospective thematic review (PTR) on the impact of TDR. The task of the PTR was to prepare an analytical framework required to assess TDR's impact with regard to:

(i) TDR target diseases
(ii) use of TDR-supported tools in disease control
(iii) tropical diseases research; and
(iv) research capability in endemic countries.

The Report of the PTR Meeting in September 1995 was submitted to the Scientific and Technical Advisory Committee at its Eighteenth Meeting (STAC-18) held on 4-6 March 1996 and is annexed to the report of STAC-18, document TDR/STAC-18/96.3.

3. OBJECTIVES OF THE REVIEW

The objectives of the third external review and evaluation of the Special Programme are as follows:

1. **Fundamental Basis:** to review the continuing need for the Special Programme, bearing in mind the contexts of changes in disease patterns and changes in the international environment

2. **Research Progress and Links to Control:**

   - to examine progress and effect/impact under the strategy for TDR towards the year 2000: by the consolidated areas of strategic research, product research and development, applied field research (including research on cross-cutting issues) and research capability strengthening (including the functions and activities of the Research Strengthening Group); and by disease

   - to examine links between TDR’s research activities and the operational control of tropical diseases and to what extent TDR’s strategic research priorities are influenced by control issues

   - to review the methods currently used to measure performance and progress in achieving positive outcomes and to make recommendations for improving Programme evaluation
3. **Future Directions:**

- to review the future portfolio of TDR’s target diseases, the Programme’s future directions and its priorities into the next millennium

- to consider any implications for TDR’s priorities resulting from the report and recommendations of the *Ad Hoc* Committee on Health Research Relating to Future Intervention Options

- to examine future resource needs, opportunities and implications for tropical disease research; and to propose alternative financing requirements for the next ten years by Programme component, based on two scenarios: (i) all future needs and (ii) highest priority needs as determined by the External Review Committee

4. **Collaboration:**

- taking into account the stage of development of each programme, to examine the effectiveness of linkages between TDR and relevant programmes inside WHO, especially the Division of Control of Tropical Diseases, the Global Tuberculosis Programme, and the Division of Emerging and other Communicable Diseases Surveillance and Control; between TDR and other tropical disease programmes outside WHO; and between TDR and the pharmaceutical industry

- to examine a global partnership for tropical disease research with other major actors in this field

5. **Organizational Structure:**

- to examine the outcome of the Programme’s new organizational structure and its ability to carry out the strategy for TDR towards the year 2000, including whether it reflects the most efficient use of the reduced funds available to the Programme

- to examine the balance of TDR’s resources allocated to the areas of strategic research, product research and development, applied field research and research capability strengthening

- to examine the prioritization of the task forces under the applied field research component

- to examine the financial management, administrative structure and governance of the Programme

4. **SPONSORSHIP OF THE REVIEW**

The review and evaluation of the Special Programme will be conducted under the authority of the TDR Joint Coordinating Board.

The review will be carried out by an independent *External Review Committee* (ERC) which will report to the JCB.
5. COMPOSITION OF THE EXTERNAL REVIEW COMMITTEE

The External Review Committee will consist of five experts in one or more of such fields as disease control, epidemiology and public health in tropical countries; scientific research and development, especially related to the scope of the Special Programme: the biological, economic and social sciences; and research management. The Committee members should not be receiving financial support from the Special Programme, or be serving as members of the Scientific and Technical Advisory Committee or other TDR scientific committees. There should be a balance of representatives from both developed and developing countries and from the different regions.

One member of the second External Review Committee will take part in the third External Review Committee.

Members of the Committee will serve in their personal capacities.

JCB members and observers were invited to submit names of potential candidates which were reviewed by the Standing Committee, the Chairperson and Vice-Chairperson of the JCB. Their joint proposals for membership of the External Review Committee were submitted to JCB(19) and approved by the Board. The list of members of the External Review Committee is contained in the Annex to this document.

In case, at the last minute, any member of the External Review Committee is unable to participate in the review, the Standing Committee, the Chairperson and Vice-Chairperson of the JCB will appoint a replacement.

6. SUPPORT FOR THE REVIEW

The Standing Committee is responsible for ensuring that appropriate administrative arrangements are made for the External Review Committee. The Executing Agency (WHO) will arrange secretariat support and other services and facilities as may be required. An executive secretary to the External Review Committee will be appointed to assist the Committee in its work. The executive secretary will be responsible for preparing or organizing special studies, reviews and discussions for the Committee, for drafting reports for the consideration of the Committee and for organizing its work including meetings and site visits.

The name of the executive secretary approved by the JCB is included in the Annex to this document.

7. FUNDING OF THE REVIEW

The budget for the review is estimated at US$ 340 000, but the cost of the review should be kept as low as possible without compromising its quality. In view of TDR’s financial constraints, the cost of the review is not included in the TDR Programme Budget for the 1996-1997 Biennium. As far as possible, TDR will seek additional funds to cover the cost of the review.

JCB participants are called upon to provide the additional funds required and to submit pledges and contributions to the Special Programme Coordinator.

If insufficient additional funds are received, the cost will have to be included in the budget and the balance of funds taken from the regular contributions to the Programme.
8. OPERATION OF THE REVIEW

The External Review Committee will develop its own plans for the review following the guidelines provided by the JCB and the Standing Committee and taking note of the mechanisms employed by and the reports of the first and second External Review Committees. The External Review Committee will benefit from the preparatory phase of the review and will receive the STAC report on the prospective thematic review on the impact of TDR. The External Review Committee will have access to records and reports of TDR, as well as to persons responsible for the implementation of all aspects of the Special Programme. The Twelfth Programme Report, covering the 20 years of TDR, the Thirteenth Programme Report covering the 1995-1996 biennium and the document on TDR Towards the Year 2000: Strategic Considerations will serve as major background documents for the Committee. The External Review Committee will also receive the report of the Ad Hoc Committee on Health Research Relating to Future Intervention Options entitled “Investing in Health Research and Development”.

The External Review Committee will begin reading all the background documentation after the Nineteenth Session of the Joint Coordinating Board in June 1996. To ensure the linkage between the Committee and STAC, the first meeting of the External Review Committee will be held in conjunction with the Nineteenth Meeting of the Scientific and Technical Advisory Committee in March 1997. The External Review Committee will prepare its strategy for presentation to the Twentieth Session of the Joint Coordinating Board in June 1997. This will provide the Committee with the opportunity to discuss its mandate and strategy with the Board and to raise any questions for clarification. The External Review Committee will prepare a report for comments by the Executing Agency, the Scientific and Technical Advisory Committee and the Standing Committee by 31 January 1998. This report, together with the comments of the Executing Agency, STAC and the Standing Committee, will be submitted to the Twenty-first Session of the Joint Coordinating Board in June 1998. The Chairperson of the External Review Committee will be present at the Twenty-first Session of the JCB.

9. REVIEW PROCESS

The External Review Committee will meet as required, to:

(a) review TDR documentation;

(b) interview (as necessary) representatives of the co-sponsors, Joint Coordinating Board including major contributors, Scientific and Technical Advisory Committee and other TDR scientific committees, TDR secretariat and staff in related WHO programmes, members of the WHO Global Advisory Committee on Health Research, research scientists and trainees, scientists involved in disease control activities, and representatives of other agencies working in the field of tropical disease research;

(c) visit (as necessary) selected sites of projects, institutions, public health services, ministries or agencies, including in advanced developing countries and the least developed countries in different geographical areas; and

(d) carry out any other investigations or activities deemed necessary for the review by the External Review Committee, the Standing Committee or the JCB.
COMPOSITION OF THE THIRD EXTERNAL REVIEW COMMITTEE

Members

Professor Gelia T. Castillo, Professor Emeritus, University of the Philippines at Los Baños and Part-time Consultant, International Rice Research Institute, Manila, Philippines (Member of Second External Review Committee of TDR)

Professor Francis Kwesi Nkrumah, Director, Noguchi Memorial Institute for Medical Research, University of Ghana, Legon, Ghana

Dr Jaime Sepúlveda Amor, Director General, National Institute of Public Health, Cuernavaca, Morelos, Mexico

Mr Wilfried P. Thalwitz, Former Vice-President, The World Bank, Washington, D.C., USA

Professor Hans Wigzell, Rector, Karolinska Institute, Stockholm, Sweden

Executive Secretary

Ms Hélène G. Boyer, Senior Evaluation and Planning Manager, National Research Council of Canada, Ottawa, Ontario, Canada
ANNEX 2

DISEASE PORTFOLIO
## CHAGAS DISEASE

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Health Burden</th>
<th>Progress and Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Modes of transmission</strong></td>
<td><strong>Estimated Global Health Burden</strong></td>
<td><strong>Primary interventions</strong></td>
</tr>
<tr>
<td>C contact with faeces of certain parasite-</td>
<td>C overall prevalence: 16-18 million cases</td>
<td>C insecticide treatment of houses</td>
</tr>
<tr>
<td>carrying insects that bite humans</td>
<td>C deaths: &gt;45 000 per year</td>
<td>C blood screening to prevent transmission through transfusion</td>
</tr>
<tr>
<td>C blood transfusion</td>
<td>C chronic complications: 2-3 million cases</td>
<td>C drug treatment for acute early indeterminate and congenital cases</td>
</tr>
<tr>
<td>C congenital</td>
<td>C estimated number of new cases per year: 300 000</td>
<td></td>
</tr>
<tr>
<td><strong>Characteristics of illness</strong></td>
<td><strong>Endemic countries and regions</strong></td>
<td><strong>Progress</strong></td>
</tr>
<tr>
<td>C initial phase may cause illness and death</td>
<td>18 countries in Central and South America, in 2 ecological zones:</td>
<td>C designated by WHO for elimination by 2010</td>
</tr>
<tr>
<td>in children under five years of age</td>
<td>C the Southern Cone, where the vector lives inside the home</td>
<td>C incidence has decreased by 70% since 1985</td>
</tr>
<tr>
<td>C in 32% of those infected, fatal damage to</td>
<td>C northern South America (Andes) and Central America, where the vector lives</td>
<td>C estimated cost of elimination (1998-2005): US$391 million</td>
</tr>
<tr>
<td>heart and digestive tract occurs in the</td>
<td>both inside and outside the home</td>
<td>C transmission interrupted in Uruguay in 1997</td>
</tr>
<tr>
<td>chronic phase after many years of infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Issues</strong></td>
<td></td>
<td><strong>Issues</strong></td>
</tr>
<tr>
<td>C the insect carriers in Andean and Central</td>
<td></td>
<td>C the insect carriers in Andean and Central American countries can be controlled</td>
</tr>
<tr>
<td>American countries can be controlled using</td>
<td></td>
<td>using household insecticides; however, there is a need to adapt the control</td>
</tr>
<tr>
<td>household insecticides; however, there is a</td>
<td></td>
<td>strategies to the vector’s behaviour</td>
</tr>
<tr>
<td>need to adapt the control strategies to the</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## African Trypanosomiasis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Health Burden</th>
<th>Progress and Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mode of transmission</strong></td>
<td><strong>Estimated Global Health Burden</strong></td>
<td><strong>Primary interventions</strong></td>
</tr>
<tr>
<td>C bite of tsetse flies that carry the parasite from humans or animals</td>
<td>C number of new cases per year: 300,000-500,000</td>
<td>C case detection and drug treatment of infected persons</td>
</tr>
<tr>
<td></td>
<td>C deaths per year: 150,000</td>
<td>C vector control, often with community participation, using tsetse traps and screens</td>
</tr>
<tr>
<td></td>
<td>C DALYs lost in 1990: 1,470,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C number of disabled people: 100,000 (1996)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C prevalence may be over 70-80% in villages in certain foci</td>
<td></td>
</tr>
<tr>
<td><strong>Characteristics of illness</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C early symptoms include fever and enlarged lymph glands and spleen; they are more severe and acute in <em>T. b. rhodesiense</em> infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C advanced symptoms include neurological and endocrine disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C progresses slowly (generally in years) in <em>T. b. gambiense</em> infections, but rapidly (generally in weeks) in <em>T. b. rhodesiense</em> infections</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C fatal in all cases if left untreated</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Endemic countries and regions</strong></td>
<td><strong>Progress</strong></td>
</tr>
<tr>
<td></td>
<td>36 countries in sub-Saharan Africa, including:</td>
<td>C traps are effective but expensive to set up and maintain</td>
</tr>
<tr>
<td></td>
<td>C 7 countries where the disease is highly endemic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C 4 countries where the disease is epidemic</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C 12 countries where the disease is of moderate-low endemicity</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C 13 countries where the epidemiological status is poorly known</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Issues</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C although 55,000,000 people are exposed to the risk of infection, only 4,000,000 are under regular medical surveillance</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C the disease has recrudesced since the 1970s</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C available drugs have adverse side effects and/or are too expensive</td>
</tr>
<tr>
<td>Characteristics</td>
<td>Health Burden</td>
<td>Progress and Issues</td>
</tr>
<tr>
<td>-----------------</td>
<td>--------------</td>
<td>---------------------</td>
</tr>
<tr>
<td><strong>Mode of transmission</strong></td>
<td>Estimated Global Health Burden</td>
<td>Primary interventions</td>
</tr>
<tr>
<td>C thought to be human to human, via droplets from respiratory tract of untreated patients with severe disease</td>
<td>C number of new cases per year: 690 000 (1997)</td>
<td>C multidrug therapy (MDT)</td>
</tr>
<tr>
<td></td>
<td>C number of disabled people: 2-3 million</td>
<td></td>
</tr>
<tr>
<td><strong>Characteristics of illness</strong></td>
<td>Endemic countries and regions</td>
<td>Progress</td>
</tr>
<tr>
<td>C slowly affects skin, nerves and mucous membranes</td>
<td>C about 32 countries in Africa, Asia and Latin America</td>
<td>C MDT introduced in 1982, since when millions (10+) of patients have been cured of leprosy</td>
</tr>
<tr>
<td>C nerves, bones, eyes and other organs may be permanently damaged</td>
<td>C most cases in South and South-East Asia</td>
<td>C designated by WHO for elimination (reducing the prevalence to less than 1 per 10 000 population) by 2000</td>
</tr>
<tr>
<td>C deformities occur to face and extremities after many years</td>
<td></td>
<td>C estimated cost of elimination: US$230 million</td>
</tr>
<tr>
<td><strong>Issues</strong></td>
<td></td>
<td><strong>Issues</strong></td>
</tr>
<tr>
<td>C reaching every patient in every village</td>
<td></td>
<td>C reaching every patient in every village</td>
</tr>
<tr>
<td>C providing services in remote and underserved areas</td>
<td></td>
<td>C providing services in remote and underserved areas</td>
</tr>
<tr>
<td>C improving community awareness and participation</td>
<td></td>
<td>C improving community awareness and participation</td>
</tr>
<tr>
<td>C research on epidemiology and nerve damage</td>
<td></td>
<td>C research on epidemiology and nerve damage</td>
</tr>
</tbody>
</table>
### ONCHOCERCIASIS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Health Burden</th>
<th>Progress and Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mode of transmission</strong></td>
<td><strong>Estimated Global Health Burden</strong></td>
<td><strong>Primary interventions</strong></td>
</tr>
<tr>
<td>C bite of blackflies that carry the larvae from human to human</td>
<td>C prevalence: 17 655 000</td>
<td>C drug treatment</td>
</tr>
<tr>
<td><strong>Characteristics of illness</strong></td>
<td>C deaths due to blindness: 47 000</td>
<td>C insecticide spraying to control blackflies (in certain areas only)</td>
</tr>
<tr>
<td>C adult worms lodge in nodules under the skin</td>
<td>C number of disabled people: 770 000</td>
<td></td>
</tr>
<tr>
<td>C immature worms move through the body, and, after dying, cause intense itching, skin disease and visual impairment including blindness</td>
<td>C skin disease: 6 million cases</td>
<td></td>
</tr>
<tr>
<td><strong>Endemic countries and regions</strong></td>
<td>C blindness (outside the OCP area): 290 000 cases</td>
<td></td>
</tr>
<tr>
<td>C incidence (outside the OCP area) of new cases of blindness per year: 40 000</td>
<td>C DALYs lost to blindness and visual impairment in 1990: 361 484</td>
<td></td>
</tr>
<tr>
<td>C DALYs lost to skin disease in 1990: 522 427</td>
<td>C <strong>Progress</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Issues</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C 99% of infected people live in tropical Africa</td>
<td>C in 11 West African countries covered, since 1974, by the Onchocerciasis Control Programme (OCP), whose activities are based on vector control: has been controlled as a public health problem</td>
<td></td>
</tr>
<tr>
<td>C isolated foci in Latin America and Yemen</td>
<td>C in 19 African countries covered, since 1996, by the African Programme for Onchocerciasis Control (APOC), whose activities are based on treatment with ivermectin: sustainable community-directed treatment with ivermectin is being established; the vector is being eliminated in selected foci</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>C implementation of Community-Directed Treatment and effective support by the health services</td>
</tr>
<tr>
<td></td>
<td></td>
<td>C the long-term impact of large-scale treatment</td>
</tr>
</tbody>
</table>
# LYMPHATIC FILARIASIS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Health Burden</th>
<th>Progress and Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mode of transmission</strong></td>
<td>C bite of mosquitoes that carry the larvae from human to human</td>
<td><strong>Primary interventions</strong></td>
</tr>
<tr>
<td><strong>Characteristics of illness</strong></td>
<td><strong>Estimated Global Health Burden</strong></td>
<td><strong>Progress</strong></td>
</tr>
<tr>
<td>C chronic disease: may cause elephantiasis (enlargement of limbs) and hydrocoele (swelling of scrotum)</td>
<td>C prevalence: 119 100 000</td>
<td>C designated by WHO for elimination as a public health problem on a global scale by 2020</td>
</tr>
<tr>
<td>C acute disease: attacks of filarial fever (pain and inflammation of lymph nodes and ducts, often accompanied by fever, nausea and vomiting) increase with severity of chronic disease</td>
<td>C DALYs for men lost in 1990: 3 000 000</td>
<td>C some national control programmes already under way</td>
</tr>
<tr>
<td>C asymptomatic patients have hidden damage to the lymphatic system and kidneys</td>
<td>C DALYs for women lost in 1990: 1 000 000</td>
<td>C SmithKline Beecham agreed in January 1998 to donate one drug (albendazole) to all endemic countries and provide financial and human resources support to the elimination goal</td>
</tr>
<tr>
<td><strong>Endemic countries and regions</strong></td>
<td>C lymphoedema: 16 200 000</td>
<td><strong>Issues</strong></td>
</tr>
<tr>
<td>C chronic filarial disease (mostly swollen limbs): 15 000 000 cases</td>
<td>C hydrocoele: 27 000 000 men</td>
<td>C sustained drug delivery at community level</td>
</tr>
<tr>
<td>C acute disease may cause 30 days of filarial fever per patient per year</td>
<td>C more than 73 countries in Africa, Asia, South and Central America, and the Pacific islands</td>
<td>C assessment of distribution of the disease and target populations for treatment</td>
</tr>
<tr>
<td>C one-third of infected people live in Africa; more than half live in India</td>
<td></td>
<td>C long-term impact of large-scale treatment</td>
</tr>
</tbody>
</table>
**LEISHMANIASIS**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Health Burden</th>
<th>Progress and Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mode of transmission</strong></td>
<td><strong>Estimated Global Health Burden</strong></td>
<td><strong>Primary interventions</strong></td>
</tr>
<tr>
<td>C bite of sandflies that carry the parasite from humans or animals</td>
<td>Not counting devastating epidemics, the:</td>
<td>C early case detection and drug treatment where the reservoir is infected people</td>
</tr>
<tr>
<td>C activities such as extracting timber, mining, building dams, widening areas under cultivation, new irrigation schemes, road construction in primary forests, economic migration and fast urbanization increase exposure to the sandfly vector</td>
<td>C annual incidence of new CL and MCL cases is: 1 500 000</td>
<td>C serological diagnosis (Direct Agglutination Test) for VL</td>
</tr>
<tr>
<td>C prevalence of CL and MCL is: 2 550 000</td>
<td>C annual incidence of new VL cases is: 500 000</td>
<td>C vector control where transmission occurs in and around the home, but not where transmission occurs in the wild</td>
</tr>
<tr>
<td>C prevalence of VL is: 1 270 000</td>
<td><strong>Endemic countries and regions</strong></td>
<td><strong>Progress</strong></td>
</tr>
<tr>
<td></td>
<td>C 88 countries on 4 continents</td>
<td>C primate models for CL and VL developed</td>
</tr>
<tr>
<td></td>
<td>C more than 90% of VL cases occur in Bangladesh, Brazil, India and Sudan</td>
<td>C field trials of CL and VL vaccines, constituted from killed <em>Leishmania</em> parasites, are in progress</td>
</tr>
<tr>
<td></td>
<td>C more than 90% of CL cases occur in Afghanistan, Iran, Saudi Arabia, Syrian Arab Republic, Brazil and Peru</td>
<td>C 2nd generation ‘cocktail’ vaccines under development</td>
</tr>
<tr>
<td></td>
<td><strong>Issues</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td>C the leishmaniases, as a complex of diseases, are impossible to control with a single approach or tool as yet (a vaccine may prove an exception)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C there is a disturbing increase in the number of people infected, the diseases being related to economic development and man-made environmental changes which increase exposure to the sandfly vector</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C Leishmania/HIV co-infection is considered an ‘emerging disease’, especially in southern Europe</td>
<td></td>
</tr>
</tbody>
</table>
## SCHISTOSOMIASIS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Health Burden (1996)</th>
<th>Progress and Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mode of transmission</td>
<td>Estimated Global Health Burden</td>
<td>Primary interventions</td>
</tr>
<tr>
<td>C the intermediate snail host releases infective forms of the parasite into water</td>
<td>number of people infected:  more than 200 000 000</td>
<td>morbidity control through integration of the following strategies:</td>
</tr>
<tr>
<td>C people are infected by contact with water where infected snails live (e.g. during washing, swimming, fishing, rice cultivation, irrigation)</td>
<td>number of symptomatic patients:  120 000 000</td>
<td>C diagnosis using urine filtration and faecal smear techniques; antigen or antibody tests in non-endemic areas</td>
</tr>
<tr>
<td>C number of severely infected people:  20 000 000</td>
<td>deaths: about 100 000</td>
<td>C drug treatment with praziquantel (and oxamniquine)</td>
</tr>
<tr>
<td>C diagnosis using urine filtration and faecal smear techniques</td>
<td>snail control through focal mollusciciding</td>
<td>C provision of safe and adequate water supply and sanitation</td>
</tr>
<tr>
<td></td>
<td>snail control through focal mollusciciding</td>
<td>C health education</td>
</tr>
<tr>
<td></td>
<td>provision of safe and adequate water supply and sanitation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>C health education</td>
<td></td>
</tr>
</tbody>
</table>

### Characteristics of illness

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Endemic countries and regions</th>
<th>Progress</th>
<th>Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>C urinary symptoms (e.g. blood in the urine) are due to <em>Schistosoma haematobium</em></td>
<td>endemic in 74 developing countries</td>
<td>C the global distribution of schistosomiasis has not changed significantly in the past 50 years but the intensity of the disease has decreased considerably in most parts of the world</td>
<td>C recent environmental changes, closely linked to water resources development and increases in population densities, have led to the spread of the disease to previously low- or non-endemic areas</td>
</tr>
<tr>
<td>C intestinal symptoms (initially atypical) are due to <em>S. intercalatum</em>, <em>S. japonicum</em>, <em>S. mansoni</em> or <em>S. mekongi</em></td>
<td>more than 80% of all infected people live in sub-Saharan Africa where populations are at risk from <em>S. mansoni</em>, <em>S. haematobium</em> and <em>S. intercalatum</em></td>
<td>C control has been particularly successful in China and the Philippines in the Far East, the Americas, North Africa and Middle East</td>
<td>C <em>S. mansoni</em> is replacing <em>S. haematobium</em> in some epidemiological settings</td>
</tr>
<tr>
<td>C immune reactions to worm eggs in the body damage various organs, in particular the liver in intestinal schistosomiasis and the bladder in urinary schistosomiasis</td>
<td><em>S. mansoni</em> is the only species found in the Americas</td>
<td>C success is linked to political commitment and the implementation of a concerted control strategy based primarily on chemotherapy</td>
<td></td>
</tr>
<tr>
<td>C sufferers become seriously weakened by the disease and in some cases the functioning of organs such as spleen and kidneys becomes impaired</td>
<td><em>S. haematobium</em> is now the most prevalent and widespread species in Africa and the Middle East</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C death is mostly due to bladder cancer associated with urinary schistosomiasis and to bleeding from varicose veins in the oesophagus associated with intestinal schistosomiasis</td>
<td><em>S. intercalatum</em> occurs in 10 countries in the rain forest belt of central Africa</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>S. japonicum</em> is found in four countries in the Western Pacific region, mainly China and the Philippines</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td><em>S. mekongi</em> is found in limited areas of Cambodia and in Laos</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
MALARIA

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Health Burden</th>
<th>Progress and Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mode of transmission</strong></td>
<td><strong>Estimated Global Health Burden</strong></td>
<td><strong>Primary interventions</strong></td>
</tr>
<tr>
<td>C bite of female anopheline mosquitos which carry the parasite from human to human</td>
<td>C the malaria situation is serious and becoming worse</td>
<td>C early diagnosis, based on clinical symptoms and microscopic examination of blood where possible</td>
</tr>
<tr>
<td></td>
<td>C risk currently exists in 100 countries and territories; in 92 there is transmission of <em>P. falciparum</em></td>
<td>C prompt, adequate treatment</td>
</tr>
<tr>
<td></td>
<td>C annual global incidence: 300-500 million clinical cases</td>
<td>C vector control</td>
</tr>
<tr>
<td></td>
<td>C deaths: 1.5 - 2.7 million a year</td>
<td>C hospital care for cases of severe disease including cerebral malaria</td>
</tr>
<tr>
<td></td>
<td>C deaths, attributable to malaria alone or in combination with other diseases, among children under five years of age: 1 million a year</td>
<td>C early detection, containment or prevention of epidemics</td>
</tr>
<tr>
<td></td>
<td>C over 40% of the world’s population lives in areas with malaria risk</td>
<td>C research to permit regular assessment of a country’s malaria situation</td>
</tr>
<tr>
<td><strong>Characteristics of illness</strong></td>
<td><strong>Endemic countries and regions</strong></td>
<td><strong>Progress</strong></td>
</tr>
<tr>
<td>C symptoms include: fever with or without other indications e.g. headache, muscular aches and weakness, vomiting, diarrhoea, cough</td>
<td>C malaria is now mainly confined to poorer tropical areas of Africa, Asia and Latin America</td>
<td>C some control programmes have achieved considerable reduction in the burden of malaria</td>
</tr>
<tr>
<td>C parasites break down red blood cells, inducing bouts of fever and anaemia</td>
<td>C more than 90% of malaria cases and the great majority of malaria deaths occur in tropical Africa</td>
<td>C over 90% of endemic countries are implementing appropriate control programmes in line with the global strategy for malaria control</td>
</tr>
<tr>
<td>C in cerebral malaria, infected blood cells obstruct blood vessels in the brain; other vital organs can also be damaged, often leading to death of the patient</td>
<td>C <em>Plasmodium falciparum</em> is the predominant malaria parasite in tropical Africa, the Amazon area, Southeast Asia, and Oceania</td>
<td>C</td>
</tr>
<tr>
<td>C <em>Plasmodium falciparum</em> is the main cause of severe clinical malaria and mortality</td>
<td>C</td>
<td></td>
</tr>
</tbody>
</table>

**Issues**
- endemic malaria has become re-established in some countries following large-scale epidemics; malaria transmission has been re-introduced in some countries (e.g. Central Asia and the Caucasus) following socio-economic degradation and collapse of health and social services
- drug resistance of the parasite
- insecticide resistance of the vector
ANNEX 3

METHODOLOGY FOR CASE STUDIES
Methodology for case studies

Objectives

The overall purpose of the study was to review TDR’s contributions in the development of three products that are currently used for tropical disease control and treatment:

- Ivermectin for the treatment of onchocerciasis
- Multidrug therapy (MDT) for the treatment of leprosy
- Fumigant canisters for the vector control of Chagas disease

The broad objective of the study was to assist in evaluating TDR’s past actions, in order to shape decisions about TDR’s future role and strategies for product development for tropical diseases.

Methods of the study

The analysis of the processes of product development was based on the results of a major study of the development of praziquantel for treatment of schistosomiasis, previously carried out by the principal investigator (Reich et al., 1996). That study examined the roles of four major actors (international agencies, developing country governments, private suppliers including non-governmental organizations, and pharmaceutical producers) across a series of specific processes in product development. Those processes were adapted for the current TDR study into seven stages:

- Discovery,
- Clinical trials,
- Registration,
- Production,
- Pricing,
- Distribution, and
- Program implementation.

For each stage in the product development cycle, this study sought to describe and assess TDR’s role and actions, and particularly how TDR interacted with other major actors involved in product development. One of the major findings of the praziquantel study was the importance of cross-organizational relationships. The development of effective products for tropical diseases requires multiple organizations working together. This study sought to examine how TDR managed cross-organizational relationships for the three selected products.
The study’s analysis was guided by five main questions:

C What were the disease control problems that TDR sought to resolve through its program for each product?
C What were the major activities carried out by TDR for each product?
C How did TDR’s activities affect product development at each stage?
C What were the major contributions made by TDR for each product?
C In what ways could TDR have improved its contributions for each product?

To address these questions, information on TDR’s activities were collected through: a review of the published literature; on-site examination of unpublished documents and memoranda at TDR; and interviews with key persons at WHO and at other organizations involved with the development of each product. Throughout, the study attempted to collect different perspectives on TDR’s role and activities, in order to provide a more balanced viewpoint on TDR’s contributions and limitations. Table 1 presents the kinds of information sought at each stage in the product development cycle, and the data sources used (in addition to interviews) for the analysis of TDR’s involvement.

Based on the data collected, the study used qualitative and semi-quantitative methods to assess TDR’s involvement in each stage of product development. In the qualitative methods, the information collected was presented in a descriptive text, using a common structure for each study. The first section presented the disease control ‘problem’ as perceived and defined by TDR in the 1970s. The second section presented the activities of major players, with a focus on TDR, for each of the seven stages of product development. The final section then presented a series of conclusions and themes drawn from the case study.

Each study also included a table that assessed the contributions of the major actors at each stage of product development. Three ‘levels’ of contribution were used in the assessment: negligible (-), moderate (+), and significant (++). This assessment necessarily required some judgment on the part of the researchers. The category of “negligible” was defined as no activity during a specific stage, or no activity that had an impact on the course of events. In most cases, this assessment was fairly clear from the data collected. The distinction between “moderate” and “significant” contribution required more judgment. A contribution was defined as “significant” if it involved substantial resources and if it also resulted in a major impact on the course of events. Actions that did not meet these two criteria were considered to make “moderate” contributions. The assessments for each actor, at each stage of product development, were discussed among the researchers, and the assessments were reviewed by interviewees and experts in the field, to provide feedback and some consensus on the level of contributions.
Limitations of the study

This study is subject to a number of limitations, which should be considered in any use of the findings.

First, the study was carried out with limited time, limited resources, and limited access to documents and individuals. The study was not designed or intended to be a full historical review of the archival record; and, indeed, the archives of some key institutions had been destroyed or were not openly available to the researchers. The study was designed as a background document for the Third External Review Committee of TDR, and each case study, therefore, was circumscribed in its scope, its data, and its style of presentation. The study is more of a focused evaluation than a full scholarly research project.

Second, the study examined institutional questions rather than scientific issues, and was carried out by researchers with political and organizational expertise rather than biological or parasitological expertise. The study addressed issues of institutional performance, and was not designed as a scientific review. The draft reports for each study were reviewed by individuals who were interviewed, in an effort to avoid scientific errors and factual mistakes.

Third, the cases of product development were selected by TDR, not by the researchers. The three cases represent successful instances of product development by TDR, and therefore cannot be interpreted as representing the full universe of TDR activities for product development. The study did not address the proportion of successful cases to unsuccessful cases of product development; nor did the study explore instances of failure in product development.

Fourth, the methods used to assess institutional performance and contribution are not well developed or universally accepted. This study sought to provide, from a position of independent observation, a narrative account of what happened at each stage of product development, and a description of the actions taken by TDR. The study sought to validate these observations by including differing perspectives on the same event, when possible. In addition, the narrative was reviewed by interviewees, to assure as much accuracy as possible. The semi-quantitative assessments of level of contribution for each actor, similarly, were reviewed by interviewees, and were revised when disagreement occurred and when a persuasive argument for revision was presented. Necessarily, these assessment and the revisions required some judgment by the researchers, based on the quality of evidence and the strength of arguments presented.

The assessment of contribution, thus, was complicated by a number of factors, from the perspective of methods. The three cases all involved events that happened years ago and all involved many players. In addition, the successes of the three cases depended on multiple players, with different interests and different organizational perspectives. These organizational pressures probably coloured
the recall of individuals and the representations of the past by institutions. Sometimes, different parts of the same organization had different views about what had happened and why. Finally, the successes of these three cases of product development resulted from multiple factors and multiple organizations. The nature of success complicates efforts to attribute causal contributions, and especially to attribute relative weightings of contributions, because all the involved organizations seek to claim responsibility. (For failures, similar complications arise, but the claims of attribution usually seek to assign blame to other players.) For this study, the researchers sought to parse the multiple claims for success with as much independence and good judgment as could be mustered. But inaccuracies in fact and controversy over interpretation no doubt remain, for which the researchers accept responsibility.
### Table 1. Data Sources for Each Stage of Product Development

<table>
<thead>
<tr>
<th>Stage of Product Development</th>
<th>Information of Interest</th>
<th>Source of Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>Budget and funding</td>
<td>Financial reports</td>
</tr>
<tr>
<td></td>
<td>TDR’s strategy and policy</td>
<td>Annual reports</td>
</tr>
<tr>
<td></td>
<td></td>
<td>TDR mission statement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Records of meetings</td>
</tr>
<tr>
<td></td>
<td></td>
<td>World Health Assembly resolutions</td>
</tr>
<tr>
<td>Discovery</td>
<td>Process of discovery (who, when &amp; how)</td>
<td>Scientific literature</td>
</tr>
<tr>
<td></td>
<td>Prior agreements between TDR and researchers</td>
<td>Letters between WHO and researchers, or pharmaceutical industry</td>
</tr>
<tr>
<td></td>
<td>Financial or technical support from TDR and other sources</td>
<td>Agreements</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Funding records</td>
</tr>
<tr>
<td>Clinical Trials</td>
<td>List of clinical trials (researchers &amp; results)</td>
<td>Scientific literature</td>
</tr>
<tr>
<td></td>
<td>Funding arrangements</td>
<td>Funding records</td>
</tr>
<tr>
<td></td>
<td>Technical support provided by TDR</td>
<td>Program reports</td>
</tr>
<tr>
<td></td>
<td>Process of negotiations about future development</td>
<td>Meeting records and letters</td>
</tr>
<tr>
<td>Registration</td>
<td>Patent information</td>
<td>Pharmaceutical industry sources</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Regulatory authority information</td>
</tr>
<tr>
<td>Production</td>
<td>Manufacturers</td>
<td>Pharmaceutical industry sources</td>
</tr>
<tr>
<td></td>
<td>Production level</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Production process and source of essential ingredients</td>
<td></td>
</tr>
<tr>
<td>Pricing</td>
<td>Price level and its changes</td>
<td>Records of meetings</td>
</tr>
<tr>
<td></td>
<td>Process of price negotiation</td>
<td>Correspondence between WHO, researchers, and pharmaceutical industry</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Agreements</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pharmaceutical industry sources</td>
</tr>
<tr>
<td>Distribution</td>
<td>Plan and agreements for distribution arrangements between manufacturers</td>
<td>Correspondence between WHO, researchers, and pharmaceutical industry</td>
</tr>
<tr>
<td></td>
<td>Need and availability of the products in the endemic countries</td>
<td>Agreements</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Records of meetings</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Annual reports of entities involved in distribution</td>
</tr>
<tr>
<td>Program Implementation</td>
<td>Contents of supporting program</td>
<td>Program plans and reports</td>
</tr>
<tr>
<td></td>
<td>Budget and funding</td>
<td>Financial reports</td>
</tr>
<tr>
<td></td>
<td>Collaborations with other parties</td>
<td>Scientific literature</td>
</tr>
<tr>
<td></td>
<td>Impacts of programs</td>
<td>Evaluation reports</td>
</tr>
<tr>
<td></td>
<td>Impact on disease control strategy and disease prevalence</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Monitoring system in place</td>
<td></td>
</tr>
</tbody>
</table>
ANNEX 4

COLLABORATIONS
SELECTED EXAMPLES
SELECTED EXAMPLES
COLLABORATIONS AND PARTNERSHIPS

1. Organizations/Agencies

Asian Development Bank, Manila, Philippines
The Bank recently invited TDR to attend a conference promoting sub-regional cooperation among countries of the Mekong region. A project on a coordinated approach to malaria control was identified as a high priority and TDR will collaborate with the Bank in the implementation of this project.

British Leprosy Relief Association/International Federation of Anti-Leprosy Associations (LEPRA/ILEP), Colchester/London, United Kingdom of Great Britain and Northern Ireland
TDR and LEPRA/ILEP are co-sponsoring a major leprosy vaccine trial in Malawi, with TDR providing the leprosy vaccine and a small annual grant for the trial and covering the cost of an independent trial monitor. LEPRA/ILEP covers the local costs of the trial.

Child to Child Trust, London, United Kingdom of Great Britain and Northern Ireland
Collaboration on health education and communication research related to the healthy school-aged child initiative.

Childwatch International, Oslo, Norway
Collaboration on health education and communication research related to the healthy school-aged child initiative.

Cochrane Collaboration (Infectious Diseases Group), Liverpool School of Tropical Medicine and Hygiene, GB
Systematic reviews of clinical data on drugs/interventions

Conselho Nacional de Desenvolvimento Científico e Tecnológico (National Council of Scientific and Technological Development) - CNPq, Brasilia, Brazil
Memorandum of Understanding signed in 1992 between CNPq and TDR concerning a partnership for training Brazilian research workers in disciplines related to TDR target diseases prevalent in Brazil. CNPq funds fellowships in conjunction with research and development and institution strengthening projects funded by TDR in Brazil.
Council on Health Research for Development (COHRED), Geneva, Switzerland
TDR collaborates with COHRED in the Essential National Health Research initiative. Following the co-funding of a national workshop on identification of health research priorities in Guinea, a five-year research agenda has been set for the country and TDR plans to collaborate in the capacity building component of the agenda. Co-funding of a similar national workshop is planned in Niger.

Danish International Development Agency (DANIDA), Ministry of Foreign Affairs, Copenhagen, Denmark
DANIDA and TDR have collaborated in providing institution strengthening and training to the Medical Research Centre in Mwanza, United Republic of Tanzania and to the Blair Research Laboratories in Harare, Zimbabwe. Much of the training component of this collaboration has been carried out through the Danish Bilharziasis Laboratory (DBL). DANIDA has provided financial support for curtain material and insecticide to the Centre de Lutte contre le Paludisme, Ouagadougou, Burkina Faso, for the TDR studies on impregnated bednets and curtains in Africa.

Directorate General for Development Cooperation, Ministry of Foreign Affairs of Italy, Rome, Italy
Collaboration includes support for Chagas disease control programmes in Argentina and Uruguay; joint strengthening of the research capability of the Centre de Lutte contre le Paludisme, Ouagadougou Burkina Faso; and funding of the protocols by scientists from Burkina Faso compiled during a workshop, jointly conducted with TDR, on the development of research protocols for malaria control.

Edna McConnell Clark Foundation, New York, N.Y., United States of America
TDR collaborates with the Foundation to coordinate schistosomiasis vaccine research and the Foundation financially supports TDR in this area. TDR has also collaborated with the Foundation in the development of an onchocerciasis vaccine. The Foundation participates in the Partnership for Child Development - see below.

European Commission (EC), Brussels, Belgium
TDR collaborates with the Commission’s Life Sciences and Technologies for Developing Countries Research and Development Programme which includes research on tropical diseases.

TDR has initiated, together with the EC and the United States Agency for International Development, the establishment of "A Coordinated Global Strategy for Malaria Vaccine Development and Clinical Testing". The three agencies share information and are developing a plan to coordinate research and development of malaria vaccines, including clinical and field trials of candidate vaccines in endemic countries.

A joint malaria vaccine antigen database has been set up.
There is co-sponsorship of scientific meetings and mutual invitations to meetings on topics of interest to both the EC and TDR.
Indian Council of Medical Research (ICMR), New Delhi, India
TDR and ICMR closely collaborate in the clinical trials carried out in India on leprosy vaccine; on ivermectin, diethylcarbamazine and other drugs for lymphatic filariasis; in preclinical studies on vaccine against visceral leishmaniasis; and drugs for visceral leishmaniasis.

Indian Institute of Chemical Technology, Hyderabad, India
TDR is collaborating with this institute in a pilot project to produce efloornithine by a novel technology for chemical analysis and comparison with the efloornithine produced by Marion Merrell Dow Pharmaceuticals Inc.

Integrated Control of Vector-Borne Diseases (ICOVED) Project, Malaria and Parasitic Diseases Control Directorate, Ministry of Health and Family Welfare, Government of the People's Republic of Bangladesh, Dhaka, Bangladesh
TDR collaborates in the research component of this project for strengthening the applied field research capacities of junior staff working in the National Malaria and Vector-Borne Diseases Control Programme. This is carried out through the planning and implementation of well-designed, time-limited projects on issues directly related to improving the control of some of the TDR target diseases widely prevalent in Bangladesh, i.e. malaria, leishmaniasis and filariasis.

International Development Research Centre (IDRC), Ottawa, Canada
Collaboration with IDRC includes support for a small grants programme in Africa on social and economic aspects of tropical diseases; support to the Task Force on Gender Research for research on the Healthy Women Counselling Guide and on healthy communication with rural women; joint funding of an IDRC/TDR award for the best research paper on gender and tropical diseases (begun in 1991 and now in its fourth year); joint workshop on gender analysis in 1993; research on the environment and tropical diseases; field research on artemisinin derivatives in Viet Nam; research on control strategies for leishmaniasis in Latin America, focusing on community participation; programme on house improvement to control Chagas disease in collaboration with the University of Asunción and the Ministry of Public Health and Social Welfare of Paraguay; and installation of ground stations for the satellite information network HealthNet administered by SatelLife in each of the four sites in Africa for the TDR studies on the use of insecticide-impregnated bednets for the reduction of childhood mortality from malaria, and support for training and maintenance of the ground station equipment. In addition, IDRC will provide (with funds made available by the Canadian International Development Agency) major financial support for the insecticide and bednets required for the studies and for workshops to determine the future directions of research on insecticide-impregnated materials.

IDRC is represented on several of TDR's Steering Committees and Task Forces: the Steering Committee on Applied Field Research, the Task Force on Gender Research, the Task Force on Tropical Diseases and the Environment and will be invited to be represented on the Task Force on Bednets.
International Livestock Research Institute (ILRI), Nairobi, Kenya

The laboratory is one of the centres of the global agricultural research network sponsored by the Consultative Group on International Agricultural Research and has as part of its mandate research on animal African trypanosomiasis. Collaboration with TDR involves sharing of results and scientists. ILRI collaborate in the parasite genome network.

John D. and Catherine T. MacArthur Foundation, Chicago, Illinois, United States of America

Coordination of research on molecular entomology, including joint funding of projects and training of scientists from developing countries. The Foundation is phasing out its support.

Ministère de la Coopération, Paris, France

Funding of Chagas disease research projects with institutions in Bolivia and collaboration with institutions in West Africa working on tropical disease research.

Ministry of Public Health of the People’s Republic of China, Beijing, China

Memorandum of Understanding signed in 1992 between the Ministry of Public Health of the Government of the People's Republic of China and TDR to collaborate in promoting and implementing a programme for training research workers at the Master's level in areas related to the TDR target diseases prevalent in China.

The Ministry obtained a loan from the World Bank to fund its schistosomiasis control programme. The World Bank and the Chinese Government invited TDR to participate in a Joint (TDR/Chinese Government) Research Management Committee (JRMC) to oversee the scientific integrity of operational research relating to schistosomiasis control. TDR provides technical expertise for research funded under the Bank loan.

National Institutes of Health (NIH), Bethesda, Maryland, United States of America

TDR collaborates with the Division of Microbiology and Infectious Diseases, Parasitology and Tropical Diseases Branch, National Institute of Allergy and Infectious Diseases (NIAID), in the Global Alliance Against Tropical Diseases. A major joint effort is underway to develop Pf-25, a leading malaria transmission blocking vaccine candidate.

Other collaboration is in the areas of schistosomiasis vaccine research and strategic research (pathogenesis), mutual invitations to meetings on topics of interest to both parties, and a representative of NIAID is co-opted on the Steering Committee on Immunology of Mycobacterial Diseases.

There is also collaboration on parasite genome mapping with the National Center for Biotechnology Information, National Library of Medicine.

NIH continues to be a strong Northern partner in research activities carried out at the Ecole de Médecine, Bamako, Mali. (The Ecole de Médecine received a partnership grant under the former joint TDR-Rockefeller Foundation venture and has recently received a TDR partnership grant.)
Collaboration on health education and communication research related to the healthy school-aged child initiative.

**Onchocerciasis Control Programme in West Africa (OCP), Ouagadougou, Burkina Faso**
Joint OCP/TDR project for the development of macrofilaricidal drugs (MACROFIL). The project includes all research required to bring products to the point of registration.

Field trials of products developed with TDR support to control onchocerciasis, such as DNA probes for differentiating forest and savanna onchocerciasis, are done in collaboration with OCP. Products which are ready for control use are handed over for use in the OCP area.

Participation of OCP staff in the Task Force on Operations Research on Onchocerciasis for improved ivermectin delivery in endemic areas outside the OCP area.

**Organisation de Coordination et de Coopération pour la Lutte contre les Grandes Endémies (OCCGE), Bobo-Dioulasso, Burkina Faso, and Organisation de Coordination pour la Lutte contre les Endémies en Afrique centrale (OCEAC), Yaoundé, Cameroon**
TDR collaborates with these two organizations, especially in the field evaluation of new tools for the control of sleeping sickness.

**Partnership for Child Development (PCD), Oxford, United Kingdom of Great Britain and Northern Ireland**
PCD collaborates with TDR (and the Edna McConnell Clark Foundation, the James S. McDonnell Foundation, the Rockefeller Foundation, the United Nations Development Programme, and the WHO Divisions of Communicable Diseases and Control of Tropical Diseases) concerning multidisease chemotherapy of school-aged children with schistosomiasis and geohelminth infections, through the exchange of information, coordination of projects, joint meetings, and the TDR Product Development Unit gives support with respect to contacts with the pharmaceutical industry.

**Rockefeller Foundation, New York, N.Y., United States of America**
The Foundation collaborates with WHO/TDR in several areas, including in the Partnership for Child Development (see above). The five-year joint TDR-Rockefeller Foundation partnership grant venture was completed at the end of 1993.

**South East Asian Ministers of Education Organization, Regional Tropical Medicine and Public Health Project (SEAMEO-TROPMED), Bangkok, Thailand**
Memorandum of Undertaking signed in 1991 between SEAMEO-TROPMED and TDR to collaborate in a scheme for training research workers at the Ph.D. level in areas related to the TDR target diseases prevalent in the South-East Asian region. The scheme is called the Joint SEAMEO-TROPMED/TDR Fellowships.
Swedish Agency for Research Cooperation with Developing Countries (SAREC), Stockholm, Sweden

Collaboration with SAREC includes funding of Chagas disease research projects in institutions in Argentina, Chile and Uruguay; joint development of a research agenda for tropical diseases and the environment; and training of Somali scientists. TDR reviews proposals for SAREC-supported research on the TDR diseases.

Swiss Tropical Institute, Basel, Switzerland

Collaboration in a joint international training workshop at the Ifakara Centre, United Republic of Tanzania on qualitative research methods for social science research on tropical diseases. The STI has played a major role in the collaborative testing of Spf66, asexual blood stage vaccine in Tanzania.

A filariasis serum bank is based at the Institute which provides services to scientists in both developed and developing countries for testing diagnostic products. A chemical compound screening facility has been established and supported by TDR.

United Nations Children's Fund (UNICEF)

UNICEF has collaborated with TDR in the large-scale trials of insecticide-impregnated bednets in Africa to reduce childhood mortality from malaria by providing bednets or curtain material and insecticide for some of the trials.

UNICEF also acts as the recipient of Mectizan for treatment of onchocerciasis as approved by the Mectizan Expert Committee. Mectizan is then issued free of charge to control programmes.

United Nations Development Programme (UNDP), New York, N.Y., United States of America

Collaboration with UNDP includes production of press releases, reports for broadcast in UNDP's regular televsional magazine programme AZIMUTHS and of compilation of footage for future news, training, education or exhibition purposes; participation in the Partnership for Child Development (see above); and co-sponsorship of meetings.

United States Agency for International Development (USAID), Washington, D.C., United States of America

USAID, the European Commission (EC) and TDR have initiated the establishment of "A Co-ordinated Global Strategy for Malaria Vaccine Development and Clinical Testing" (See under EC for details) TDR has increased its input into the USAID MSP-1 Malaria Vaccine Task Force activities.

USAID also collaborates with TDR in the organization of the country control programme on Chagas disease in Bolivia and testing of efficacy of insecticidal paints and fumigant canisters following the standard Montevideo protocol.

USAID continues to participate with TDR in supporting the partnership grant at the Ecole de Médecine, Bamako, Mali.
USAID has funded research into home management practices related to malaria under the sick child initiative.

**United States Army Medical Research and Development Command (USAMRDC), Frederick, Maryland, United States of America**

In 1990, the World Health Organization and USAMRDC entered into a Cooperative Research and Development Agreement. A Memorandum of Understanding was drawn up to define the cooperation of the parties on the development of drugs and vaccines against parasitic and infectious diseases in view of their mutual desire that effective products be developed as rapidly as possible and made widely available to populations at risk. Under the agreement TDR collaborates with USAMRDC, especially the Walter Reed Army Institute of Research, Washington, D.C., on the development of arteether for the treatment of patients with severe malaria, as well as providing technical advice and independent monitoring for the ongoing SPf66malaria vaccine trial in Thailand. In addition, TDR is funding safety and immunogenicity studies in Rhesus monkeys for RTSS, a leading pre-erythrocytic malaria vaccine candidate.

**University of the Witwatersrand, Johannesburg, South Africa**

Collaboration on a five country study in Africa to investigate the woman client - health provider relationship, using experimental qualitative research methods.

**Walter Reed Army Institute for Research, Washington**

WRAIR has been collaborating with TDR in screening antimalarial compounds, toxicology, metabolism and pharmacokinetic studies and has been TDR’s partner in the development of additional drugs and vaccines.

**Wellcome Trust, London, United Kingdom of Great Britain and Northern Ireland**

Cooperation in the clinical monitoring of a Wellcome Trust-sponsored Phase III comparative clinical trial of artether injection versus quinine in the treatment of severe malaria in Viet Nam, and collaboration on an artether Phase III trial in Kenya.

Collaboration with the TDR Image Library on the Videodisc project, involving the production of graphics and video-compatible material for training and education, etc.

**The World Bank, Washington, D.C., United States of America**

The World Bank has given a loan to the Ministry of Public Health of the Government of the People's Republic of China to fund its schistosomiasis control programme. The World Bank and the Chinese Government invited TDR to participate in a Joint (TDR/Chinese Government) Research Management Committee (JRMC) to oversee the scientific integrity of operational research relating to schistosomiasis control. TDR provides technical expertise for research funded under the Bank loan. Other possibilities for similar types of collaboration are being explored.
2. **Other Nongovernmental Organizations**

TDR collaborates with relevant NGOs, e.g. for onchocerciasis operational research.

3. **Other Collaborative Activities**

Some activities are carried out through contributions to TDR, which may or may not be formally designated contributions, e.g. contributions from the Arab Fund for Economic and Social Development in support of small grants programmes for schistosomiasis and leishmaniasis, jointly sponsored by the WHO Regional Office for the Eastern Mediterranean, the WHO Division of Control of Tropical Diseases and TDR; contributions from the Department for International development, United Kingdom of Great Britain and Northern Ireland, towards the cost of the coordinator of the TDR funded large-scale trials of insecticide impregnated bednets and curtains in Africa; contributions from the Government of the Netherlands designated for collaboration on the advanced development of novel artemisinin derivatives and formulations of antimalarial drugs based on artemisinin; and contributions from the Government of Belgium designated for the component on integrated chemotherapy for African trypanosomiasis, Chagas disease and leishmaniasis, towards the screening of lead compounds against *trypanosoma, leishmania, plasmodium and filaria*.

The Government of Norway continues to pay for the secondment of a communication expert to assist TDR in the development of a health communication strategy for tropical diseases.

4. **Pharmaceutical Industry**

**ACF Beheer, B.V., Maarssen, Netherlands**

Agreement for collaboration in the development, registration, manufacturing and marketing of arteether injection, a drug for the parenteral treatment of multidrug resistant, severe malaria, based upon the natural product extracted from the herbal plant, *Artemisia annua*. Partial funding for this project has been provided by the Netherlands Ministry for Development Cooperation. The product will be made available to the developing country public sector market at a preferential price.

**Aquila Bio Pharmaceuticals, Worcester, Ma, USA**

TDR is collaborating closely with Aquila in evaluating leading malaria vaccine candidate antigens with their novel adjuvant QS-21.

**Bayer A.G., Leverkusen, Germany**

This company collaborates with TDR on multidisease chemotherapy of school-aged children with schistosomiasis and geohelminth infections. Bayer provided free of charge the follow-up praziquantel doses required for the treatment of formerly placebo-treated children, and for community treatment of the population in the study villages.
Biobras-Bioquimica do Brasil, Montes Claros, Brazil
Production of killed leishmanial vaccine under Good Manufacturing Practices (GMP) for clinical trials in Brazil.

Burroughs Wellcome Company, Research Triangle Park, North Carolina, United States of America
Collaboration on efficacy of allopurinol against leishmaniasis and Chagas disease and supply of chemical compounds for screening against TDR target disease parasites.

Cymbus Biotechnology Ltd., Chandlers Ford, Hants, UK
TDR is collaborating with Cymbus to produce gram amounts of a monoclonal antibody to be used as a global reference standard for use in calibration of in vitro assays for MSP-1 functional activity.

Daiichi Pharmaceutical Co. Ltd., Tokyo, Japan
The company is collaborating with the Chemotherapy of Mycobacterial Diseases component by providing ofloxacin free of charge for drug trials.

Entremed, Inc., Rockville, MD, USA
TDR is collaborating with Entremed in the development of a P. falciparum malaria vaccine based on EBA-175, an invasion ligand.

F. Hoffmann - La Roche
TDR has entered into discussions on taking over former Roche research related projects to the development of antimalarials. Placement of technology transfer scientist from DEC for project on protein crystallisation

Glaxo Wellcome Research and Development Limited, Stevenage, Herts, GB
Supply of compounds for screening in TDR screens. Assistance with the screening of target enzymes and receptors in high throughput screens. Assistance in training of TDR staff in Planning

IHARABRAS S.A., Industrias Quimicas, Sao Paulo, Brazil
Production and commercialization of insecticidal paints for the control of Chagas disease transmission by triatomine insects.

ILEX Oncology, San Antonio, Texas, USA
The Company has been licenced by Hoechst Marion Rousell Inc., the manufacturer of eflornithine, to produce the drug for oncological studies. TDR/WHO is examining with the company the feasibility of producing eflornithine for African trypanosomiasis, the production of an oral formulation for clinical trials; and the development of an alternative, more effective and less expensive method of synthesis of eflornithine.
Janssen Research Foundation, Beerse, Belgium
Screening and development of Janssen compounds against five diseases (malaria, filariasis, African trypanosomiasis, Chagas disease and leishmaniasis).

Laboratorios Gador, Buenos Aires, Argentina
Development and commercialization of a test to detect anti*Trypanosoma cruzi* antigens for blood screening using defined parasite antigens produced by DNA recombination techniques.

Marion Merrell Dow Pharmaceuticals Inc. (now Hoechst Marion Roussel Inc), Kansas City, Missouri, United States of America
TDR is collaborating with the company in the further development of eflornithine for the treatment of *Trypanosoma brucei gambiense* sleeping sickness through a comparative study of 14-day and 7-day durations of treatment and in the identification of a suitable producer of eflornithine in a developing country for the transfer of technology.

Merck and Co. Inc., Rahway, New Jersey, United States of America
Close collaboration in carrying out operational research on onchocerciasis in West Africa and in conducting clinical trials with ivermectin in lymphatic filariasis. The drug ivermectin is provided at no cost by the company which also provides expert advice.

Merck and Co. Inc., also makes financial contributions to the Pan American Health and Education Foundation intended for the Foundation to use for support to TDR, towards the costs of the clinical trials of ivermectin for lymphatic filariasis.

E. Merck Pharma, Darmstadt, Germany
This company collaborates with TDR concerning multidisease chemotherapy of school-aged children with schistosomiasis and geohelminth infections. Cooperation includes supply of study drugs free of charge (praziquantel, brand name Biltricide) and placebos which were specifically produced for the TDR Product Development Unit in cooperation with Bayer, A.G.

Novo Nordisk A/S, Bagsvaerd, Denmark
Close collaboration in carrying out operational trials of *Bacillus sphaericus* against *Culex* mosquito vectors of lymphatic filariasis in Brazil, Cameroon, Côte d’Ivoire, India, Sri Lanka and the United Republic of Tanzania. The company has provided, at no cost, new formulations of the bioinsecticide.

Pasteur-Mérieux-Connaught, Swiftwater, Pennsylvania, United States of America
Collaboration on schistosomiasis vaccine development.

Pfizer limited, Sandwich, Kent, GB
Discussions on screening of target enzymes and receptors for identification of new lead compounds. Discussion on supply of compounds for evaluation in TDR screens.
Pharmacia and Upjohn, Milan, Italy
The company provided study material for trials on an ointment containing aminosidine for treatment of cutaneous leishmaniasis and an injectable against visceral leishmaniasis. Manufacturers are being sought in DECs to produce finished product to be made available to the public sector market of some developing countries at a preferential price.

Rhône-Poulenc Rorer Doma, Antony, France
Agreement for collaboration in the registration and marketing of artemether injection, a drug intended for use in the parenteral treatment of multidrug resistant, severe malaria. This product is manufactured by the Kunming Pharmaceutical Factory, Kunming, People's Republic of China, under an agreement with Rhône-Poulenc. The drug is being made available to the developing country public sector market at a preferential price.

Supply of compounds for screening against parasites.

Shanghai Institute of Pharmaceutical Industry, Shanghai, China
This Institute has developed a lead compound for veterinary use but has been found to be active against trypanosomes which cause human African trypanosomiasis. TDR has provided funds to the Institute to synthesize derivatives of the lead compound to improve effectiveness against late stage African trypanosomiasis.

SmithKline Beecham Pharmaceuticals, London, United Kingdom of Great Britain and Northern Ireland
This company collaborates with TDR concerning multidisease chemotherapy of school-aged children with schistosomiasis and geohelminth infections. Cooperation includes supply of study drugs free of charge (albendazole, brand name Zentel); randomization, coding and labelling of the study drugs including praziquantel obtained from E. Merck Pharma and Bayer A.G.; packing and shipping of the drugs to the study sites; provision free of charge of the follow-up albendazole doses required for the treatment of the formerly placebo-treated children, and for community treatment of the population in the study villages.

Development of chlorproguanil and dapsone for oral treatment of uncomplicated malaria

SmithKline Beecham Biologicals, Rixensart, Belgium
TDR is providing independent clinical monitors for a Phase IIb trial of a leading pre-erythrocytic malaria vaccine, RTS,S.

NeXstar Inc., San Dimas, California, United States of America
Clinical trials for visceral and mucosal leishmaniasis using AmBisome. The drug has been registered in Europe for visceral leishmaniasis in 1994. The drug will be made available to the developing country public sector market at a preferential price.
**Zambon SpA, Milan, Italy**
Audit of clinical and analytical study centres

Screening of selected compounds for malaria and kinetoplastidae

**5. Other Collaborative Activities**

TDR is receiving chemical compounds for screening against TDR target disease parasites from a number of companies including: Ciba Geigy Ltd., Basle, Switzerland; Eli Lilly and Company, Greenfield, Indiana, United States of America; Glaxo Group Research Limited, Greenford, United Kingdom of Great Britain and Northern Ireland; and Zeneca Pharmaceuticals, Macclesfield, United Kingdom of Great Britain and Northern Ireland.
ANNEX 5

LIST OF COUNTRIES

BY

DEVELOPMENT STATUS
# List of WHO Member States and Associate Members

## By Various Groupings*

**As of 1 May 1998**

<table>
<thead>
<tr>
<th>Member States</th>
<th>(191)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) Developed market-economy countries</td>
<td>(27)</td>
</tr>
<tr>
<td>(b) Developing countries</td>
<td>(137)</td>
</tr>
<tr>
<td>of which</td>
<td></td>
</tr>
<tr>
<td>Least developed countries</td>
<td>(48)</td>
</tr>
<tr>
<td>Other developing countries</td>
<td>(89)</td>
</tr>
<tr>
<td>(c) Economies in transition</td>
<td>(27)</td>
</tr>
</tbody>
</table>

**Associate Members**

(2)

* Based on the classification used by the United Nations in the *World Economic and Social Survey 1997*. The above groupings are employed for analytical purposes only and do not have any official status.

## Acronyms for the Following Tables

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMR</td>
<td>United Nations American Region</td>
</tr>
<tr>
<td>AFR</td>
<td>United Nations African Region</td>
</tr>
<tr>
<td>EMR</td>
<td>Eastern Mediterranean Region</td>
</tr>
<tr>
<td>EUR</td>
<td>European Region</td>
</tr>
<tr>
<td>SEAR</td>
<td>South-East Asia Region</td>
</tr>
<tr>
<td>WPR</td>
<td>Western Pacific Region</td>
</tr>
</tbody>
</table>
(A) **DEVELOPED MARKET-ECONOMY COUNTRIES**  
* (27 Member States)  

<table>
<thead>
<tr>
<th>AMR</th>
<th>Canada</th>
<th>United States of America</th>
</tr>
</thead>
<tbody>
<tr>
<td>EUR</td>
<td>Andorra</td>
<td>Austria</td>
</tr>
<tr>
<td></td>
<td>Austria</td>
<td>Belgium</td>
</tr>
<tr>
<td></td>
<td>Belgium</td>
<td>Denmark</td>
</tr>
<tr>
<td></td>
<td>Denmark</td>
<td>Finland</td>
</tr>
<tr>
<td></td>
<td>Finland</td>
<td>France</td>
</tr>
<tr>
<td></td>
<td>France</td>
<td>Germany</td>
</tr>
<tr>
<td></td>
<td>Germany</td>
<td>Greece</td>
</tr>
<tr>
<td></td>
<td>Greece</td>
<td>Iceland</td>
</tr>
<tr>
<td></td>
<td>Iceland</td>
<td>Ireland</td>
</tr>
<tr>
<td></td>
<td>Ireland</td>
<td>Italy</td>
</tr>
<tr>
<td></td>
<td>Italy</td>
<td>Luxembourg</td>
</tr>
<tr>
<td></td>
<td>Luxembourg</td>
<td>Malta</td>
</tr>
<tr>
<td></td>
<td>Malta</td>
<td>Monaco</td>
</tr>
<tr>
<td></td>
<td>Monaco</td>
<td>Netherlands</td>
</tr>
<tr>
<td></td>
<td>Netherlands</td>
<td>Norway</td>
</tr>
<tr>
<td></td>
<td>Norway</td>
<td>Portugal</td>
</tr>
<tr>
<td></td>
<td>Portugal</td>
<td>San Marino</td>
</tr>
<tr>
<td></td>
<td>San Marino</td>
<td>Spain</td>
</tr>
<tr>
<td></td>
<td>Spain</td>
<td>Sweden</td>
</tr>
<tr>
<td></td>
<td>Sweden</td>
<td>Switzerland</td>
</tr>
<tr>
<td></td>
<td>Switzerland</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>WPR</td>
<td>Australia</td>
<td>Japan</td>
</tr>
<tr>
<td></td>
<td>Japan</td>
<td>New Zealand</td>
</tr>
</tbody>
</table>
### (B) DEVELOPING COUNTRIES

**Least developed countries**  
*(48 Member States)*

<table>
<thead>
<tr>
<th>Region</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFR</td>
<td>Angola, Benin, Burkina Faso, Burundi, Cape Verde, Central African Republic, Chad, Comoros, Democratic Republic of the Congo, Equatorial Guinea, Eritrea, Ethiopia, Gambia, Guinea, Guinea-Bissau, Lesotho, Liberia, Madagascar, Malawi, Mali, Mauritania, Mozambique, Niger, Rwanda, Sao Tome and Principe, Sierra Leone, Togo, Uganda, United Republic of Tanzania, Zambia</td>
</tr>
<tr>
<td>AMR</td>
<td>Haiti</td>
</tr>
<tr>
<td>SEAR</td>
<td>Bangladesh, Bhutan, Maldives, Myanmar, Nepal</td>
</tr>
<tr>
<td>EMR</td>
<td>Afghanistan, Djibouti, Somalia, Sudan, Yemen</td>
</tr>
<tr>
<td>WPR</td>
<td>Cambodia, Kiribati, Lao People’s Democratic Republic, Samoa, Solomon Islands, Tuvalu, Vanuatu</td>
</tr>
</tbody>
</table>
### (B) DEVELOPING COUNTRIES

Other developing countries (excluding least developed countries)

**(89 Member States)**

<table>
<thead>
<tr>
<th>AFR</th>
<th>Mauritius</th>
<th>Namibia</th>
<th>Nigeria</th>
<th>Senegal</th>
<th>Seychelles</th>
<th>South Africa</th>
<th>Swaziland</th>
<th>Zimbabwe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Algeria</td>
<td>Botswana</td>
<td>Cameroon</td>
<td>Congo</td>
<td>Côte d’Ivoire</td>
<td>Gabon</td>
<td>Ghana</td>
<td>Kenya</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMR</td>
<td>Guatemala</td>
<td>Guyana</td>
<td>Honduras</td>
<td>Jamaica</td>
<td>Mexico</td>
<td>Nicaragua</td>
<td>Panama</td>
<td>Paraguay</td>
</tr>
<tr>
<td>Antigua and Barbuda</td>
<td>Argentina</td>
<td>Bahamas</td>
<td>Barbados</td>
<td>Belize</td>
<td>Bolivia</td>
<td>Brazil</td>
<td>Chile</td>
<td>Colombia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SEAR</td>
<td>Democratic People’s Republic of Korea</td>
<td>Sri Lanka</td>
<td>Thailand</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>India</td>
<td>Indonesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EUR</td>
<td>Israel</td>
<td>Turkey</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMR</td>
<td>Bahrain</td>
<td>Morocco</td>
<td>Oman</td>
<td>Pakistan</td>
<td>Qatar</td>
<td>Saudi Arabia</td>
<td>Syrian Arab Republic</td>
<td>Tunisia</td>
</tr>
<tr>
<td></td>
<td>Cyprus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>United Arab Emirates</td>
</tr>
<tr>
<td>Egypt</td>
<td>Iran (Islamic Republic of)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iran</td>
<td>Iraq</td>
<td>Jordan</td>
<td>Kuwait</td>
<td>Lebanon</td>
<td>Libyan Arab Jamahiriya</td>
<td>Niue</td>
<td>Palau</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Papua New Guinea</td>
<td>Philippines</td>
</tr>
<tr>
<td>Cook Islands</td>
<td>Fiji</td>
<td>Malaysia</td>
<td>Marshall Islands</td>
<td>Micronesia</td>
<td>Republic of Korea</td>
<td>Singapore</td>
<td>Tonga</td>
<td>Viet Nam</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(Federated States of)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WPR</td>
<td>Brunei Darussalam</td>
<td></td>
<td></td>
<td></td>
<td>Niue</td>
<td>Palau</td>
<td>Papua New Guinea</td>
<td>Republic of Korea</td>
</tr>
<tr>
<td>China</td>
<td>Cook Islands</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Philippines</td>
<td>Singapore</td>
</tr>
<tr>
<td>Fiji</td>
<td>Malaysia</td>
<td></td>
<td></td>
<td>Marshall Islands</td>
<td>Micronesia</td>
<td></td>
<td>Tonga</td>
<td>Viet Nam</td>
</tr>
<tr>
<td>Malaysia</td>
<td>Marshall Islands</td>
<td>Micronesia</td>
<td>Republic of Korea</td>
<td>Singapore</td>
<td>Toga</td>
<td>Viet Nam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Micronesia</td>
<td>Tonga</td>
<td></td>
<td>Republic of Korea</td>
<td></td>
<td></td>
<td>Viet Nam</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Federated States of)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nauru</td>
<td>Niue</td>
<td>Palau</td>
<td>Papua New Guinea</td>
<td>Republic of Korea</td>
<td>Singapore</td>
<td>Tonga</td>
<td>Viet Nam</td>
<td></td>
</tr>
</tbody>
</table>
(C) ECONOMIES IN TRANSITION  
(27 Member States)

<table>
<thead>
<tr>
<th>EUR</th>
<th>Albania</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Armenia</td>
</tr>
<tr>
<td></td>
<td>Azerbaijan</td>
</tr>
<tr>
<td></td>
<td>Belarus</td>
</tr>
<tr>
<td></td>
<td>Bosnia and Herzegovina</td>
</tr>
<tr>
<td></td>
<td>Bulgaria</td>
</tr>
<tr>
<td></td>
<td>Croatia</td>
</tr>
<tr>
<td></td>
<td>Czech Republic</td>
</tr>
<tr>
<td></td>
<td>Estonia</td>
</tr>
<tr>
<td></td>
<td>Georgia</td>
</tr>
<tr>
<td></td>
<td>Hungary</td>
</tr>
<tr>
<td></td>
<td>Kazakhstan</td>
</tr>
<tr>
<td></td>
<td>Kyrgyzstan</td>
</tr>
<tr>
<td></td>
<td>Latvia</td>
</tr>
<tr>
<td></td>
<td>Lithuania</td>
</tr>
<tr>
<td></td>
<td>Poland</td>
</tr>
<tr>
<td></td>
<td>Republic of Moldova</td>
</tr>
<tr>
<td></td>
<td>Romania</td>
</tr>
<tr>
<td></td>
<td>Russian Federation</td>
</tr>
<tr>
<td></td>
<td>Slovakia</td>
</tr>
<tr>
<td></td>
<td>Slovenia</td>
</tr>
<tr>
<td></td>
<td>Tajikistan</td>
</tr>
<tr>
<td></td>
<td>The former Yugoslav Republic of Macedonia</td>
</tr>
<tr>
<td></td>
<td>Turkmenistan</td>
</tr>
<tr>
<td></td>
<td>Ukraine</td>
</tr>
<tr>
<td></td>
<td>Uzbekistan</td>
</tr>
<tr>
<td></td>
<td>Yugoslavia</td>
</tr>
</tbody>
</table>

ASSOCIATE MEMBERS (2)  
Developing

<table>
<thead>
<tr>
<th>AMR</th>
<th>Puerto Rico</th>
</tr>
</thead>
<tbody>
<tr>
<td>WPR</td>
<td>Tokelau</td>
</tr>
</tbody>
</table>
ANNEX 6

REFERENCES
References

Background Material

The global burden of disease - summary, Christopher J.L. Murray and Alan D. Lopez, WHO, 1996

The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020, Christopher J.L. Murray and Alan D. Lopez (Eds), WHO, 1996

Malaria research - an audit of international activity, PRISM Report No. 7, J. Anderson, M. MacLean and C. Davies, 1996


Investing in health research and development - report of the ad hoc committee on health research relating to future intervention options, WHO, 1996

Cooperation for health development - extrabudgetary funds in the World Health Organization, sponsored by Australian Agency for International Development, Royal Ministry of Foreign Affairs Norway, and Overseas Development Administration, United Kingdom, 1995

Cooperation for health development - the World Health Organization’s support to programmes at country level, sponsored by the Governments of Australia, Canada, Italy, Norway, Sweden and the United Kingdom, 1997

Sector strategy paper - health, nutrition and population, HNP family, human development network, World Bank, 1997

Think and act globally and intersectorally to protect national health, WHO, 1997 (WHO/PPE/PAC/97.2)

Intersectoral action for health: addressing health and environment concerns in sustainable development, WHO, 1997 (WHO/PPE/PAC/97.1)

Renewing the health-for-all strategy elaboration of a policy for equity, solidarity and health, consultation document, WHO, 1995
Steps to inform resource allocation for health research and development - application of a five-step process in the areas of child health, reproductive health and selected major infectious diseases, prepared for the First Global Forum on Health Research, 1997

Alliance for health policy/systems research, report and proposals from an international consultation - Editors: Karl Eric Knutsson, Göran Tomson, Karl-Olaf Wathne, Swedish International Development Cooperation Agency (SIDA) and Royal Ministry of Foreign Affairs (Norway), 1997

A research policy agenda for science and technology to support global health development - a synopsis, 1997 (WHO/RPS/ACHR/97.3)

UNDP, capacity development, technical advisory paper 2, United Nations Development Programme, Management Development and Governance Division, Bureau for Policy Development, 1997

TDR Programme

TDR basic documents, WHO, 1989 (TDR/BD/89E)

Report of the external review committee - Special Programme for Research and Training in Tropical Diseases, presented to the Fifth session of the Joint Coordinating Board, 1982 (TDR/JCB(5)/82.6)

Report of the second external review committee - Special Programme for Research and Training in Tropical Diseases, Eleventh session of the Joint Coordinating Board, 1988 (TDR/JCB(11)/88.6 Rev.1)

Terms of reference - third external review and evaluation of TDR, presented to the nineteenth session of the Joint Coordinating Board, 1996 - Annex 4 to the Report of the Nineteenth session of the Joint Coordinating Board (TDR/JCB(19)/96.6 Rev.1)

Report of the meeting on the prospective thematic review (PTR) on the impact of TDR, Prospective thematic review on the impact of TDR, 1995 (TDR/PTR-IMPACT/95.3)


TDR towards the year 2000, TDR, 1993 (TDR/PTR-SCI/92.3 Rev4)
The burden of tropical diseases among the poorest and richest 20% of the global population, Davidson R. Gwatkin and Michel Guillot, International Health Policy Program, Washington D.C Report prepared for the UNDP/World Bank/WHO Special programme for research and training in tropical diseases (TDR), 1998 (TDR/ER/RD/98.1)


TDR’s contribution to the development of the fumigant canister for controlling chagas disease, Tomoko Fujisaki and Michael Reich, Harvard School of Public Health. Report prepared for the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), 1998 (TDR/ER/RD/98.5)


Research capability strengthening (RCS): updating the strategy, UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR). Report presented to the nineteenth session of the Joint Coordinating Board, 1996 (TDR/JCB(19)/96.5)

A study of TDR research training grants, Margareta Strömbo. Report prepared for the UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), 1990 (TDR/RSG/RTG/90.1)


Prospects for elimination - Chagas disease, leprosy, lymphatic filariasis, onchocerciasis TDR/Gen/97.1

Global Programme for Vaccines and Immunization (GPV)

CVI/Rockefeller Foundation Conference on the global supply of new vaccines, Bellagio, Italy, 3-7 February 1997 (CVI/GEN/98.01)

Report of the meeting of the Scientific Group of Experts (SAGE) of the Children’s Vaccine Initiative and the Global Programme for vaccines and immunization, WHO, 1996 (WHO/GPV/96-06)

Report of the meeting of interested parties for the Global Programme for Vaccines and Immunization, WHO, 1996 WHO/GPV/96.05

Emerging and Other Communicable Diseases Surveillance and Control (EMC)


Strengthening of WHO Collaborating Centres working with EMC, WHO Collaborating Centres and National Laboratories (background material and paper) (WHO/EMC/98.4)

African Programme for Onchocerciasis Control (APOC)

Onchocerciasis Control Program (OCP)

African Programme for Onchocerciasis Control - Programme document, Committee of Sponsoring Agencies, 1996 (APOC/JAF212)

Expert Advisory Committee, Onchocerciasis Control Programme in West Africa, report of the seventeenth session, 1996 (OCP/JPC17.3)

External review of the Onchocerciasis Control Programme, 1990

Mid-term (Phase IV) prospective evaluation of the Onchocerciasis Control Programme in West Africa, 1994 (OCP/JPC15.7)

Control of Tropical Diseases (CTD)


A global strategy for malaria control, WHO, 1993


Report of the WHO informal consultation on the evaluation and testing of insecticides, Division of Control of Tropical Diseases, WHO, 1996, limited distribution (CTD/WHOPES/IC/96.1)

The burden of malaria, J.A. Nájera and J. Hempel, Malaria unit, Division of Control of Tropical Diseases, WHO, limited distribution (CTD/MAL/96.10)

Harare declaration on malaria prevention and control in the context of African economic recovery and development, Organization of African unity, Assembly of heads of state and government, thirty-third ordinary session, Zimbabwe


The Director-General’s task force on malaria prevention and control - Reports of the first and second meetings, 1996 (WHO/CTD/TF/98.1)

Action Programme for the Elimination of Leprosy (LEP)


Special Programme of Research, Development, and Research Training in Human Reproduction (HRP)


Thirteenth meeting of the scientific and technical advisory group (STAG), UNDP/UNFPA/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), WHO, 1996